Adrenoceptor and Tetrabenazine Antagonism Activities of Some Pyridinyltetrahydropyridines

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A series of pyridinyltetrahydropyridine derivatives was synthesized and evaluated as adrenoceptor and tetrabenazine antagonists. 4-(3-Fluoro-2-pyridinyl)-1,2,5,6-tetrahydropyridine proved to be the most potent and selective α_2-adrenoceptor antagonist of the series as measured in vitro by displacement of [^{3}H]clonidine and [^{3}H]prazosin from membrane binding sites of calf cerebral cortex and by antagonism of the effects of clonidine and methoxamine in the rat isolated, field-stimulated vas deferens. In addition, this compound, and the corresponding desfluoro derivative, blocked tetrabenazine-induced ptosis in the mouse.

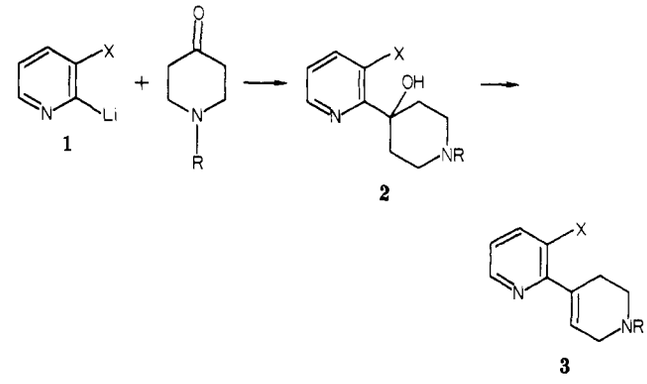
In addition to the α_1-adrenoceptors of effector cells that mediate sympathetic postjunctional responses to the neurotransmitter norepinephrine, other adrenergic receptors are known to be present at both pre- and postjunctional sites. While the functional relevance of postsynaptic α_2-adrenoceptors is only beginning to be understood,[1] it is now well-established that presynaptic α_2-adrenergic receptors constitute a negative feedback system that modulates noradrenergic neurotransmission through regulation of the release of norepinephrine during nerve stimulation.[2] Activation of presynaptic α_2-adrenergic receptors results in a decrease in the amount of norepinephrine normally released while antagonism of these α_2-adrenoceptors increases norepinephrine release.

Development of central, presynaptic α_2-adrenoceptor subsensitivity is a well-substantiated feature of the chronic administration of antidepressants that are adrenergic amine-uptake inhibitors. Since receptor desensitization leads to effectual blockade of the α_2-adrenoceptor mediated regulatory mechanism, the resulting increase in adrenergic function may represent an important aspect of this type of antidepressant therapy.[3,4] Therefore, agents possessing selective presynaptic α_2-adrenoceptor blocking activity in addition to amine-uptake blocking properties may constitute a more efficacious treatment of depression.[5]

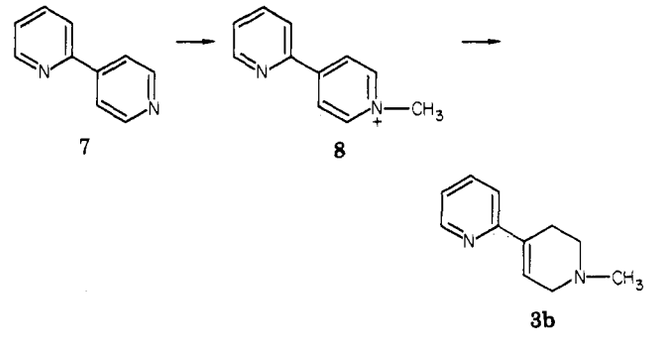
As part of a program aimed at the development of improved antidepressant therapy, compounds found to have α_2-adrenoceptor blocking activity were examined for antagonism of tetrabenazine-induced ptosis in the mouse, an established assay for antidepressants of the protriptyline class. This article describes some pyridinyltetrahydropyridines that have been found to possess both selective α_2-adrenoceptor and tetrabenazine antagonism activities.

Chemistry. Most of the pyridinyltetrahydropyridines of Table I were prepared by reaction of the appropriate pyridyllithium **1** with 1-methyl-4-piperidone followed by dehydration of the intermediate tertiary alcohols **2** in $SOCl_2$ at reflux. This route, using $SOCl_2$ in C_6H_6 at reflux as the dehydrating agent, had been used previously for synthesis of **3b**, X = H, R = CH_3.[6] Other methods investigated for conversion of one of the alcohols, **2**, X = Cl, R = CH_3, to olefin were 85% H_2SO_4 at 90 °C for 24 h, CF_3CO_2H–$(CF_3CO)_2O$ (1:1) at reflux for 20 h, and polyphosphoric acid at 100 °C for 5 h. Surprisingly, this alcohol was recovered unchanged from all of these procedures. However, the 3-pyridinyl analogue **5**, Table I, could be obtained in excellent yield by dehydration of the corresponding tertiary alcohol with 80% H_2SO_4 at 60 °C for 5 h.

