determined according to the method of Bradford.[41]

For analysis of binding characteristics of nonlabeled test compounds, binding assays were performed with 32 concentrations of the competitive drug, each logarithmic decade subdivided into five increments and each concentration step assayed in duplicate. This protocol allowed for a total concentration range of more than six logarithmic decades to be covered in each separate concentration–effect curve (i.e., the highest concentration = 2×10^6 times the lowest concentration studied) and, thus, provided a high-resolution sequence of data points.

Graphic analysis of the data were performed by a computer-aided nonlinear regression, using a least-squares curve-fitting procedure. Assuming simple Michaelis–Menten kinetics of the interaction between radioligand and competing drug on any hypothesized number of coexpressed specific receptor types, the computation procedure fit the sigmoidal concentration effect curve defined by the law of mass action to the untransformed data. The analytical procedure allows for evaluation of the affinity of the competing drug for one or more subtypes of receptors that the radioligand nonselectively recognizes as specific binding sites. Calculation of K_d from the observed IC_{50} value (concentration of test compound that caused 50% inhibition of specific binding of NTP) was performed according to Cheng and Prusoff.[42] Multicomponent curve fitting furthermore allows for determination of relative density of receptor subtypes. It should be emphasized that accurate determination of specific/nonspecific binding ratio of the radioligand is absolutely essential for validation of multicomponent curve analysis.

All compounds were dissolved in 99% ethanol at a concentration of 1 mM and diluted 1000-fold in Tris-isosaline containing 0.2% BSA and 2.5% ascorbic acid. The final concentration of ethanol in the incubation cocktail was thus less than 0.02%, which has previously been found to be without detrimental effect on receptor integrity in the plasma membrane.[43] For a valid calculation of specific binding, the total binding assays (absence of nifedipine) contained the same concentration of ethanol as the nonspecific binding assays.

Acknowledgment. We thank Joseph Schwartz, Kaye Smillie, Russell J. Brittain, and Ophelia Hadjilambris for technical assistance, Mary Young and her associates for microanalytical data, and Alicia Kahle for nuclear magnetic resonance data.

Note Added in Proof

Subsequent to submission of this manuscript, there appeared a report of another ortho-substituted phenyl-1,4-dihydropyridine analogue that was observed to crystallize in the antiperiplanar conformation.[45]

Registry No. 1, 32947-20-9; **2**, 21881-77-6; **3**, 43067-01-2; 4, 112969-06-9; **5**, 112969-07-0; **6**, 21829-30-1; **7**, 21829-09-4; 2-Cl-3-$NO_2C_6H_3CO_2H$, 3970-35-2; 2-Cl-3-$NO_2C_6H_3CH_2OH$, 89639-98-5; 2-Cl-3-$NO_2C_6H_3CHO$, 58755-57-0; $AcCH_2CO_2Me$, 105-45-3; 2-Cl-4-$NO_2C_6H_3CHO$, 5568-33-2; nifedipine, 21829-25-4.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles (33 pages). Ordering information is given on any current masthead page.

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Indoline Analogues of Idazoxan: Potent α_2-Antagonists and α_1-Agonists

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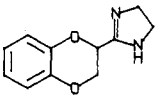
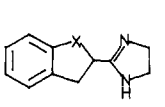
The synthesis and α-adrenergic activity of a series of substituted 2-imidazolinylindolines are described. Substitution in the indoline ring generated compounds with a spectrum of adrenoceptor antagonist/agonist profiles that proved sensitive to both the nature and position of the substituent. Many of the derivatives possess greater presynaptic antagonist potency than the corresponding benzodioxan 1, dihydrobenzofuran **2**, and indan **3** analogues; however, this α_2-antagonism is often accompanied by α_1-agonist activity. It was not possible to separate α_2-antagonist from α_1-agonist properties in this series. Compounds of most interest proved to be the *N*-ethyl **6**, 5-chloro-*N*-methyl 18, and 5-chloro-*N*-ethyl **23** derivatives, all being potent α_2-antagonists and α_1-agonists. Substitution at the 4- and 7-position of the indoline ring generally gave compounds with nonselective agonist properties.

