α_2-Adrenergic Agonists/Antagonists: The Synthesis and Structure–Activity Relationships of a Series of Indolin-2-yl and Tetrahydroquinolin-2-yl Imidazolines[1]

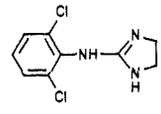
Dennis J. Hlasta,*† Daniel Luttinger,‡ Mark H. Perrone,‡ Marla J. Silbernagel,† Susan J. Ward,‡ and Dean R. Haubrich‡

Departments of Medicinal Chemistry and Pharmacology, Sterling-Winthrop Research Institute, Rensselaer, New York 12144.
Received December 8, 1986

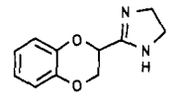
The synthesis and α_2-adrenergic activity of a series of indolin-2-yl and tetrahydroquinolin-2-yl imidazolines are described. The indolin-2-yl imidazoline **4b** was found to possess potent α_2-adrenergic agonist and antagonist activity. The modification of the substituents on the indoline ring of **4b** has led to the separation of these activities. Substitution on the aromatic ring of **4b** with halogen or increasing the size of the *N*-alkyl substituent of **4b** gave α_2-adrenergic antagonists without agonist activity. The *N*-allylindoline **4d** is more potent than idazoxan in vitro and is equipotent in vivo, but is less receptor selective (α_2 vs. α_1) than idazoxan. The *cis*-1,3-dimethylindolin-2-yl imidazoline **6a** is an α_2-adrenergic agonist equal in potency to clonidine in vitro, while the *trans*-1,3-dimethylindolin-2-yl imidazoline **6b** is a moderately potent α_2-adrenergic antagonist.

The identification of α_2-adrenergic receptors at nerve terminal presynaptic sites in the central and peripheral nervous systems has intensified the search for agents that selectively activate or block these receptor sites.[2] The α_2-adrenergic agonist clonidine is a clinically useful antihypertensive agent. Clonidine stimulates α_2-adrenergic receptors in the central nervous system, resulting in the inhibition of peripheral sympathetic tone. This is manifested in humans as hypotension and bradycardia.

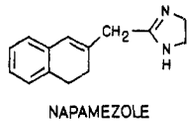
The common mechanism of action of antidepressant agents appears to involve the increase of synaptic levels of norepinephrine or serotonin in the central nervous system. α_2-Adrenergic antagonists should prove useful as antidepressants since they increase norepinephrine release centrally. The α_2-adrenergic antagonists idazoxan[3] and napamezole[4] are undergoing clinical evaluation as antidepressants.



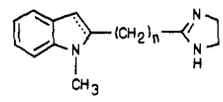
CLONIDINE



IDAZOXAN



NAPAMEZOLE



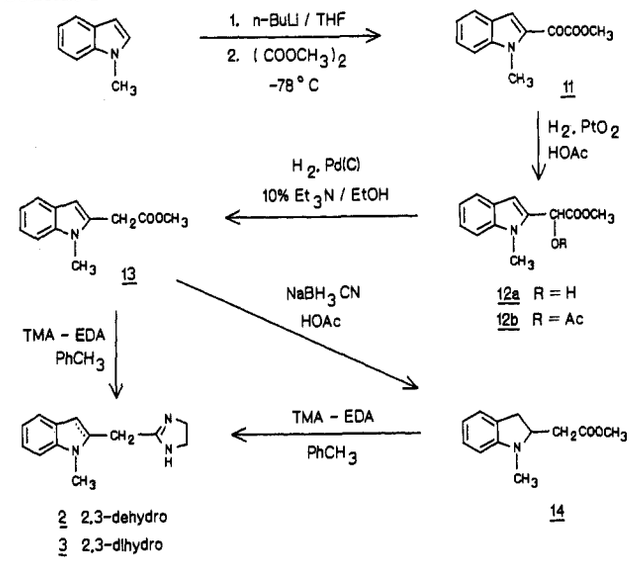
2 n = 1: 2,3-DEHYDRO
4b n = 0: 2,3-DIHYDRO

The indol-2-yl imidazolines **2** and **4b**, which are structurally analogous to napamezole and to idazoxan, were prepared to examine their activity at α_2-adrenergic receptors. The indole imidazoline **2** is a moderately potent α_2-adrenergic antagonist. However, the indolin-2-yl imidazoline **4b** is a potent mixed α_2-adrenergic agonist/antagonist. Structural modification of **4b** has led to identification of selective α_2-adrenergic agonists and antagonists. This paper describes the synthesis and structure–activity relationships of this series of compounds.[5]

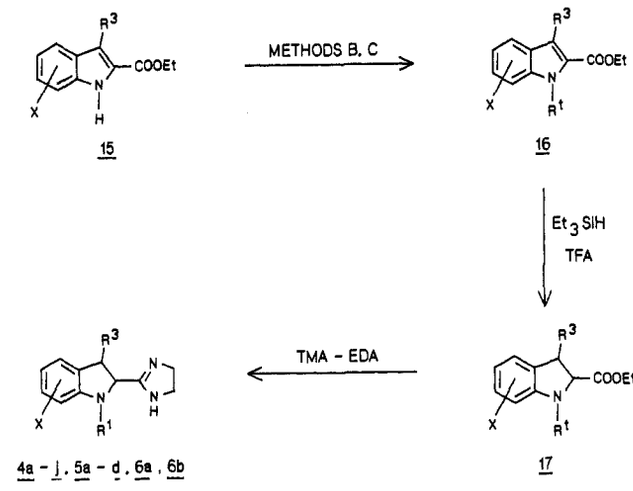
Chemistry

The indol-2-yl imidazolines **2** and **3** were prepared as shown in Scheme I. The glyoxylate **11**[6] could not be reduced directly to the indole-2-acetate **13** under a variety of conditions (Zn, HOAc; H_2, Pd(C), HOAc; $NaBH_3CN$,

Scheme I



Scheme II



(1) Presented in part at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 8, 1986; MEDI 17.

(2) Timmermans, P. B. M. W. M.; van Zwieten, P. A. *J. Med. Chem.* **1982**, *25*, 1389. DiJoseph, J. F.; Taylor, J. A.; Mir, G. N. *Life Sci.* **1984**, *35*, 1031. Lal, H.; Fielding, S., Eds. *Progress in Clinical and Biological Research*; Alan R. Liss: New York, 1981; Volume 71.

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

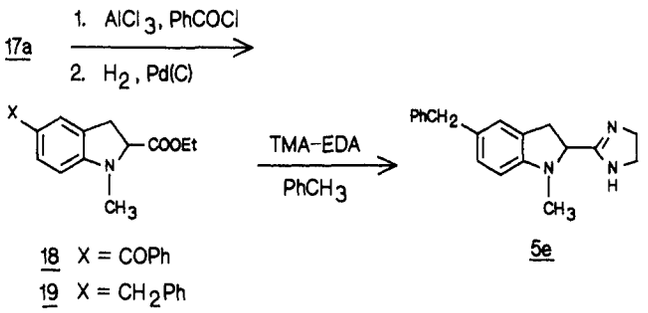
0022-2623/87/1830-1555$01.50/0

Table I. Intermediate Indole-2-carboxylates

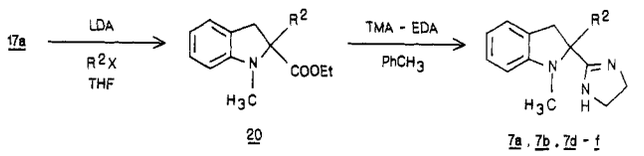
compd[a]	R^1	X	mp, °C	formula[b]	method	yield, %
16a	CH_2CH_3	H	(bp 103–105 °C, 0.20 mmHg)	$C_{13}H_{15}NO_2$	B	100
16b	$CH_2CH{=}CH_2$	H	oil	$C_{14}H_{15}NO_2$	B	100
16c	$CH_2CH_2CH_3$	H	oil	$C_{14}H_{17}NO_2$	B	100
16d	$CH_2CH_2CH_2CH_3$	H	(bp 108–109 °C, 0.075 mmHg)	$C_{15}H_{19}NO_2$	B	50
16e	$CH_2CH_2OCH_2CH_3$	H	oil	$C_{15}H_{19}NO_3$[c]	B	90
16f	CH_2Ph	H	60–61	$C_{18}H_{17}NO_2$	C	77
16g	CH_2CH_2Ph	H	82–83.5	$C_{19}H_{19}NO_2$	B	26
16h	CH_3	5-F	70–72	$C_{12}H_{12}FNO_2$	C	100
16i	CH_3	7-Cl	oil	$C_{12}H_{12}ClNO_2$	C	37
16j	CH_3	5,7-Cl_2	75–76	$C_{12}H_{11}Cl_2NO_2$	C	46

[a] Where R^3 = H. [b] Carbon, hydrogen, and nitrogen analysis were within ±0.4% of the theoretical values. [c] N: calcd, 5.36; found, 5.88.