Scheme I



Scheme II



Synthesis of **3a**, X = R = H, was accomplished through protection of the piperidone N as the *tert*-butoxy carbamate. In this case, the BOC-protected alcohol **2**, X = H, R = CO_2CMe_3, was dehydrated with Burgess' reagent[7] followed by removal of the BOC protective group with CF_3CO_2H.

Although the *N*-methyl analogue **3b**, X = H, R = CH_3, can be prepared by the route outlined in Scheme I, a more convenient procedure is shown in Scheme II. Quaternization of commercially available 2,4′-dipyridyl, **7**, gave

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(2) Langer, S. Z. *Biochem. Pharmacol.* **1974**, *23*, 1793; *Br. J. Pharmacol. Chemother.* **1977**, *60*, 481.
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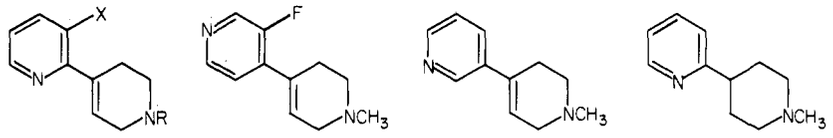
Table I. Physical and Chemical Properties of the Pyridinyltetrahydropyridines

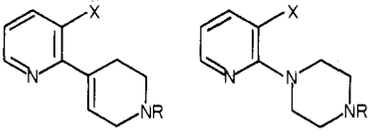


3 4 5 6

compd	X	R	formula	dec pt, °C	method	yield, %	recrystn solv
3a	H	H	$C_{10}H_{12}N_2 \cdot C_4H_4O_4$[a]	178–180	A	17	MeOH–Et_2O
3b	H	CH_3	$C_{11}H_{14}N_2 \cdot C_4H_4O_4$[b]	126–128	B	53	*i*-PrOH–Et_2O
3c	F	CH_3	$C_{11}H_{13}FN_2 \cdot C_4H_4O_4$[b]	130–133	C	24	Me_2CO–Et_2O
3d	Cl	CH_3	$C_{11}H_{13}ClN_2 \cdot C_4H_4O_4$[b]	118–120	C[c]	15	Me_2CO–Et_2O
3e	CH_3	CH_3	$C_{12}H_{16}N_2 \cdot C_6H_6O_6$[d]	129–131	C[e]	17	EtOH–EtOAc
4			$C_{11}H_{13}FN_2 \cdot C_4H_4O_4$[b]	107–109	C[f]	3	Me_2CO–Et_2O
5			$C_{11}H_{14}N_2 \cdot 2HCl \cdot H_2O$	248–251	D	5	*i*-PrOH
6			$C_{11}H_{16}N_2 \cdot C_4H_4O_4$[b]	140–143	E	64	Me_2CO–Et_2O

[a] Hydrogen fumarate. [b] Hydrogen maleate. [c] Intermediate 2-bromo-3-chloropyridine prepared by method of Maki and Takahashi.[21] [d] Sesqui hydrogen tartrate. [e] Intermediate 2-bromo-3-methylpyridine prepared by diazotization[22] of 2-amino-3-methylpyridine. [f] 3-Fluoropyridine used in place of 2-bromo-3-fluoropyridine.

Table II. Radioligand Binding and Rat Vas Deferens Results



3 9

			calf cerebral cortex radioligand binding, K_i, nM[a]			rat vas deferens pA_2[b] for antagonism of		
compd	X	R	[^{3}H]clonidine	[^{3}H]prazosin	selectivity ratio,[c] α_2/α_1	clonidine	methoxamine	selectivity ratio[d] α_2/α_1
3a	H	H	144 ± 12	4000 ± 300	28	<5.7		
3b	H	CH_3	57 ± 5	2500 ± 300	44	6.2 ± 0.1	5.4 ± 0.1	6
3c	F	CH_3	22 ± 3	3300 ± 500	150	6.8 ± 0.5[e]	5.3 ± 0.2[e]	32
3d	Cl	CH_3	72 ± 5	2260 ± 200	31	<5.9		
3e	CH_3	CH_3	170 ± 10	2500 ± 700	15	<5.8		
4[f]			720 ± 200	7700 ± 700	11	<5.8		
5[f]			750 ± 70	4800 ± 400	6.4	<5.8		
6[f]			420 ± 30	2500 ± 200	6	<5.8		
9a[g]	H	H	37 ± 3	2400 ± 600	65	6.4 ± 0.1	5.7 ± 0.1	5
9b[g]	F	CH_3	5 ± 0.3	490 ± 50	98	7.4 ± 0.1	6.20 ± 0.04[h]	16
rauwolscine			18 ± 0.7	940 ± 40	52	7.90 ± 0.21[e]	6.00 ± 0.17[e]	79
yohimbine			49 ± 1	200 ± 10	4.5	7.65 ± 0.13[e]	6.52 ± 0.29[e]	14
mianserin			17 ± 3	43 ± 7	2.5	7.27 ± 0.31[e]	7.24 ± 0.31[e]	1.1