The synthesis and pharmacological activities of a wide range of analogues of the potent and selective α_2-adrenoreceptor antagonist idazoxan (**1**) have been reported[1-3] in which the effects of substitution and modification of the dioxan and imidazoline rings were examined. The replacement of the dioxan ring in **1** by a variety of six- and five-membered heterocyclic systems has in many cases proven deleterious in terms of α_2-antagonist potency and selectivity.[2] From our own investigations the dihydrobenzofuranylimidazoline **2** has emerged as the only analogue possessing prejunctional antagonist potency and selectivity comparable to that of **1**, although the corresponding indanylimidazoline **3** has also been described as a potent α_2-antagonist by other workers.[4]



1



2 X = O
3 X = CH_2

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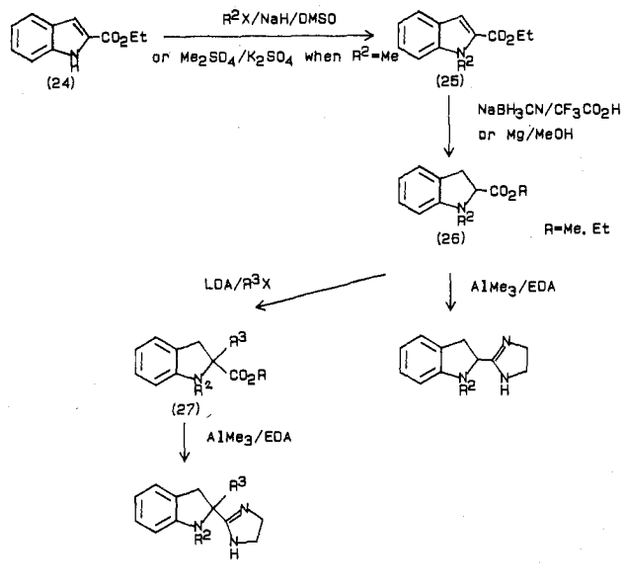
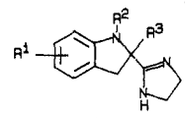
Scheme I



LDA = Lithium diisopropylamide
EDA = Ethylenediamine

Recent disclosures of α_2-antagonist activity in the corresponding indoline area[5-7] has prompted the publication of our own findings in this closely related series. We report here the synthesis and pharmacological activity of a series of indolinylimidazolines **4**.



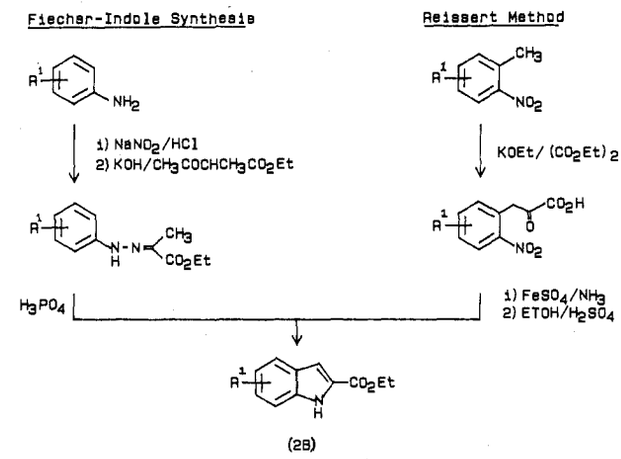
4

Chemistry

The 1-alkyl (**5–7**, **9**, **10**) and the 1,2-dialkyl (**11**, **12**) derivatives were obtained from indoline-2-carboxylic acid by adopting the route outlined in Scheme I. The *N*-phenyl compound **8** was prepared by using the same route; however, in this particular case the intermediate ester (**25**; R = Ph) was not accessible by simple arylation of the corresponding NH compound **24**. The required ethyl 1-phenylindole-2-carboxylate was therefore prepared by the method of Dolby and Lord.[8] N-Alkylation was performed on the indole ester **24** with base and dimethyl sulfate[9] or with the appropriate alkyl halide[10] before reducing the resulting N-substituted indole **25** to the corresponding indoline **26**. The reduction was achieved with either sodium cyanoborohydride in trifluoroacetic acid or magnesium in methanol, which also resulted in transesterification; the former method gave a slightly higher yield.

For those analogues containing only a 1-alkyl or 1-aryl substituent (**5–10**), the *N*-alkylindoline **26** was converted to the desired imidazoline by treatment with ethylenediamine and trimethylaluminum.[11] Where necessary, introduction of a 2-alkyl substituent was performed on the indoline ester **26** to give **27** prior to imidazoline formation.

Scheme II



Those indolines containing aromatic substituents, compounds (**13–23**), were synthesized from the appropriately substituted indole-2-carboxylate **28**, which was obtained by one of two methods (Scheme II).