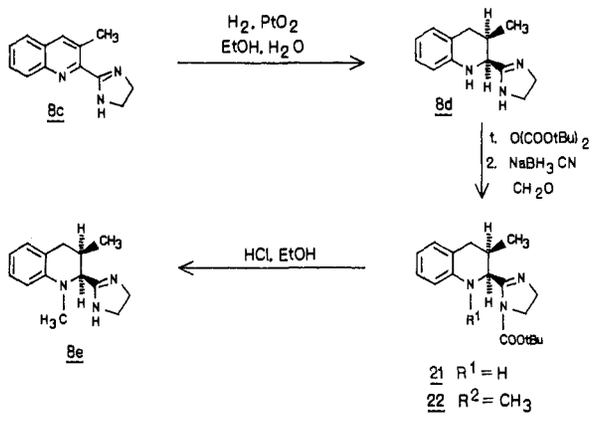
Scheme III



Scheme IV



Scheme V



HOAc, MeOH; BH_3, THF; H_2, Pd(C), HCl, EtOH). However, reduction to the alcohol **12a**, acetylation (Ac_2O, pyridine), and hydrogenolysis of **12b** gave the indole-2-acetate **13** in good overall yield. The alcohol **12a** could also be reduced directly to **13** with $Ph_3P{\cdot}I_2$ in benzene although in lower yield. The indole-2-acetates **13** and **14** were converted to the imidazolines **2** and **3**, respectively, on treatment with trimethylaluminum–ethylenediamine complex (TMA–EDA) in refluxing toluene (method A).[7]

The substituted indole-2-carboxylates **15** (Scheme II) were prepared by the Fisher indole synthesis by cyclization of the intermediate hydrazone esters or acids with polyphosphoric acid or with catalytic sulfuric acid in ethanol, respectively. The hydrazones were prepared by condensation of substituted phenylhydrazines with pyruvates or pyruvic acids in refluxing ethanol. The following substituted ethyl indole-2-carboxylates were prepared by these methods: 5-fluoro,[8] 7-chloro,[9] 5,7-dichloro,[9] 3-methyl,[10] 1,3-dimethyl,[11] 1-phenyl,[12] 1-methyl,[10] and 5-chloro-1-methyl.[13]

The indole-2-carboxylates **15** were alkylated (Scheme II) to give the N-substituted indole-2-carboxylates **16** listed in Table I. Reduction of the indoles **16** with triethylsilane in refluxing trifluoroacetic acid gave the indolines **17**, except for the indoline **17** (R^1 = R^3 = X = H), which was prepared by reduction of ethyl indole-2-carboxylate with tin metal in ethanolic HCl.[14] The indolines **17** were converted, usually without purification to the imidazolines **4–6**, by treatment with trimethylaluminum–ethylenediamine complex (TMA–EDA). The cis–trans isomers **6a** and **6b** were separated by chromatography on silica by gradient elution with triethylamine–methanol–ethyl acetate mixtures. The structure assignments of *cis*-**6a** and *trans*-**6b** were made on the basis of the relative positions of the ^1H NMR chemical shifts of the C-2 proton, the C-3 proton, and the C-3 methyl relative to the corresponding chemical shifts reported for *cis*- and *trans*-2,3-dimethylindolines.[15,16] In addition, heating the indoline hydrotosylate **6a** in ethanol resulted in epimerization to **6b**.

The synthesis of the 5-benzylindoline **5e** is outlined in Scheme III. Friedel–Crafts acylation of ethyl 1-methyl-

(3) 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.
(4) Bailey, D. M.; Alexander, E. J.; Castaldi, M. J.; Ferrari, R. A.; Haubrich, D. R.; Luttinger, D. A.; Perrone, M. H.; Wentland, M. P. 191st National Meeting of the American Chemical Society, New York, NY, April 1986; MEDI 57. Perrone, M. H.; Hamel, L. T.; Luttinger, D.; Bailey, D. M.; Ferrari, R. A.; Haubrich, D. R. *Pharmacologist* **1986**, *28*, 90, Abstract 8.
(5) The indol-2-yl imidazoline **4b** and related structures have been claimed in the patent literature as α_2 antagonists (JP 6 058 976 (*Chem. Abstr.* **1985**, *103*, 87877*h*) and FR 2 550 532 (*Chem. Abstr.* **1985**, *103*, 71189*z*)).
(6) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146.
(7) Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824.
(8) Allen, F. L.; Brunton, J. C.; Suschitzky, H. *J. Chem. Soc.* **1955**, 1283.
(9) Ishii, H.; Murakami, Y.; Furuse, T.; Hosoya, K.; Ikeda, N. *Chem. Pharm. Bull.* **1973**, *21*, 1495.
(10) Johnson, J. R.; Hasbrouck, R. B.; Dutcher, J. D.; Bruce, W. F. *J. Am. Chem. Soc.* **1945**, *67*, 423.
(11) Shafiee, A.; Sattari, S. *Synthesis* **1981**, 389.
(12) Dolby, L. J.; Lord, P. D. *J. Org. Chem.* **1969**, *34*, 2988.
(13) Inaba, S.; Akatsu, M.; Hirohashi, T.; Yamamoto, H. *Chem. Pharm. Bull.* **1976**, *24*, 1076.
(14) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476.
(15) Anet, F. A. L.; Muchowski, J. M. *Chem. Ind.* **1963**, 81.
(16) The reported changes in chemical shifts ($\Delta\delta$) for the C-2 protons, the C-3 protons, and the C-3 methyl protons for the *cis*- vs. *trans*-2,3-dimethylindolines recorded in CCl_4 solution are +0.51, +0.25, and −0.09, respectively. The 2,3-proton coupling constants are J_{cis} = 8.83 Hz and J_{trans} = 8.85 Hz.[15] The change in chemical shifts ($\Delta\delta$) for the C-2 protons, the C-3 protons, and the C-3 methyl protons for *cis*-**6a** vs. *trans*-**6b** recorded in $CDCl_3$ solution are +0.46, +0.47, and −0.39, respectively. The 2,3-proton coupling constants for **6a** and **6b** are J_{cis} = 9.3 Hz and J_{trans} = 10.2 Hz.

indoline-2-carboxylate (**17a**) followed by hydrogenation of the 5-benzoylindoline **18** over palladium on carbon gave the 5-benzylindoline **19**. Treatment of the ester **19** with the TMA–EDA complex in refluxing toluene gave the imidazoline **5e**.

The preparation of the 2-substituted indolines is described in Scheme IV. Addition of the indoline **17a** to lithium diisopropylamide in tetrahydrofuran at −78 °C resulted in anion formation, which on treatment with alkyl halides gave the 2-substituted indolines **20**. In one example, the addition of Eschenmoser's salt resulted in the in situ formation of *N,N*-diisopropyl-*N*-methyleneammonium iodide from the diisopropylamine present; thus the indoline **20** where $R^2 = CH_2N(i\text{-}Pr)_2$ was obtained. The indolines **20** were converted with the TMA–EDA complex to the imidazolines **7** except for **7c**. The indoline **7c** (R = *n*-Pr) was prepared from **7b** ($R^2 = CH_2CH{=}CH_2$) by hydrogenation over palladium on carbon.

The tetrahydroquinoline **8a** was prepared from the known ethyl 1,2,3,4-tetrahydroquinoline-2-carboxylate[17] by treatment with the TMA–EDA complex. Reductive methylation of the known ester [CH_2O, H_2 (50 psi), Pd(C), EtOH] followed by imidazoline formation with the trimethylaluminum–ethylenediamine complex gave the quinoline **8b**. The known methyl 3-methylquinoline-2-carboxylate[18] was converted by method A to the quinoline **8c**, which on hydrogenation gave the tetrahydroquinoline **8d** (Scheme V). Attempts to convert **8d** by reductive methylation to the *N*-methylquinoline **8e** resulted in the methylation of the imidazoline nitrogen as determined by ^1H NMR. Therefore, the imidazoline of **8d** was protected, and reductive methylation of **21** gave the *N*-methyltetrahydroquinoline **22**. Deprotection in refluxing ethanolic hydrogen chloride gave the desired quinoline **8e** without epimerization. The stereochemistry of the *cis*-tetrahydroquinolines **8d** and **8e** was assigned on the basis of the ^1H NMR of the quinolines **22** and **8e**. The tetrahydroquinoline C-2 protons of **22** and **8e** displayed coupling constants of 5.2 and 4.7 Hz, respectively. The magnitude of the coupling constants confirmed a cis orientation of the protons at positions 2 and 3 of the quinoline.

The structures and physical properties of the imidazolines that were prepared are listed in Table II.