[a] Reported values are the mean of at least two independent determinations plus or minus the range. [b] Reported values are the mean of at least three tissues per determination plus or minus standard error. [c] Ratio of K_i(prazosin)/K_i(clonidine). [d] Ratio of –log methoxamine pA_2/–log clonidine pA_2. [e] From Schild plot evaluation.[19] [f] See Table I for structure. [g] Synthesis and α_2-adrenoceptor antagonism activities have been reported previously.[16] [h] This compound also produced a 29% reduction of contractions at 1.5×10^{-6} M.

monomethylated product **8**[8] in high yield, which upon $NaBH_4$ reduction afforded **3b** in 53% yield. The product obtained by this route was identical with that prepared by the method of Scheme I. Catalytic reduction of **3b** led to the piperidine derivative **6**.

Since it has been reported[9] that mixtures of 2- and 4-(3-hydroxy-3-pentyl)-3-fluoropyridines can be obtained from reaction of lithiated 3-fluoropyridine with 3-pentanone, those conditions found to favor substitution in the 2-position were used in an attempted synthesis of **3c** from 3-fluoropyridine. However, the only isolated product proved to be the isomer resulting from reaction of 3-fluoropyridine at the 4-position.[10] Dehydration of this alcohol in refluxing $SOCl_2$ gave **4** (Table I). Fluoro derivative **3c** was prepared successfully from 2-bromo-3-fluoropyridine by the route outlined in Scheme I.

Results and Discussion

Relative affinities of the pyridinyltetrahydropyridines of Table I for central α-adrenergic binding sites were determined by measurement of radioligand displacement from membrane binding sites of calf cerebral cortex. Displacement of [^{3}H]clonidine was used as a measure of interaction with α_2-adrenergic binding sites while [^{3}H]-pyrazosin displacement served as an assay for α_1-adrenoceptor affinity.

In this series, the 3-F, *N*-Me derivative **3c** exhibited the greatest affinity for α_2-adrenoceptor binding sites (Table II). Although this binding was comparable in potency to the reference agent rauwolscine, **3c** proved to be approximately 3 times more selective than rauwolscine for the [^{3}H]clonidine receptor compared to the [^{3}H]prazosin receptor. Replacement of the 3-F group in **3c** by H (**3b**), Cl (**3d**), or Me (**3e**) or removal of the *N*-Me group to give **3a**

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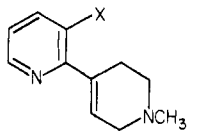
(9) Marsais, F.; Mallet, M.; Queguiner, G.; Pastour, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1972**, *275*, 1535.
(10) Gribble and Saulnier (Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137) have reported regioselective reactions at the 4-position in similar lithiations of 3-halopyridines.

Table III. Antagonism of Tetrabenazine-Induced Ptosis



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compd	X	ED_{50} ± SD, mg/kg iv
3b	H	0.50 ± 0.21
3c	F	0.35 ± 0.24
desmethylimipramine		0.07 ± 0.03

all led to decreased α_2-adrenoceptor binding. Affinity for the α_2-site was further reduced in the 4-pyridyl (**4**), 3-pyridyl (**5**), and dihydro (**6**) derivatives.

Antagonistic activities of these compounds upon pre- (α_2) and postsynaptic (α_1) adrenoceptors were determined in the rat isolated, field-stimulated vas deferens. In this tissue, presynaptic adrenergic agonists such as clonidine characteristically inhibit stimulation-induced contractions, whereas postsynaptic agonists such as methoxamine enhance contractions. These pre- and postysynaptic adrenergic agonist effects are preferentially blocked by known selective inhibitors of α_2- and α_1-adrenoceptors.[11-13]

As was observed in the radioligand binding procedure, the most potent member of the tetrahydropyridine series in the vas deferens proved to be the 3-F, *N*-Me derivative **3c** with the desfluoro compound **3b** being slightly less active. However, in contrast to the receptor binding results, these tetrahydropyridines were less potent and less selective α_2-adrenoceptor antagonists than rauwolscine in the vas deferens.