The Fischer–Indole synthesis provided a route to the 5- and 7-substituted indole-2-carboxylate derivatives,[12-14] and the remaining congeners were prepared by the Reissert method.[13,15] Subsequent conversion of the substituted indole ester **28** to the required imidazoline was accomplished by using the method described in Scheme I.

Results and Discussion

All compounds were examined for α_1- and α_2-adrenoreceptor agonist and antagonist properties by using standard testing procedures,[3] and the results are presented in Table I. A selected number of compounds were also examined in vivo and in binding studies (Table II).

A wide range of prejunctional antagonist potencies was encountered within the indoline series, with compounds **5–7**, **15**, **18**, **22**, and **23** being more potent than idazoxan (**1**), the dihydrobenzofuran **2**, and the indan **3** analogues; in addition, however, many of these indolines were found to be potent α_1-agonists.

Of the indolines prepared, only three derivatives (**9–11**) are devoid of α_1-agonist properties in vitro; however, compound **9**, a potent and selective α_1-antagonist in vitro, was found in vivo to be a partial agonist at both α_1- and α_2-receptors.

The in vitro results (Table I), supported by in vivo and binding studies (Table II), demonstrate that in terms of α_2-antagonism the size of the 1-alkyl or 1-aryl substituent plays a crucial role; potency increases from methyl (**5**) to ethyl (**6**) but then decreases on homologation or increasing the steric bulk of this substituent. The incorporation of an alkyl group in the 2-position of the indoline ring, as in **11** and **12**, leads to a dramatic reduction in potency at both the α_1- and α_2-adrenoreceptor; for example, introduction of a 2-ethyl group in the *N*-methyl derivative **5** to give compound **11** resulted in a 1000-fold decrease in α_2-antagonism. In contrast, 2-substitution in the corresponding dihydrobenzofuran and benzodioxan series in many cases gives compounds that either retain the potency of the parent structure or that show increased potency and selectivity.[2,3] In the case of the indolines **11** and **12**, the

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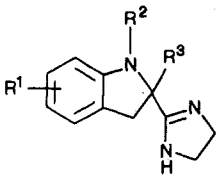
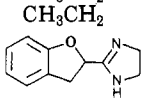
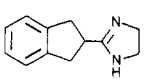
Table I



no.	R^1	R^2	R^3	mp, °C	formula	anal.	in vitro pharmacological results: ag[a,b]	ant.[c]	ag[d]	ant.[e]
5	H	CH_3	H	119–120	$C_{12}H_{15}N_3$	C, H, N	0.77	5.5	3.8	ag
6	H	CH_3CH_2	H	120–121	$C_{13}H_{17}N_3$	C, H, N	0	9.1	1.4	ag
7	H	$CH_3CH_2CH_2$	H	96–97	$C_{14}H_{19}N_3$	C, H, N	0	3.2	3.9	ag
8	H	Ph	H	208–209	$C_{17}H_{17}N_3 \cdot HCl$	C, H, N	0	0.5	5.3	ag
9	H	$PhCH_2$	H	141–143	$C_{18}H_{19}N_3$	C, H, N	0.02	ag[f]	0[f]	120
10	H	$PhCH_2OCH_2CH_2$	H	73–74	$C_{20}H_{23}N_3O$	C, H, N	0	0.05	0	18
11	H	CH_3	CH_3CH_2	242–246	$C_{14}H_{19}N_3 \cdot HCl$	C, H, N	0	0.005	0	<0.012
12	H	CH_3CH_2	CH_3	243–244	$C_{14}H_{19}N_3 \cdot HCl$	C, H, N	0	0.1	0.03	ag
13	4-Br	CH_3	H	140–141	$C_{12}H_{14}BrN_3$	C, H, N	0.34	ag	3.4	ag
14	4-F	CH_3	H	138–139	$C_{12}H_{14}FN_3$	C, H, N	1	ag	6.0	ag
15	4-Cl	CH_3	H	263–265	$C_{12}H_{14}ClN_3 \cdot HCl$	C, H, N	0.29	10	17	ag
16	4-OH	CH_3	H	195–198	$C_{12}H_{15}N_3O$[g]	C, H, N	0.16	ag	6.7	ag
17	4-OCH_3	CH_3	H	145–146	$C_{13}H_{17}N_3O$	C, H, N	0	0.27	0.62	ag
18	5-Cl	CH_3	H	143–144	$C_{12}H_{14}ClN_3$	C, H, N	0	6.8	2	ag
19	6-Cl	CH_3	H	134–136	$C_{12}H_{14}ClN_3$	C, H, N	0.019	ag	0.67	ag
20	7-Cl	CH_3	H	146–147	$C_{12}H_{14}ClN_3$	C, H, N	0.3	ag	3.5	ag
21	7-OCH_3	CH_3	H	140–141	$C_{13}H_{17}N_3O$	C, H, N	0.4	ag	8.0	ag
22	4-Cl	CH_3CH_2	H	118–119	$C_{13}H_{16}ClN_3$	C, H, N	0.51	8	4.4	ag
23	5-Cl	CH_3CH_2	H	114–118	$C_{13}H_{16}ClN_3$	C, H, N	0	8	5	ag
2							0	1.70	0.01	0.16
3							0	0.4	0	0.8