Table II. Imidazolines

no.[a]	mp, °C	formula[b]	yield,[c] %	recryst solvent
1	260–280[d]	$C_{12}H_{13}N_3$·HCl	37	EtOH–EA
2	122–134[d]	$C_{13}H_{15}N_3$	60	EA–cyclohexane
3	201–204	$C_{13}H_{17}N_3$·HCl·$^1/_4H_2O$	59	EtOH
4a	140–148	$C_{11}H_{13}N_3$	10	EA
4b	182–207	$C_{12}H_{15}N_3$·HCl	89	EtOH–EA
4c	95–99	$C_{13}H_{17}N_3$·HCl·H_2O	93	EtOH–EA
4d	147–149	$C_{14}H_{17}N_3$·$C_7H_8O_3S$	57	*i*-PrOH
4e	113–115	$C_{14}H_{19}N_3$·$C_4H_4O_4$	53	EA
4f	135–137	$C_{15}H_{21}N_3$·$C_7H_8O_3S$	19	*i*-PrOH–ether
4g	178–179	$C_{15}H_{21}N_3O$·HCl	59	EtOH–ether
4h	176.5–178	$C_{17}H_{17}N_3$·$C_4H_4O_4$	66	EA
4i	143–145	$C_{18}H_{19}N_3$·$C_4H_4O_4$	30	EA
4j	134.5–136	$C_{19}H_{21}N_3$	88	EA
5a	272–274	$C_{12}H_{14}FN_3$·HCl	85	EA–ether
5b	250–253	$C_{12}H_{14}ClN_3$·HCl	95	EtOH–ether
5c	135.5–137	$C_{12}H_{14}ClN_3$·$C_4H_4O_4$	28	EA
5d	189–191	$C_{12}H_{13}Cl_2N_3$·$C_7H_8O_3S$	57	EA
5e	152–155	$C_{19}H_{21}N_3$·$C_4H_4O_4$	*e*	EtOH–ether
6a	173.5–174.5	$C_{13}H_{17}N_3$·$C_7H_8O_3S$	10	*i*-PrOH–ether
6b	163–165	$C_{13}H_{17}N_3$·$C_7H_8O_3S$	27	*i*-PrOH–ether
7a	140.5–143.5	$C_{13}H_{17}N_3$·$C_4H_4O_4$	85	EA–ether
7b	242–247[d]	$C_{15}H_{19}N_3$·HCl	93	EtOH–ether
7c	241–245[d]	$C_{15}H_{21}N_3$·HCl	*e*	EtOH–EA
7d	245–251	$C_{14}H_{19}N_3O$·HCl	87	EtOH–ether
7e	193–194	$C_{14}H_{19}N_3S$·$C_7H_8O_3S$	28	EA
7f	137.5–139	$C_{19}H_{30}N_4$·$C_4H_4O_4$	72	*i*-PrOH–ether
8a	210–230[d]	$C_{12}H_{15}N_3$·HCl·$^1/_4H_2O$	57	EtOH–EA
8b	237–252[d]	$C_{13}H_{17}N_3$·HCl	19	EtOH–ether
8c	>300	$C_{13}H_{13}N_3$·HCl	86	EtOH–ether
8d	145–147	$C_{13}H_{17}N_3$·$C_4H_4O_4$	*e*	EtOH–ether
8e	142–144	$C_{14}H_{19}N_3$·$C_4H_4O_4$	*e*	EA
9	137.5–140.5	$C_{11}H_{15}N_3$·$C_4H_4O_4$	ref 22	*i*-PrOH–Et_2O
10	160–162	$C_{11}H_{13}N_3$·$C_4H_4O_4$	ref 23	EtOH–Et_2O

[a] See Tables III and V for structures. [b] Carbon, hydrogen, and nitrogen analysis were within ±0.4% of the theoretical values. Maleate = $C_4H_4O_4$ and *p*-toluenesulfonate = $C_7H_8O_3S$. [c] The yields listed are for the preparation of the imidazoline from the corresponding ethyl ester by method A. [d] Decomposition point. [e] See the Experimental Section.

Results and Discussion

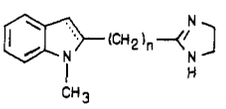
The affinity of the imidazolines for the α_2 receptor was determined by their ability to displace [^3H]clonidine from homogenized rat cortical membranes. The rat vas deferens possesses presynaptic α_2 receptors; α_2 agonists inhibit the electrically stimulated release of norepinephrine in the rat vas deferens in a dose-related manner. Thus, IC_{50} values to inhibit twitch contractions of the rat vas deferens were determined for α_2 agonists. An α_2 antagonist produces rightward parallel shifts in the concentration–effect curve for the α_2 agonist clonidine, allowing pA_2 values to be determined for α_2 antagonists. In the mouse, clonidine is antinociceptive as measured by protection from phenyl-*p*-quinone (PPQ) induced writhing. In a dose-related manner, α_2 antagonists block the antinociceptive effect of clonidine (0.2 mg/kg, sc).

α_2-Adrenergic Antagonist Structure–Activity Relationships (SAR). The indol-2-yl imidazoline **2** was prepared and shown to be an antagonist in vitro, but the compound had poor oral activity. We chose to examine which ring system and what degree of saturation of that ring system (Table III) would lead to optimum α_2-antagonist activity. A comparison of the activities of the imidazolines **1–3**, **4b**, and **8b** show that direct attachment of the imidazoline to the 2-position of an indoline as in **4b** was optimum. The indoline **4b** is a mixed α_2 agonist/antagonist at the same concentrations (see Table V), and the compound exhibited good oral activity as an α_2 antagonist. The quinoline **8b** was less potent as an antagonist than **4b**, while the indole **1** and indoline **3** were weakly active at best. The ring-opened analogue **9** bound well to the α_2 receptor; however, it exhibited an α_1-agonist-like response in the vas deferens, preventing the assessment of its α_2 properties. The indoline isomer **10** was inactive.

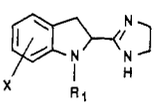
The synthesis of additional analogues resulted in the separation of the α_2 agonist and antagonist properties of the indoline **4b**. Increasing the size of the *N*-alkyl group (R^1) of **4** lead to an increase in α_2-antagonist potency and the loss of the α_2 agonism. The activity peaked where R^1 = allyl for indoline **4d**. Further increasing the size of R^1 resulted in attenuated antagonist potency for analogues **4e–j**. The *N*-phenylindoline **4h**, while displaying oral α_2-antagonist activity, was an α_1 agonist in vitro.

(17) Kocian, O.; Ferles, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1413.
(18) Danishefsky, S.; Bryson, T. A.; Puthenpurayil, J. *J. Org. Chem.* **1975**, *40*, 796.

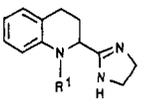
Table III. α_2-Adrenergic Antagonist Activity



1, 2, 3

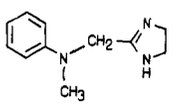


4, 5

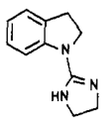


8a $R^1 = H$

8b $R^1 = CH_3$



9



10

compd	substitution[a]	[^{3}H]clonidine binding:[b] K_i, nM[c]	rat vas deferens vs. clonidine: $pA_2 \pm$ SEM	antagonism of clonidine-induced antinociception:[d] ED_{50}, mg/kg po[c]
1	n = 0; 2,3-dehydro	>1000	>6	
2	n = 1; 2,3-dehydro	46.7 (34.5–62.5)	7.48 ± 0.20	100[e]
3	n = 1; 2,3-dihydro	355 (322–391)	<6	
4a	$R^1 = H$	2.11 (1.94–2.28)	8.16 ± 0.04	1.8 (0.69–4.5)
4b	$R^1 = CH_3$	0.45 (0.27–0.75)	8.65[f]	1.3 (0.8–1.9)
4c	$R^1 = CH_2CH_3$	0.91 (0.49–1.62)	8.91 ± 0.06	2.6 (1.5–4.9)
4d	$R^1 = CH_2CH{=}CH_2$	0.47 (0.44–0.51)	9.07 ± 0.06	2.6 (1.6–4.2)
4e	$R^1 = CH_2CH_2CH_3$	1.93 (1.62–2.31)	8.76 ± 0.06	100[g]
4f	$R^1 = CH_2CH_2CH_2CH_3$	3.5 (2.9–4.3)	8.80 ± 0.04	4[h]
4g	$R^1 = CH_2CH_2OCH_2CH_3$	26.0 (21.8–31.1)	7.81 ± 0.13	20.5 (15.3–24.7)
4h	R^1 = Ph	4.2 (3.4–5.0)	*i*	19.8 (11.6–33.7)
4i	$R^1 = CH_2Ph$	2.3 (1.7–3.0)	7.93 ± 0.09	7.0 (5.3–9.6)
4j	$R^1 = CH_2CH_2Ph$	6.0 (5.2–7.0)	*j*	6[h]
5a	X = 5-F	0.91 (0.52–1.58)	8.45 ± 0.01	0.75 (0.57–1.1)
5b	X = 5-Cl	1.9 (1.6–2.3)	8.56 ± 0.08	1.5 (0.96–2.8)
5c	X = 7-Cl	0.72 (0.62–1.02)	8.80 ± 0.17	0.1[h]
5d	X = 5, 7-Cl_2	12.3 (11.1–13.7)	8.00 ± 0.19	60.1 (9.7–373)
5e	X = 5-CH_2Ph	53.6 (50.2–57.3)	7.59 ± 0.15	>100
8a		13.8 (11.2–16.9)	8.03 ± 0.15	3.8 (3.1–5.0)
8b		1.52 (0.92–1.69)	8.13 ± 0.14[k]	2.6 (1.2–4.6)
9		3.9 (3.2–4.3)	*l*	
10		>1000		
idazoxan		10 (8.5–11.5)	8.11 ± 0.05	1.6 (0.55–4.6)
yohimbine		84 (52–135)	7.91 ± 0.06	0.6 (0.50–0.79)

[a] Unless otherwise indicated $R^1 = CH_3$ and X = H. [b] In cortical membrane from rat brain. [c] 95% confidence limits are in parentheses. [d] In the mouse, n = 10. [e] Approximate ED_{50} (data insufficient for probit analysis). [f] Estimated value. The pA_2 determination was complicated by the agonist component of activity. [g] Approximate ED_{50}, ED_{50} = 0.14 mg/kg sc (0.08–0.23). [h] Approximate ED_{50} (steep dose–response curve). [i] The compound contracted the tissue at 100 nM. Prazosin reversed this response, suggesting α_1-agonist activity. [j] Non-α_2-mediated reductions of twitch height prevented the calculation of a pA_2. [k] This compound produced a 60% reduction in twitch height at 100 nM, an α_2-agonist-like response. [l] This compound contracted the tissue at 100 nM, which is an α_1-agonist-like response.

Table IV. α-Adrenergic Receptor Selectivity

compd	[^{3}H]clonidine binding: K_i, nM[a]	[^{3}H]prazosin binding: K_i, nM[a]	binding selectivity:[b] α_2/α_1	rat vas deferens vs. clonidine α_2 antagonism: $pA_2 \pm$ SEM	rat vas deferens vs. methoxamine α_1 antagonism: $pA_2 \pm$ SEM	antagonism selectivity:[c] α_2/α_1
4b	0.45 (0.27–0.75)	10.5 (4.6–30.6)	23	8.65[d]	7.75 ± 0.07	8
4d	0.47 (0.44–0.51)	6.56 (6.06–7.06)	14	9.07 ± 0.06	8.02 ± 0.18	11
5a	0.91 (0.52–1.58)	16.4 (7.8–34.6)	18	8.45 ± 0.01	8.03 ± 0.2	3
idazoxan	10 (8.5–11.5)	332 (221–499)	33	8.11 ± 0.05	6.42 ± 0.07	49
yohimbine	84 (52–135)	190 (158–228)	2	7.91 ± 0.06	6.91 ± 0.18	10
prazosin	>1000	0.4 (0.035–0.06)	<0.00004	6.14 ± 0.10	8.96 ± 0.10	0.001

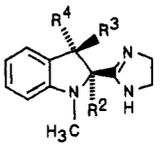
[a] 95% confidence limits are in parentheses. [b] Ratio of K_i ([^{3}H]prazosin)/K_i([^{3}H]clonidine). [c] antilog of the pA_2 vs. clonidine minus the pA_2 vs. methoxamine. [d] Estimated value. The pA_2 determination was complicated by the agonist component of activity.

Substitution on the phenyl of the indoline **4b** also resulted in the loss of α_2-agonist activity. The analogues **5a–c** were potent α_2 antagonists without α_2-agonist activity. Increasing substitution or the size of the substituent on the phenyl as in **5d** and **5e** resulted in decreased receptor affinity and in the decrease of in vitro and in vivo antagonist activity.

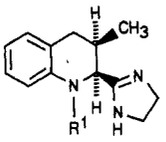
A group of the more potent indoline α_2 antagonists were examined for α-adrenergic receptor selectivity (Table IV). The indolines **4b**, **4d**, and **5a** were all more selective for α_2-receptor effects vs. α_1-receptor effects. The α_2 antagonist **4d** displayed similar α-receptor selectivity as the mixed α_2 agonist/antagonist **4b** and **4d** was 3–4 times more selective than **5a** as an antagonist; however, idazoxan is 2–4 times more α-receptor selective than **4d**.

α_2-Adrenergic Agonist SAR. The disubstituted indoline analogues **6a** and **6b** of the mixed α_2 agonist/antagonist **4b** have interesting properties (see Table V). The

Table V. α_2-Adrenergic Agonist/Antagonist Activity



6, 7



8d $R^1 = H$
8e $R^1 = CH_3$

compd	R^2	R^3	R^4	[^{3}H]clonidine binding:[a] K_i, nM[b]	rat vas deferens $pA_2 \pm$ SEM	rat vas deferens $IC_{50} \pm$ SEM,[c] nM	antagonism of clonidine-induced antinociception:[d] ED_{50}, mg/kg po[b]
4b				0.45 (0.27–0.75)	8.65[e]	4.02 ± 0.89	1.3 (0.8–1.9)
6a	H	CH_3	H	6.9 (6.5–7.3)	<6	3.29 ± 1.22	>300
6b	H	H	CH_3	72.3 (63.8–82.7)	6.96 ± 0.09	>1000	41 (9.5–175)
8d				>1000	<6	>1000	
8e				719 (566–913)	5.88 ± 0.09		
7a	CH_3	H	H	3.4 (2.6–4.4)	7.55 ± 0.12	>300	8.8 (7.3–11)
7b	$CH_2CH{=}CH_2$	H	H	77 (31–193)	6.96 ± 0.06	>1000	11.1 (8.9–14.0)
7c	$CH_2CH_2CH_3$	H	H	260 (223–302)	6.60 ± 0.09	>1000	
7d	CH_2OCH_3	H	H	38 (34–42)		131[f] ± 69	
7e	CH_2SCH_3	H	H	13.2 (11.7–15.0)		179 ± 96.7	
7f	$CH_2N(i\text{-}Pr)_2$	H	H	25.1 (20.6–30.4)		94.8 ± 55.4	
clonidine				1.8 (1.3–2.1)		3.90 ± 0.56	
idazoxan				10 (8.5–11.5)	8.11 ± 0.05		
yohimbine				84 (52–135)	7.91 ± 0.06		

[a] In cortical membrane from rat brain. [b] 95% confidence limits are in parentheses. [c] IC_{50} values are for inhibition of electrically stimulated twitch contractions of the rat vas deferens that are yohimbine reversible. [d] In the mouse, $n = 10$. [e] Estimated value. The pA_2 determination was complicated by the agonist component of activity. [f] Not yohimbine reversible.

cis-indoline **6a** is equipotent to clonidine in vitro as an α_2 agonist and is inactive as an antagonist in vitro, while the *trans*-indoline **6b** is an α_2 antagonist although much less active than **4b**. However, the *cis*-tetrahydroquinoline **8e** was weakly active as an α_2 antagonist.

The ortho disubstitution of clonidine is thought to restrict the imidazoline in a position nearly orthogonal to the 2,6-dichlorophenyl ring. This conformation is held to be responsible for the α_2-adrenergic agonist properties of clonidine.[19] Since **6a** is a potent α_2 agonist, the compound must reside in a conformation very similar to the α_2-agonist conformation proposed for clonidine. Indeed, on examining models, the imidazoline of the *cis*-indoline **6a** has restricted rotational freedom as a result of the steric crowding by the 3-methyl substituent. The imidazoline of the *trans*-indoline **6b** is much less sterically restricted than **6a**. The *cis*-quinoline derivative **8e** also possesses more degrees of conformational freedom relative to the *cis*-indoline **6a**. Presumably **6b** and **8e** are not restricted to the agonist conformation, and the 3-methyl substituent of **6b** and **8e** produces an unfavorable steric interaction at the receptor site, greatly reducing receptor affinity and antagonist activity.

Increasing the size of the C-2 substituent on the indoline **4b** gave selective antagonists as in **7a–c**; however, potency decreased as the substituent size increased. The presence of a heteroatom in the side chains of **7d–f** affected a change in the SAR. Although CH_2OCH_3 and CH_2SCH_3 are of similar size to *n*-Pr, the analogues **7d** and **7e** had a higher receptor affinity than **7c**. Perhaps the receptor affinity of **7d** and **7e** is increased relative to **7c** due to the formation of a hydrogen bond between the heteroatoms in the side chains and an additional binding site at the α_2 receptor. The compound **7d** inhibited the twitch contractions in the rat vas deferens; however, this effect was not α_2 agonist mediated since it was not antagonized by yohimbine. The compounds **7e** and **7f** were α_2 agonists although less potent than the *cis*-indoline **6a**.