[a] Prejunctional agonist potency (*p*-aminoclonidine = 1). [b] Compounds found to exhibit α_1-agonism were tested in the presence of prazosin (260 nm). [c] Prejunctional antagonist potency (idazoxan = 1). [d] Postjunctional agonist potency (phenylephrine = 1). [e] Postjunctional antagonist potency (idazoxan = 1). [f] Shown in an in vivo test situation to be a partial agonist. [g] C: calcd, 63.39; found, 63.80.

Table II. In Vivo Pharmacological Screening and in Vitro Binding Results

no.	in vivo (pithed rat)[a]: prejunctional ag: ED_{25}[c]	prejunctional ant.: DR2[d]	postjunctional ag: ED_{40}[e]	postjunctional ant.: DR2[d]	binding studies:[b] K_i, nm [^{3}H]idazoxan	[^{3}H]prazosin
5	4.1 ± 1.5	3.7 ± 0.6	0.5 ± 0.05	ag	0.69 ± 0.23	3.86 ± 1.32
6	ant.	1.6 ± 0.3	3.3 ± 0.4	ag	0.24 ± 0.06	3.72 ± 1.41
7	ant.	7.1 ± 0.6	3.8 ± 0.7	ag	0.96 ± 0.05	3.70 ± 0.64
8	ant.	9.4 ± 1.9	1.1 ± 0.1	ag	3.0 ± 0.80	8.40 ± 4.20
9	9.5 ± 1.5	8.7 ± 0.8	308 ± 103	54.3 ± 11.7	1.87 ± 0.39	17.5 ± 6.0
13	1.1 ± 0.5	ND	0.3 ± 0.03	ag		
14	0.8 ± 0.1	ND	0.8 ± 0.07	ag		
15	ant.	2.4 ± 0.4	0.2 ± 0.03	ag	0.16 ± 0.09	13.1 ± 2.6
16	0.2 ± 0.06	ND	0.3 ± 0.06	ag		
18	ant.	12.7 ± 2.3	14.3 ± 5.8	ag		
20	2.2 ± 0.5	ND	1.4 ± 0.2	ag		
22	ant.	1.5 ± 0.3	0.8 ± 0.2	ag	0.42 ± 0.13	1.9 ± 0.47
23	ant.	5.9 ± 0.9	4.2 ± 0.5	ag		
p-aminoclonidine	0.4 ± 0.2		0.7 ± 0.2			
phenylephrine			0.9 ± 0.06			
idazoxan		20.2 ± 2.3	65.5 ± 30.4	1427 ± 149		
prazosin		5437 ± 993		9.4 ± 1.0		

[a] Ag = agonist; ant. = antagonist; ND = not determined. [b] K_i = concentration inhibiting by 50% the saturable binding of [^{3}H]idazoxan to α_2-sites and [^{3}H]prazosin to α_1-sites in rat cerebral cortical membranes. [c] ED_{25} = dose (μg/kg) inhibiting was deferens contraction by 25%. [d] ED_{40} = dose (μg/kg) raising diastolic blood pressure (DBP) by 40 mmHg. [e] DR2 = antagonist dose (μg/kg) producing twofold shift of UK-14,304 (pre, vas deferens) or cirazoline (post: DBP) dose–response curves.

imidazoline ring, which is thought to bind to the receptor via one of the nitrogen atoms, is possibly constrained in an unfavorable conformation for interaction at the α_2- and α_1-adrenoreceptors as a result of the steric-buttressing effect of the *N*-alkyl and 2-alkyl substituents, and this may explain the significant drop in potency seen in these compounds.