Summary. The partial α_2-agonist effects of the α_2 antagonist idazoxan have been described at peripheral and central sites.[20,21] Although idazoxan did not display partial agonist activity in our test systems, the partial agonist effects of our initial lead compound **4b** were noted at the same concentrations in the rat vas deferens that caused antagonism of clonidine. In this SAR study the structural modification of **4b** has resulted in the separation of the α_2-agonist and α_2-antagonist components of activity. The *cis*-1,3-dimethylindoline **6a** was equipotent to clonidine as an α_2 agonist in vitro and was inactive as an α_2 antagonist. A series of selective α_2 antagonists have been identified, which include the indolines **4c**, **4d**, **4f**, and **5a–c**, which are 2–9 times more potent as antagonists in vitro than idazoxan and which are orally equipotent to idazoxan in the mouse. Of these α_2 antagonists, the indoline **4d** had the best potentcy in both in vitro test systems. The indoline **4d** was less receptor selective than idazoxan; however, **4d** was 10–20 times more potent in vitro.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 spectrophotometer or on a Nicolet 10DX FTIR. ^{1}H NMR spectra were determined in the indicated solvent on a Perkin-Elmer R24B, an IBM NR/200 FTNMR, or a JEOL-FX270 instrument. Mass spectra were recorded on a JEOLCO JMS-1-OCS instrument for electron impact (EI) or on a Hewlett-Packard 5980A GS/MS/DS instrument for chemical ionization (CI). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and carbon, hydrogen, and nitrogen analyses were within ±0.4% of the theoretical values. Preparative HPLC's were performed on a Waters Prep LC/System 500A.

(19) Stahle, H. In *Chronicles of Drug Discovery*; Wiley-Interscience: New York, 1982; Vol. 1, Chapter 4, p 87.

(20) Limberger, N.; Starke, K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1983**, *324*, 75.

(21) Goldstein, J. M.; Knobloch, L. C.; Malick, J. B. *Eur. J. Pharmacol.* **1983**, *91*, 101.

Methyl 1-Methyl-1*H*-indole-2-acetate (13). To a mechanically stirred solution of 25.0 g (190 mmol) of 1-methylindole in 750 mL of tetrahydrofuran at −20 °C and under nitrogen was added dropwise 115 mL (240 mmol) of a 2.1 M solution of *n*-butyllithium in hexanes. After completion of the addition, the reaction mixture was allowed to come to room temperature and stirred for 3.5 h. The reaction mixture was cooled to −78 °C and a solution of 28.3 g (240 mmol) of dimethyl oxalate in 250 mL of tetrahydrofuran was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 1 h. A 10% aqueous acetic acid solution (200 mL) was added and the reaction mixture was concentrated. The residue was diluted with water and extracted twice with ether. The combined organic layers were washed successively with saturated sodium bicarbonate, water, and then saturated sodium chloride. After drying over magnesium sulfate, filtration, and concentration, 19.3 g (47%) of the glyoxalate **11**[6] was obtained as a red oil and was used without purification: NMR ($CDCl_3$) δ 3.92 (s) and 4.00 (s) (6 H), 6.9–7.8 (cm, 5 H).

A solution of 31.5 g (145 mmol) of crude glyoxalate **11** in 250 mL of acetic acid was hydrogenated over 0.5 g of platinum oxide at 50 psi of hydrogen and at room temperature for 2 h. After filtration and concentration, the intermediate alcohol **12a** was dissolved in 110 mL of pyridine and 30 mL of acetic anhydride was added. The reaction mixture was stirred at room temperature overnight and then concentrated. The residue was diluted with ether and washed successively with cold dilute hydrochloric acid, water, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 37.8 g of the crude acetate **12b** as a brown oil. The acetate **12b** was hydrogenated at 50 psi in 250 mL of 10% triethylamine in ethanol over 2 g of 10% palladium on carbon for 14 h at room temperature. The reaction mixture was filtered through filter aid and concentrated. The residue was diluted with ether and the solution was washed successively with water, dilute hydrochloric acid, water, dilute sodium carbonate, water, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated to give 25.9 g of a brown oil. Preparative HPLC of the crude ester on silica gel eluted with 10% ethyl acetate in hexane gave 20.0 g (68%) of the ester **13** as a light yellow oil: MS (EI), *m/e* 203 (M^+); NMR ($CDCl_3$) δ 3.52 (s), 3.59 (s), and 3.68 (s) (8 H), 6.26 (s, 1 H), 6.8–7.2 (cm, 3 H), 7.45 (m, 1 H). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

General Procedure for the Preparation of Imidazolines. Method A. 2-[(4,5-Dihydro-1*H*-imidazol-2-yl)methyl]-1-methyl-1*H*-indole (2). To a mechanically stirred solution of 21 mL (42 mmol) of 2 M trimethylaluminum in toluene diluted with 35 mL of toluene at 0 °C and under nitrogen was added dropwise a solution of 2.8 mL (42 mmol) of ethylenediamine in 15 mL of toluene. After being stirred at room temperature for 1 h, the solution was recooled to 0 °C and a solution of 4.3 g (21 mmol) of the methyl ester **13** in 25 mL of toluene was added dropwise. The reaction mixture was refluxed for 45 min, cooled to 0 °C, and quenched cautiously with 10 mL of methanol followed by 2 mL of water. After addition of 80 mL of chloroform, the mixture was refluxed for 1 h on a steam bath to ensure the precipitation of the aluminum salts. The mixture was dried with magnesium sulfate, filtered, diluted with chloroform, and washed twice with water. The extract was dried with magnesium sulfate, filtered, and concentrated to give 5.0 g of a yellow solid, which was recrystallized from ethyl acetate–cyclohexane to give 2.7 g (60%) of the imidazoline **2** as yellow crystals: IR (KBr) 1603 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (s), 3.69 (s), and 3.78 (s) (9 H), 6.32 (s, 1 H), 7.16 (m, 3 H), 7.50 (m, 1 H). Anal. ($C_{13}H_{15}N_3$) C, H, N.

2-[(4,5-Dihydro-1*H*-imidazol-2-yl)methyl]-2,3-dihydro-1-methyl-1*H*-indole Hydrochloride (3). To an ice bath cooled solution of 5.7 g (28 mmol) of the ester **13** in 140 mL of acetic acid was added over 10 min in several portions 8.8 g (140 mmol) of sodium cyanoborohydride. The reaction mixture was stirred for 4.5 h at room temperature and then diluted with ice water and poured onto 300 mL of 35% sodium hydroxide. The mixture was extracted twice with ether, and the combined extracts were washed twice with water. The product was extracted from the organics into ice-cold 12 N hydrochloric acid, then freed with 35% sodium hydroxide, and extracted into ether. The organic layer was washed with water and then with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give 1.3 g (23%) of the indoline ester **14**[24] as a yellow oil: NMR ($CDCl_3$) δ 2.2–4.0 (cm), 2.66 (s), and 3.60 (s) (11 H), 6.2–7.2 (cm, 4 H).

The crude ester **14** was converted without purification following the general trimethylaluminum procedure (method A) to give 0.95 g (59%) of the imidazoline hydrochloride **3** as tan crystals from ethanol: IR (KBr) 1605 cm^{-1}; NMR (Me_2SO-d_6) δ 2.71 (m) and 2.73 (s) (5 H), 3.08 (m, 2 H), 3.49 (s, HOD), 3.75 (m) and 3.83 (s) (5 H), 6.52 (d) and 6.63 (t) (2 H), 7.04 (m, 2 H), 10.40 (br s, 2 H). Anal. ($C_{13}H_{17}N_3 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3-dihydro-1-methyl-5-(phenylmethyl)-1*H*-indole (*Z*)-2-Butenedioate (5e). To a stirred suspension of 13.1 g (98 mmol) of aluminum chloride in 75 mL of ethylene dichloride under nitrogen and at room temperature was added dropwise a solution of 6.5 mL (56 mmol) of benzoyl chloride in 35 mL of ethylene dichloride. After 30 min a solution of 10.0 g (49 mmol) of **17a** in 35 mL of ethylene dichloride was added and the reaction mixture was heated on a steam bath for 6 h. The reaction mixture was poured onto ice water and extracted twice with ethyl acetate. The combined extracts were washed successively with water, dilute sodium chloride, and saturated sodium chloride, dried over magnesium sulfate, and concentrated to give 15.4 g of a brown oil. Preparative HPLC of the crude product on silica gel eluted with 15% ethyl acetate in hexane gave 6.7 g (44%) of **18** as a yellow oil: NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H), 2.87 (s, 3 H), 3.21 (m, 2 H), 4.1 (m) and 4.14 (q, J = 7 Hz) (3 H), 6.26 (d, J = 8 Hz, 1 H), 7.45 (cm, 7 H).

A mixture of 5.7 g (18 mmol) of **19**, 0.5 g of 10% palladium on carbon, and 200 mL of absolute ethanol was hydrogenated at 50 psi of hydrogen at room temperature for 3 days. After filtration through a pad of filter aid and concentration, a yellow oil was obtained. Preparative HPLC of the crude product on silica gel eluted with 10% ethyl acetate in hexane gave 2.8 g (53%) of **19** as a colorless oil: IR (film) 1745, 1617 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 2.74 (s, 3 H), 3.09 (m, 2 H), 3.77 (s), 3.95 (m), and 4.13 (q, J = 7 Hz) (5 H), 6.28 (d, J = 8 Hz, 1 H), 6.6–7.4 (m, 7 H); MS (EI), *m/e* 295 (M^+), 222 (M^+ − COOEt).

Via the general trimethylaluminum procedure (method A), 2.5 g (8.5 mmol) of the ester **19** gave 2.4 g (69%) of the imidazoline maleate **5e** as tan crystals from ethanol–ether: IR (KBr) 1615, 1585, 1470 cm^{-1}; NMR (Me_2SO-d_6) δ 2.71 (s, 3 H), 2.96 (dd, J = 11 and 16 Hz, 1 H), 3.38 (dd, J = 11 and 16 Hz, 1 H), 3.82 (s) and 3.88 (s) (6 H), 4.30 (apparent t, J = 11 Hz, 1 H), 6.00 (s, 2 H), 6.57 (d, J = 9 Hz, 1 H), 7.46 (m, 2 H), 7.70 (m, 5 H), 10.10 (br s, 2 H). Anal. ($C_{19}H_{21}N_3 \cdot C_4H_4O_4$) C, H, N.

***cis*- and *trans*-2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3-dihydro-1,3-dimethyl-1*H*-indole 4-Methylbenzenesulfonate (6a and 6b): 6a:** NMR ($CDCl_3$) δ 0.92 (d, J = 7.2 Hz, 3 H), 2.26 (s, 3 H), 2.57 (s, 3 H), 3.60 (m) and 3.77 (s) (5 H), 4.29 (d, J = 9.3 Hz, 1 H), 6.43 (d, J = 7.8 Hz, 1 H), 6.76 (d, J = 7.4 Hz), 6.94 (m), and 7.08 (t, J = 7.5 Hz) (5 H), 7.57 (d, J = 8.2 Hz, 2 H), 9.97 (s, 2 H). Anal. ($C_{13}H_{17}N_3 \cdot C_7H_8O_3S$) C, H, N. **6b:** NMR ($CDCl_3$) δ 1.31 (d, J = 6.8 Hz, 3 H), 2.28 (s, 3 H), 2.57 (s, 3 H), 3.13 (m, 1 H), 3.73 (s) and 3.83 (d, J = 10.2 Hz) (5 H), 6.42 (d, J = 7.8 Hz, 1 H), 6.76 (t, J = 7.3 Hz) and 6.98 (cm) (5 H), 7.53 (d, J = 7.9 Hz, 2 H), 10.01 (s, 2 H). Anal. ($C_{13}H_{17}N_3 \cdot C_7H_8O_3S$) C, H, N.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,3-dihydro-1-methyl-2-propyl-1*H*-indole Hydrochloride (7c). A mixture of 6.0 g (22 mmol) of **7b**, 0.5 g of 10% palladium on carbon, and 300 mL of absolute ethanol was hydrogenated at 50 psi of hydrogen at room temperature for 2 h. After filtration through a pad of filter aid, concentration, and recrystallization from ethanol–ethyl acetate, light bluish crystals of **7c** were obtained, 4.7 g (76%): IR (KBr) 1600, 1495 cm^{-1}; NMR (Me_2SO-d_6) δ 0.85 (m) and 1.16 (m) (5 H), 1.91 (m, 2 H), 2.75 (s, 3 H), 3.36 (s, HOD), 3.86 (s, 4 H), 6.43 (d, J = 7.8 Hz, 1 H), 6.61 (t, J = 7.3 Hz, 1 H), 7.03 (m, 2 H), 9.89 (br s, 2 H). Anal. ($C_{15}H_{21}N_3 \cdot HCl$) C, H, N.

***cis*-2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1,2,3,4-tetrahydro-3-methylquinoline (*Z*)-2-Butenedioate (8d).** A mixture of 8.5

(22) Urech, E.; Marxer, A.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 1386.
(23) Wu, Y-H.; Lobeck, W. G., Jr.; Kissel, J. W. *J. Med. Chem.* **1970**, *13*, 975.
(24) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

g (34 mmol) of **8c**, 0.60 g of platinum oxide, and 2 mL of concentrated hydrochloric acid in 300 mL of 66% aqueous ethanol was hydrogenated at 50 psi of hydrogen at room temperature for 3 h. After filtration through a pad of filter aid and concentration of the filtrate, the residue was diluted with ice-cold 5% sodium hydroxide and extracted with chloroform (3×). The combined extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated to a yellow oil. Chromatography of the crude product on a silica gel column ($2^1/_2$ in. × 15 in.) with gradient elution from 1% triethylamine and 4% methanol in ethyl acetate up to 5% triethylamine and 50% methanol in ethyl acetate gave 2.0 g (27%) of free base **8d** as a yellow oil. The maleate salt was prepared with 1.0 g of maleic acid in ethanol–ether to give 1.3 g (12%) of **8d** as light yellow crystals: NMR (Me_2SO-d_6) δ 0.93 (d, J = 6.7 Hz, 3 H), 2.32 (cm, 2 H), 2.92 (dd, J = 4.1 and 16 Hz, 1 H), 3.34 (br s, HOD), 3.87 (s, 4 H), 4.41 (br s, 1 H), 6.02 (s, 2 H), 6.60 (m, 2 H), 6.95 (m, 2 H), 9.91 (br s, 2 H); MS (CI), 216 (MH^+). Anal. ($C_{13}H_{17}N_3 \cdot C_4H_4O_4$) C, H, N.

1,1-Dimethylethyl *cis*-4,5-Dihydro-2-(1,2,3,4-tetrahydro-3-methyl-2-quinolinyl)-1*H*-imidazole-1-carboxylate (21). A mixture of 16.4 g (66 mmol) of **8c** and 0.6 g of platinum oxide in 300 mL of 50% aqueous ethanol was hydrogenated at 50 psi of hydrogen at room temperature for 6.5 h. After filtration through a pad of filter aid and concentration of the filtrate, the light yellow paste residue (crude **8d**) was dissolved in 200 mL of dioxane–water (1:1) and cooled to 0 °C. To the stirred solution was added 12 mL (86 mmol) of triethylamine, followed by the dropwise addition of a solution of 17.3 g (79 mmol) of di-*tert*-butyl dicarbonate in 80 mL of dioxane. The mixture was stirred at room temperature for 2.5 h and then was diluted with water and extracted twice with ethyl acetate. The combined extracts were washed with water (3×) and then with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give 21.4 g of a pale yellow oil. Preparative HPLC of the crude product eluted with 25% ethyl acetate in hexane gave 9.1 g (44% from **8c**) of a white foam. Crystallization from hexane gave 6.54 g (31% from **8c**) of **21** as white crystals: mp 138–139 °C; IR (KBr) 1700, 1630, 1600, 1370 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (d, J = 6.6 Hz, 3 H), 1.52 (s, 9 H), 2.54 (m) and 2.61 (m) (2 H), 3.21 (dd, J = 5.5 and 16 Hz, 1 H), 3.84 (cm, 4 H), 4.64 (br s, 1 H), 4.79 (br s, 1 H), 6.62 (m, 2 H), 6.98 (m, 2 H). Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

1,1-Dimethylethyl *cis*-4,5-Dihydro-2-(1,2,3,4-tetrahydro-1,3-dimethyl-2-quinolinyl)-1*H*-imidazole-1-carboxylate (22). To a stirred mixture of 4.72 g (15 mmol) of **21**, 1.51 g (24 mmol) of sodium cyanoborohydride, and 6 mL of 37% formaldehyde in 100 mL of acetonitrile at room temperature was added 1.2 mL of acetic acid. After 2.5 h, an additional 0.6 mL of acetic acid was added and stirring was continued for 30 min. The mixture was diluted with ethyl acetate and washed with dilute sodium chloride and then saturated sodium chloride. The organic layer was dried with magnesium sulfate and concentrated to 5.37 g of a yellow solid. Preparative HPLC of the crude product eluted with 20% ethyl acetate in hexane gave 3.83 g (77%) of **22** as white crystals: mp 123.5–128.5 °C; IR (KBr) 1712 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3 H), 1.53 (s, 9 H), 2.36 (cm), 2.58 (dd, J = 4.3 and 15.6 Hz), 2.78 (dd, J = 11.8 and 15.6 Hz), and 2.91 (s) (6 H), 3.72 (cm, 4 H), 5.44 (d, J = 5.2 Hz, 1 H), 6.58 (m, 2 H), 6.92 (apparent d, 1 H), 7.06 (apparent triplet, 1 H). Anal. ($C_{19}H_{27}N_3O_2$) C, H, N.