Aromatic substitution was examined in both the *N*-methyl- and *N*-ethylindolines **5** and **6** in order to determine the possible effects of such substitution on pre- and postjunctional antagonist and/or agonist potencies and on selectivity. Introduction of a 4-chloro substituent into the *N*-methyl (**5**) and *N*-ethyl (**6**) compounds proved more beneficial in the former analogue. In addition, the 4-chloro-*N*-ethyl compound **22** was found in vitro (Table I) to be a partial agonist at the α_2-adrenoreceptor unlike the parent *N*-ethyl compound **6**, which failed to exhibit prejunctional agonism. Consequently, further aromatic sub-

stitution was examined in the *N*-methylindoline **5** and only one additional derivative was prepared in the *N*-ethyl series.

The position of the chloro group in **5** was found to have a strong influence on the molecule's prejunctional antagonist/agonist profile. The 5-chloro compounds **18** and **23** proved the most interesting, being the only chloro analogues not possessing α_2-partial agonist activity though retaining the α_2-antagonist and α_1-agonist potencies of the parent molecules **5** and **6**.

Alternative aromatic substituents were introduced into the *N*-methylindoline **5** in the 4-position. This position was chosen in particular because the 4-chloro compound proved to be the most potent at both the pre- and the postjunctional adrenoreceptors. Replacement of the 4-chloro group with bromo, fluoro, and hydroxy substituents gave compounds with nonselective agonist properties, and although the corresponding 4-methoxy compound **18** was found to be an α_2-antagonist, it displayed a lower affinity at both the α_2- and α_1-adrenoreceptor sites than that of the parent compound **16**. Introduction of a substituent in the 7-position, as well as the 4-position, gave rise to compounds possessing α_2-agonist activity. A similar effect was observed in the dihydrobenzofuran series.[2]

In summary, indoline analogues showing a wide range of pre- and postjunctional antagonist/agonist profiles have been prepared. A number of compounds possess potent α_2-antagonist and α_1-agonist activity, in particular the *N*-ethyl (**6**), 5-chloro-*N*-ethyl (**23**), and 5-chloro-*N*-methyl (**18**) derivatives. It was not possible to separate α_2-antagonist from α_1-agonist properties in this series.

Experimental Section

Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. IR and MS spectra were recorded on Perkin-Elmer 710B and LKB-2091 instruments respectively, and NMR spectra were recorded on a Jeol FX90 instrument. These 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. Where purifications were carried out with column chromatography, silica gel refers to Kieselgel 60, 70–230 mesh ASTM, and alumina refers to Aluminumoxid 90 aktiv, neutral, activity I, 70–230 mesh ASTM. Chromatography on a Chromatotron (Model 7924T) was done on 1–4-mm plates made up with silica gel PF-254 with $CaSO_4 \cdot H_2O$ Type 60 TLC, Merck (7749). Petroleum ether refers to petroleum ether, bp 40–60 °C.

2-(4,5-Dihydro-2-1*H*-imidazolyl)-1-ethyl-2,3-dihydro-1*H*-indole (6). A solution of indole-2-carboxylic acid (27 g, 0.17 mmol) in ethanol (400 mL) and concentrated sulfuric acid (4 mL) was heated under reflux for 18 h. The cooled reaction mixture was concentrated in vacuo, and the residue was partitioned between dichloromethane and dilute sodium hydroxide solution. The organic layer was separated, washed with water, and dried over magnesium sulfate. Evaporation of the filtered solution gave ethyl 1*H*-indole-2-carboxylate (**24**) as an off-white solid: yield 30.2 g (95%); mp 120–121 °C.

Treatment of the indole **24** (6.1 g, 32 mmol) with ethyl iodide (2.6 mL, 32.5 mmol) and sodium hydride (60% dispersion in oil; 1.4 g, 35 mmol) in dimethyl sulfoxide (80 mL)[10] gave ethyl 1-ethyl-1*H*-indole-2-carboxylate (**25**; R^2 = Et). Purification by column chromatography on silica gel by eluting with 10% diethyl ether in petroleum ether gave a colorless oil: NMR ($CDCl_3$) δ 7.35 (5 H, m, Ar CH, aryl H), 4.60 (2 H, AB q, J = 8 Hz, NCH_2), 4.36 (2 H, AB q, J = 8 Hz, CH_2), 1.40 (6 H, t, 2 CH_3).