***cis*-2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1,2,3,4-tetrahydro-1,3-dimethylquinoline (*Z*)-2-Butenedioate (8e).** A solution of 2.94 g (8.9 mmol) of **22** in 50 mL of 5.44 N ethanolic hydrogen chloride was refluxed for 2 h, cooled, and concentrated. The residue was dissolved in water, poured into ice-cold 5% sodium hydroxide, and extracted with chloroform (3×). The combined extracts were washed once with water, dried over magnesium sulfate, filtered, and concentrated to 2.45 g of a tan oil. The residue was dissolved in 150 mL of warm ethyl acetate and treated with 1.24 g of maleic acid to give on cooling 2.58 g (84%) of **8e** as greenish needles: NMR ($CDCl_3$) δ 1.13 (d, J = 6.4 Hz, 3 H), 2.46 (m, 2 H), 2.81 (m) and 2.97 (s) (4 H), 4.00 (s, 4 H), 4.65 (d, J = 4.7 Hz, 1 H), 6.07 (s, 2 H), 6.68 (m, 2 H), 6.96 (d, J = 6.6 Hz, 1 H), 7.11 (t, J = 7.6 Hz, 1 H), 10.26 (vbs, 1 H). Anal. ($C_{14}H_{19}N_3 \cdot C_4H_4O_4$) C, H, N.

Preparation of Indoline-2-carboxylates 17 and 20. The indolines **17** and **20** were prepared by the methods given below for **17a** and **20a**. All compounds were TLC homogeneous oils and were converted by method A to the corresponding imidazolines listed in Table I.

Ethyl 2,3-Dihydro-1-methyl-1*H*-indole-2-carboxylate (17a). To 26.3 g (130 mmol) of ethyl 1-methyl-1*H*-indole-2-carboxylate[10] was added 130 mL of ice-cold trifluoroacetic acid followed by dropwise addition of 41 mL (260 mmol) of triethylsilane. The mixture was refluxed on a steam bath for 2 h, cooled, poured onto a mixture of ice and 250 mL of 35% sodium hydroxide, and extracted twice with ether. The product was extracted from the organics into ice-cooled 12 N hydrochloric acid, then freed with 35% sodium hydroxide, and extracted into ether. The organic layer was washed with water and then with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give 17.9 g (67%) of **17a** as a pale yellow oil. An analytical sample was obtained by vacuum distillation to give a colorless oil: bp 94–96 °C (0.03 mmHg); IR (film) 1745, 1609, 1488 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3 H), 2.84 (s, 3 H), 3.12 (dd, J = 9.8 and 16 Hz, 1 H), 3.34 (dd, J = 9.8 and 16 Hz, 1 H), 4.05 (apparent t, J = 9.8 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 6.50 (d, J = 7.8 Hz, 1 H), 6.70 (t, J = 7.3 Hz, 1 H) 7.08 (m, 2 H); MS (CI), 206 (MH^+). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

Ethyl 2,3-Dihydro-1-methyl-2-(2-propenyl)-1*H*-indole-2-carboxylate (20a). To a solution of 9.0 mL (64 mmol) of diisopropylamine in 250 mL of tetrahydrofuran at −78 °C and under nitrogen was added dropwise 28 mL (59 mmol) of a 2.1 M solution of *n*-butyllithium in hexanes and stirring continued for 45 min. A solution of 10.8 g (53 mmol) of **17a** in 50 mL of tetrahydrofuran was added dropwise. After 30 min at −78 °C, 5.5 mL (64 mmol) of allyl bromide in 30 mL of tetrahydrofuran was added dropwise and stirring continued for 1.5 h. The reaction mixture was quenched with 70 mL of saturated ammonium chloride, diluted with water, and extracted with ether. The organic layer was washed twice with water and then with saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give 13.7 g of a yellow oil. Preparative HPLC of the crude product on silica gel eluted with 3% ethyl acetate in hexane gave 11.8 (91%) of **20a** as a yellow oil: IR (film) 1730, 1610, 1490 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 2.68 (m) and 2.84 (s) (5 H), 3.12 (d, J = 16 Hz, 1 H), 3.39 (d, J = 16 Hz, 1 H), 4.15 (q, J = 8 Hz, 2 H), 5.12 (m, 2 H), 5.5–5.9 (cm, 1 H), 6.29 (d, J = 7 Hz, 1 H), 6.58 (t, J = 7 Hz, 1 H), 6.96 (m, 2 H); MS (EI), m/e 245 (M^+). Anal. ($C_{15}H_{19}NO_2$) C, H, N.

Preparation of N-Substituted Indole-2-carboxylates 16. Method B. Ethyl 1-Propyl-1*H*-indole-2-carboxylate (16c). To a stirred suspension of 4.2 g (88 mmol) of 50% sodium hydride in mineral oil (pentane prewashed) in 50 mL of *N*,*N*-dimethylformamide at 0 °C and under nitrogen was added dropwise a solution of 15.0 g (79 mmol) of ethyl indole-2-carboxylate in 175 mL of *N*,*N*-dimethylformamide. After being stirred at room temperature for 20 min, a solution of 10.7 mL (110 mmol) of 1-iodopropane in 25 mL of *N*,*N*-dimethylformamide was added. The mixture was heated on a steam bath for 1 h, cooled, poured onto ice water, and extracted with ether. The extracts were washed with water (5×) and then saturated sodium chloride, dried with magnesium sulfate, filtered through a pad of magnesium silicate, and concentrated to give 19.0 g of **16c** as a light yellow oil: NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz), 1.30 (t, J = 7 Hz) and 1.75 (sextet) (8 H), 4.26 (m, 4 H), 6.7–7.3 (cm, 4 H), 7.50 (m, 1 H).

An analytical sample was obtained by molecular distillation at 70 °C (0.05 mmHg). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

Method C. Ethyl 1-(Phenylmethyl)-1*H*-indole-2-carboxylate (16f). A mixture of 20.0 g (106 mmol) of ethyl indole-2-carboxylate, 44 g (320 mmol) of milled anhydrous potassium carbonate, and 37 mL (320 mmol) of benzyl chloride in 200 mL of *N*,*N*-dimethylformamide was heated on a steam bath for 1.5 h. On cooling the reaction mixture was poured into ice water and extracted with ether. The extract was washed with water (6×) and then saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give a yellow oil. Trituration with 500 mL of pentane and cooling in ice gave 22.9 g (77%) of **16f** as white needles: IR (KBr) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, J = 8 Hz, 3 H), 4.31 (q, J = 8 Hz, 2 H), 5.82 (s, 2 H), 6.9–7.4 (cm, 9 H), 7.66 (m, 1 H); MS (EI), m/e 279 (M^+). Anal. ($C_{18}H_{17}NO_2$) C, H, N.

α_2-Adrenergic Receptor Binding Affinity. Affinity for α_2-adrenergic receptors in brain was assessed by measuring the ability of test compounds to displace [^{3}H]clonidine from its receptors. In this assay, the cerebral cortex of rat brain was homogenized in 20 volumes of Tris buffer (50 mM, pH 7.7) with a 10-s burst from a Brinkmann PT-10 Polytron homogenizer set at 6. The homogenate was centrifuged at 48000*g* for 10 min. The pellet was then resuspended in fresh buffer and centrifuged as before. The pellet was resuspended in 50 volumes of fresh buffer, and aliquots were incubated (2 mL final volume) with [^{3}H]clonidine (New England Nuclear Co., 20–22 Ci/mmol) at a concentration of 0.4 nM in the presence of various concentrations of test compound. Unlabeled clonidine (1 μM) was added to correct for nonspecific binding in control tubes. The samples were incubated for 30 min at 25 °C and then the membranes were harvested by filtration of the samples through a Millipore sampling manifold. Radioactivity on the filters (GF/B) in the absence and presence of test compound was measured in 10 mL of Biofluor (NEN) by a Packard 460 liquid scintillation spectrometer with 40% efficiency. All assays were performed in triplicate. Data from binding assays were plotted by the logit transformation. The IC_{50} values obtained were used to calculate apparent K_i values by the method of Cheng and Prusoff.[25]

α_1-Adrenergic Receptor Binding Affinity. Affinity for α_1-adrenergic receptors in brain was assessed by measuring the ability of test compounds to displace [^{3}H]prazosin from its receptors. In the assay, the cortex of rat brain was homogenized for 10 s in 20 volumes of Tris buffer (50 mM, pH 7.7) with a Brinkman PT 10 Polytron set at 6. The homogenate was centrifuged at 48000*g* for 10 min. The pellet was resuspended in 10 volumes of fresh buffer and the procedure repeated. The final resuspension was in 150 volumes of buffer. The homogenate was incubated (8 mL final volume) with [^{3}H]prazosin (Amersham, 18-20 Ci/mmol) at a concentration of 0.03 nM in the presence of various concentrations of test compound. Unlabeled phentolamine (10 μM) was added to correct for nonspecific binding in control tubes. The samples were incubated for 90 min at 25 °C. Then the membranes were harvested by filtration of the samples through a Millipore sampling manifold. Radioactivity on the filter (GF/B) in the absence and presence of test compound was measured in 10 mL of Biofluor (NEN) by a Packard 460 liquid scintillation spectrometer with 40% efficiency. All assays were performed in triplicate.

Data from binding assays were plotted by logit transformation. The IC_{50} values obtained were used to calculate apparent K_i values by the method of Cheng and Prusoff.[25]

Rat Vas Deferens Preparation. The isolated rat vas deferens preparation was used to assess α_2-agonist and α_1- and α_2-antagonist activity of compounds according to the method of Drew.[26] Vasa deferentia from Sprague–Dawley rats (180–250 g) were dissected free of connective tissue, mounted in 5- or 10-mL organ baths between platinum ring electrodes at a resting tension of 1 g, and bathed with warm (31 °C for α_1 assay; 37 °C for α_2 assay) oxygenated Krebs solution. For assessment of α_2-agonist or α_2-antagonist activity, preparations were stimulated electrically with single pulses (1-ms duration, 0.15 Hz, at the lowest voltage to produce a maximal contraction).

Methoxamine and clonidine were used as reference α_1 and α_2 agonists; prazosin and yohimbine were used as reference α_1 and α_2 antagonists. Antagonist potency of compounds was determined from Schild analysis of data[27] from experiments in which concentration–effect curves for an agonist were constructed in the absence and in the presence of at least three concentrations of the antagonist; preincubation time with an antagonist was 10 min. Values are the mean of at least three experiments in preparations from separate animals.

Antagonism of Clonidine-Induced Antinociception in the Mouse. The intraperitoneal administration of phenyl-*p*-quinone (PPQ) to mice elicits a nociceptive response that consists of abdominal writhing and extension of the hind limbs. This writhing response is prevented in mice treated with the α_2-adrenergic agonist clonidine. When an α_2-adrenergic antagonist is given prior to clonidine, the mice display the writhing response when PPQ is administered. For each experiment, 10 mice/treatment (18–24 g; Swiss Webster from Taconic Farms) were evaluated in separate compartments of a Plexiglas box. Compounds dissolved in 0.9% NaCl were administered orally via intubation. Clonidine (0.2 mg of base/kg) was administered subcutaneously (behind the neck). Ten minutes after administration of the test compound, clonidine was administered followed 20 min later by intraperitoneal administration of PPQ (3 mg/kg). Beginning 5 min after injection of PPQ, the mice were observed for writhing for a period of 5 min. The number of mice that writhed at least three times during the 5-min observation period was counted. In any single study, 90–100% (generally 100%) of the mice injected with vehicle plus PPQ writhed.

The number of mice that writhed was scored for each dose of the antagonist, and the percentage reversal of clonidine-induced antinociception was calculated by dividing the number of animals writhing by the total number of tested animals and multiplying the quotient by 100. All compounds were administered in a volume of 10 mL/kg; all doses were administered in terms of the free base or free acid. ED_{50} values with 95% confidence limits were determined where possible with use of the computer program of Tallarida and Murray[28] for the Litchfield–Wilcoxon test.

Acknowledgment. We thank our Analytical Chemistry Department for spectral measurements and our Chemical Development Department for supplies of chemical intermediates.

Registry No. **1**, 108796-88-9; **1**·HCl, 108797-31-5; **2**, 108796-89-0; **3**, 108796-90-3; **3**·HCl, 108797-32-6; **4a**, 108796-96-9; **4a**, 97608-34-9; **4b**·HCl, 108797-33-7; **4c**, 108796-97-0; **4c**·HCl, 108797-34-8; **4d**, 108796-98-1; **4d**·$C_7H_8O_3S$, 108797-35-9; **4e**, 108796-99-2; **4e**·$C_4H_4O_4$, 108797-36-0; **4f**, 108797-00-8; **4f**·$C_7H_8O_3S$, 108797-37-1; **4g**, 108797-01-9; **4g**·HCl, 108797-38-2; **4h**, 108797-02-0; **4h**·$C_4H_4O_4$, 108797-39-3; **4i**, 97608-37-2; **4i**·$C_4H_4O_4$, 108797-40-6; **4j**, 108797-03-1; **5a**, 108797-04-2; **5a**·HCl, 108797-41-7; **5b**, 108797-05-3; **5b**·HCl, 108797-42-8; **5c**, 108797-06-4; **5c**·$C_4H_4O_4$, 108797-43-9; **5d**, 108797-07-5; **5d**·$C_7H_8O_3S$, 108797-44-0; **5e**, 108797-08-6; **5e**·$C_4H_4O_4$, 108797-45-1; *cis*-**6a**, 108797-09-7; *cis*-**6a**·$C_7H_8O_3S$, 108797-46-2; *trans*-**6b**, 108797-10-0; *trans*-**6b**·$C_7H_8O_3S$, 108797-47-3; **7a**, 108797-11-1; **7a**·$C_4H_4O_4$, 108797-48-4; **7b**, 108797-12-2; **7b**·HCl, 108797-49-5; **7c**, 108797-13-3; **7c**·HCl, 108797-50-8; **7d**, 108815-97-0; **7d**·HCl, 108797-51-9; **7e**, 108797-14-4; **7e**·$C_7H_8O_3S$, 108797-52-0; **7f**, 108797-15-5; **7f**·$C_4H_4O_4$, 108797-53-1; **8a**, 108797-16-6; **8a**·HCl, 108797-54-2; **8b**, 106810-81-5; **8b**·HCl, 108797-55-3; **8c**, 108797-17-7; **8c**·HCl, 108797-56-4; **8d**, 108797-18-8; **8d**·$C_4H_4O_4$, 108797-57-5; **8e**, 108797-19-9; **8e**·$C_4H_4O_4$, 108797-58-6; **9**, 71649-65-5; **9**·$C_4H_4O_4$, 108797-59-7; **10**, 27244-26-4; **10**·$C_4H_4O_4$, 108797-60-0; **11**, 27167-93-7; **12a**, 108796-91-4; **12b**, 108796-92-5; **13**, 108796-93-6; **14**, 74590-82-2; **15a**, 3770-50-1; **15h**, 348-36-7; **15i**, 43142-64-9; **15j**, 4792-70-5; **16**(R^1 = CH_3, X = R^3 = H), 18450-24-3; **16** (R^1 = Ph, X = R^3 = H), 20538-24-3; **16** (R^1 = CH_3, X = 5-Cl, R^3 = H), 59908-53-1; **16** (R^1 = R^3 = CH_3, X = H), 61838-90-2; **16a**, 40913-41-5; **16b**, 108797-23-5; **16c**, 108797-24-6; **16d**, 108797-25-7; **16e**, 108797-26-8; **16f**, 17017-66-2; **16g**, 108797-27-9; **16h**, 108797-28-0; **16i**, 108797-29-1; **16j**, 108797-30-4; **17** (R^1 = Et, X = R^3 = H), 108797-61-1; **17** (R^1 = R^2 = X = H), 50501-07-0; **17** (R^1 = Ph, X = R^3 = H), 108797-70-2; **17** (R^1 = CH_3, X = 5-Cl, R^3 = H), 108797-71-3; **17** (R^1 = R^3 = CH_3, X = H), 108797-72-4; **17a**, 97608-35-0; **17b**, 108797-62-2; **17c**, 108797-63-3; **17d**, 108797-64-4; **17e**, 108797-65-5; **17f**, 97608-38-3; **17g**, 108797-66-6; **17h**, 108797-67-7; **17i**, 108797-68-8; **17j**, 108797-69-9; **18**, 108796-94-7; **19**, 108796-95-8; **20** (R^2 = CH_3), 108797-73-5; **20** (R^2 = CH_2OCH_3), 108797-74-6; **20** (R^2 = CH_2SCH_3), 108797-75-7; **20** (R^2 = CH_2NPr_2-*i*), 108797-76-8; **20a**, 108797-22-4; **21**, 108797-20-2; **22**, 108797-21-3; EDA, 107-15-3; PhCOCl, 98-88-4; methyl 3-methylquinoline-2-carboxylate, 53821-46-8; 1-methylindole, 603-76-9; ethyl 1,2,3,4-tetrahydroquinoline-2-carboxylate, 4620-34-2; $H_2C{=}CHCH_2Br$, 106-95-6.

(25) Cheng, Y-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
(26) Drew, G. M. *Eur. J. Pharmacol.* **1976**, *36*, 313.
(27) Arunlukshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.
(28) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacologic Calculations*; Springer-Verlag, New York, 1981.