A slurry of the above indole **25** (R^2 = Et) (Scheme I) (10 g, 0.046 mmol) and magnesium turnings (22 g, 0.92 mmol) in dry methanol (3000 mL) was stirred vigorously with a mechanical stirrer. After 0.5 h a mild exothermic reaction started, and the reaction mixture was cooled in an ice/water bath to maintain the reaction temperature below 10 °C. The suspension was stirred at 5–10 °C. The resultant gray mass was left to stand overnight and then cooled in ice/water before hydrochloric acid (6 M, 300 mL, 1.8 mol) was added cautiously with stirring. The suspension was stirred at room temperature for 3 h and diluted with water, and the inorganic material was filtered off. The residue was washed with dichloromethane, and the filtrate was extracted with dichloromethane. The combined organic extracts were washed with brine and dried, and the solvent was evaporated to afford the indoline as an oil. Chromatography on silica gel with dichloromethane as eluant gave methyl 1-ethyl-2,3-dihydro-1*H*-indole-2-carboxylate (**26**; R = Me, R^2 = Et): yield 6.48 g (69%); IR λ_{max} 1750 cm^{-1}; NMR ($CDCl_3$) δ 6.83 (4 H, m, aryl H), 4.27 (1 H, t, J = 9 Hz, NCH), 3.762 (3 H, s, OCH_3), 3.25 (4 H, m, NCH_2, Ar CH_2), 1.13 (3 H, t, J = 7 Hz, $NCCH_3$).

The preceding indolinic ester was converted to the imidazoline **6** by using the following modified version of the literature method.[11] Ethylenediamine (2.25 mL, 33.7 mmol) was added dropwise to a stirred solution of trimethylaluminum (2 M, 15 mL, 30 mmol) in dry toluene (100 mL) under argon at 0–5 °C. After the addition was complete, the solution was allowed to warm to room temperature, and a solution of the ester **26** (R = Me, R^2 = Et) (4.58 g, 22.3 mmol) in dry toluene (50 mL) was added dropwise. The reaction mixture was refluxed for 3 h before water (10 mL) was added dropwise at room temperature with vigorous stirring. The aluminum salts were filtered off and washed well with ethyl acetate. The filtrate was washed with water, dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo. The produce was purified by recrystallization from diethyl ether to give the imidazoline **6** as white prisms: yield 2.65 g (55%); NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7 Hz, CH_3), 3.16 (4 H, m, CH_2), 3.63 (4 H, m, NCH_2CH_2N), 4.36 (1 H, t, J = 9 Hz, CH), 6.35 (4 H, m, aryl H).

Compounds **5**, **7**, **9**, and **10** were also prepared by the procedures described above for **6**; however, methylation of ethyl 1*H*-indole-2-carboxylate (**24**) was accomplished by using dimethyl sulfate and potassium carbonate[9] to provide ethyl 1-methyl-1*H*-indole-2-carboxylate. In addition, the indoles **25** (R^2 = Me, *n*-Pr, Ph, Bzl) were reduced to the corresponding indolines with sodium cyanoborohydride as described in the following procedure. Sodium cyanoborohydride (18 g, 28.5 mmol) was added portionwise to a solution of the indole **25** (R^2 = Me) (11.1 g, 55 mmol) in trifluoroacetic acid (100 mL) under nitrogen while the temperature of the reaction mixture was maintained at 5 °C. The solution was stirred at room temperature for 2 h before it was poured into water (200 mL) and basified with sodium bicarbonate. The product was extracted with dichloromethane, and the organic solution was washed with brine and dried. Evaporation gave the 2,3-dihydroindole **26** (R = Et, R^2 = Me) as a yellow oil: yield 11.0 g (97%); NMR ($CDCl_3$) δ 1.29 (3 H, t, J = 7 Hz, CH_3), 2.83 (3 H, s, CH_3), 3.22 (2 H, t, J = 9 Hz, Ar CH_2), 3.96 (1 H, d, J = 9 Hz, CH), 4.24 (2 H, AB q, J = 7 Hz, OCH_2), 6.84 (4 H, m, aryl H). Compound **26** was converted to the required imidazoline as described above and was purified by recrystallization from either hexane or ethyl acetate or by chromatography on a chromatotron with dichloromethane/methanolic ammonia mixtures.

2-(4,5-Dihydro-2-1*H*-imidazolyl)-2-ethyl-2,3-dihydro-1-methyl-1*H*-indole (11). *n*-Butyllithium (2.5 M in hexane; 3.8 mL, 9.5 mmol) was added to a stirred solution of diisopropylamine (1.3 mL, 9.2 mmol) in dry tetrahydrofuran (80 mL) at −78 °C under argon. The solution was allowed to warm to room temperature and stirred for 0.5 h. After the mixture was recooled to −78 °C, a solution of **26** (R = Et, R^2 = Me) (Scheme I) (4.7 mmol) in dry tetrahydrofuran (40 mL) was added dropwise, and the resultant solution was stirred for 1 h at this temperature before ethyl iodide (0.75 mL, 9.4 mmol) was added. The mixture was stirred for 1 h at −78 °C followed by 1 h at 0 °C and was then poured into dilute hydrochloric acid/ice followed by extraction with diethyl ether. The combined organic extracts were washed with brine and dried over magnesium sulfate, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel with diethyl ether/petroleum ether to give ethyl 2-ethyl-2,3-dihydro-1-methyl-1*H*-indole-2-carboxylate (**27**); (R = Et, R^2 = Me, R^3 = Et) as a colorless oil: yield 0.32 g (31%); MS, m/z 219 (M^+).

Treatment of the ester with trimethylaluminum and ethylenediamine as described above gave 11, which was converted to its hydrochloride salt and recrystallized from ethanol/diethyl ether, yield 17.5%.

2-(4,5-Dihydro-2-1*H*-imidazolyl)-4-fluoro-2,3-dihydro-methyl-1*H*-indole (14). A solution of diethyl oxalate (23 mL, 0.17 mmol) and 2-fluoro-6-nitrotoluene (19 mL, 0.15 mmol) in dry ethanol was added dropwise to a stirred solution of potassium ethoxide [from potassium (6.2 g, 0.16 mmol) in ethanol (100 mL)] at 0–5 °C. The mixture was gently heated under reflux for 6 h and cooled, and the solvent was removed in vacuo. The residue was partitioned between water and ethyl acetate, the organic phase was separated off, and the aqueous solution was further extracted with ethyl acetate to remove unreacted starting materials. Acidification of the aqueous layer with dilute hydrochloric acid gave the product, which was extracted into dichloromethane. The organic solution was washed with water and dried, and the solvent was evaporated to give 4-fluoro-2-(nitrophenyl)pyruvic acid as a red oil: yield 7.3 g (21%); IR ($CHBr_3$) λ_{max} 1740 cm^{-1}; MS, *m/z* 228 ($M^+ + 1$).

The pyruvic acid was cyclized by using the method described by Uhle[15] to give 4-fluoro-1*H*-indole-2-carboxylic acid: yield 62%; MS, *m/z* 179 (M^+). The corresponding methyl ester was prepared by the conventional method and was isolated as an orange solid: IR ($CHBr_3$) λ_{max} 3340, 1705 cm^{-1}; MS, *m/z* 193 (M^+).

The preceding ester was methylated by using methyl iodide and sodium hydride in dimethyl sulfoxide following the literature procedure.[10] The crude product was purified by column chromatography on silica gel by eluting with 10% diethyl ether/petroleum ether to afford methyl 4-fluoro-1-methyl-1*H*-indole-2-carboxylate as white platelets: yield 50%; MS, *m/z* 207 (M^+).

The indole ester was converted to the imidazoline **14** by reduction with sodium cyanoborohydride, followed by reaction with trimethylaluminum and ethylenediamine as described earlier: yield 56%.

2-(4,5-Dihydro-2-1*H*-imidazolyl)-2,3-dihydro-4-methoxy-1-methyl-1*H*-indole (17). Methyl 4-methoxy-1*H*-indole-2-carboxylate[16,17] was methylated with methyl iodide in the presence of sodium hydride to give methyl 4-methoxy-1-methyl-1*H*-indole-2-carboxylate. The indolic ester was reduced with magnesium in methanol, and the product was reacted with trimethylaluminum/ethylenediamine to give **17**: yield 39%.

Compounds **18**, **20**, and **21** were prepared by the same procedure.

2-(4,5-Dihydro-2-1*H*-imidazolyl)-2,3-dihydro-4-hydroxy-1-methyl-1*H*-indole (16). Boron tribromide (0.85 mL, 9 mmol) was added dropwise to a stirred solution of the hydrochloride salt of **17** (0.59 g, 2.2 mmol) in dry dichloromethane (50 mL) at −78 °C under argon.[18] The reaction mixture was allowed to warm to room temperature, stirred for 24 h, and then cooled to −78 °C, and methanol (4 mL) was added dropwise. The solution was warmed to room temperature, and diethyl ether was added to precipitate the product, which was filtered off and washed with diethyl ether. Methanolic ammonia was added to a suspension of the solid in dichloromethane, and the resultant ammonium chloride was filtered off. The basic filtrate was evaporated to give a fawn solid, which was purified on a Chromatotron with 6% methanolic ammonia in dichloromethane. The 4-hydroxy analogue **16** was obtained as a white glass: yield 49%; MS, *m/z* 217 (M^+); NMR (CD_3OD) δ 6.90 (1 H, t, J = 8 Hz, aryl H), 6.14 (2 H, m, aryl H), 3.96 (1 H, dd, J = 11 Hz, NCH), 3.65 (4 H, m, NCH_2CH_2N), 3.0 (2 H, m, Ar CH_2), 2.66 (3 H, s, NCH_3).

Pharmacology. Details of in vitro screening procedures are presented in an earlier publication.[3]

Activity at Peripheral α_1- and α_2-Adrenoreceptors in Vivo. Prejunctional activity was studied in the vas deferens and postjunctional effects in the vasculature of pithed rats. Antagonist potencies were determined as the dose (μg/kg, iv) required to produce a two-fold shift (DR2) of the cumulative dose–response curve to UK-14,304[19] on the twitch response of the vas deferens (pre α_2-activity) or cirazoline on diastolic blood pressure (DBP) (post α_1-activity).[20] The antagonist and agonist potencies at the two receptors were determined in separate groups of pithed rats (n = 4–6). The compounds were given in a cumulative manner to obtain their prejunctional and postjunctional agonist potencies as an ED_{25} value, the dose (μg/kg, iv) required to inhibit vas deferens contraction by 25% after pretreatment with prazosin (1 mg/kg), or an ED_{40} value, the dose (μg/kg, iv) raising diastolic blood pressure by 40 mmHg.

Activity at Central α_1- and α_2-Adrenoreceptors. Radioligand Binding Studies. The affinities (K_i, nM) of the compounds were determined from their ability to displace the saturable binding of [^{3}H]prazosin and [^{3}H]idazoxan from α_1- and α_2-adrenoreceptor sites prepared from rat cerebral cortical membranes.[21] Hill coefficients were found to be approximately one, indicating that all the compounds were binding in a competitive manner at both α_2- and α_1-adrenoreceptors.

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Registry No. 1, 79944-58-4; **5**, 97608-34-9; **6**, 108796-97-0; **7**, 108796-99-2; **8**, 113162-19-9; **9**, 97608-37-2; **10**, 113162-20-2; **11**, 113162-21-3; **11** (free base), 113162-22-4; **12**, 113162-23-5; **13**, 113162-24-6; **14**, 113162-25-7; **15**, 113162-26-8; **16**, 113162-27-9; **17**, 113162-28-0; **17**·HCl, 113162-29-1; **18**, 108797-05-3; **19**, 113162-30-4; **20**, 108797-06-4; **21**, 113162-31-5; **22**, 113162-32-6; **23**, 113162-33-7; **24**, 3770-50-1; **25** (R^2 = Me), 18450-24-3; **25** (R^2 = Et), 40913-41-5; **26** (R = Me, R^2 = Et), 113162-34-8; **26** (R = Et, R^2 = Me), 97608-35-0; **27** (R = R^3 = Et, R^2 = Me), 113162-35-9; EDA, 107-15-3; $(CO_2Et)_2$, 95-92-1; 2-F-6-$NO_2C_6H_3Me$, 769-10-8; 2-NO_2-4-$FC_6H_3CH_2COCO_2H$, 7593-91-1; indole-2-carboxylic acid, 1477-50-5; 4-fluoro-1*H*-indole-2-carboxylic acid, 399-68-8; methyl 4-fluoro-1*H*-indole-2-carboxylate, 113162-36-0; methyl 4-fluoro-1-methoxy(-·1*H*-indole-2-carboxylate, 113162-37-1; methyl 4-methoxy-1*H*-indole-2-carboxylate, 111258-23-2; methyl 4-methoxy-1-methyl-1*H*-indole-2-carboxylate, 111258-25-4.

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