The tetrahydropyridines of Table I were also examined for antagonism of tetrabenzine-induced ptosis in mice. Again, **3b** and **3c** proved to be the more potent members of the series in this in vivo assay. Further comparison of **3c** and **3b** with the reference agent desmethylimipramine confirmed that these tetrahydropyridines are antagonists of tetrabenazine-induced ptosis, being approximately 5–7 times less active than desmethylimipramine (Table III). Although the demonstration of both tetrabenazine and selective α_2-adrenoceptor antagonism in the same molecule is novel, the mechanism by which **3b** and **3c** block ptosis effects of tetrabenazine and the implications for treatment of depression are unclear. Other studies from these laboratories show that with these compounds, tetrabenazine antagonism does not result from the blockade of norepinephrine, dopamine, or serotonin uptake or from inhibition of monoamine oxidase.[14]

It is of interest to compare the active tetrahydropyridines of this series with the corresponding piperazine derivatives for structure–activity relationships. The data of Table II show that substitution of an olefin group for the piperazine N (**9a** to **3a** and **9b** to **3c**) results in reduced α_2-adrenoceptor antagonism as measured by radioligand binding and in the rat vas deferens. However, the tetrahydropyridines are tetrabenazine antagonists while piperazine **9b** was inactive in this assay.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus using open capillaries and are uncorrected. NMR spectra were recorded for all intermediate and final products on either Nicolet NT-360 or Varian EM-90 instruments with either Me_4Si or $CFCl_3$ as internal standards. All spectra were consistent with assigned structures. Microanalytical results are indicated by atom symbols and are within ±0.4% of theoretical values unless otherwise indicated.

Preparation of Pyridinyltetrahydropyridines. Method A. 4-(2-Pyridinyl)-1,2,5,6-tetrahydropyridine (3a). A solution of 2-bromopyridine (0.78 g, 4.9 mmol) in Et_2O (5 mL) was added dropwise to a well-stirred mixture of *n*-BuLi in hexane (2.3 mL of a 2.18 M solution) and Et_2O (20 mL) at −50 °C under N_2, and the mixture was stirred at this temperature for 10 min. A solution of 1-(*tert*-butoxycarbonyl)-4-piperidone (1.16 g, 8.0 mmol) in Et_2O (5 mL) was then added dropwise. Following this addition, the reaction mixture was allowed to warm to −30 °C and stirred at this temperature for 1 h after which it was warmed to 0 °C and quenched with NH_4Cl (1.5 g) in cold H_2O (50 mL). After 1 h, the Et_2O layer was separated and washed with H_2O followed by three 60-mL portions of 1 N HCl. The combined HCl extracts were neutralized with solid Na_2CO_3 and reextracted with Et_2O. The Et_2O extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown residue, which was extracted with hot hexane, decolorized (C), and filtered. Removal of the hexane gave crude alcohol (0.56 g, 41%) as a yellow oil.

Dehydration was accomplished by heating the alcohol (1.9 g, 6.8 mmol) and the methyl ester of (carboxysulfamoyl)triethylammonium hydroxide inner salt[7] (3.5 g, 14.7 mmol) in benzene (30 mL) at 50 °C for 45 min and then cooling and adding H_2O (5 mL). The organic layer was separated, washed (H_2O), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residue over silica gel with 25% EtOAc–75% hexane as eluant gave 1-(*tert*-butoxycarbonyl)-4-(2-pyridinyl)-1,2,5,6-tetrahydropyridine (0.80 g, 45%) in an oil.

The olefin was immediately dissolved in CH_2Cl_2 (5 mL) and added dropwise to CF_3CO_2H (10 mL) at 0 °C. After stirring at 0 °C for 5 min, the solvent was removed under reduced pressure and the residue slurried with 5% Na_2CO_3 solution (25 mL). Water was removed in vacuo and the residue dissolved in $CHCl_3$ (50 mL), dried (Na_2SO_4), filtered, and concentrated to give deprotected product (0.45 g, 92%) as a light yellow oil. An analytical sample of the corresponding hydrogen fumarate salt, mp 178–180 °C dec, was obtained upon recrystallization from MeOH–Et_2O.

Method B. 1-Methyl-4-(2-pyridinyl)-1,2,5,6-tetrahydropyridine Hydrogen Maleate (3b). To a cooled and stirred suspension of 1-methyl-4-(2-pyridinyl)pyridinium methylsulfate[8] (5.65 g, 20 mmol) in EtOH (100 mL) was added in one portion $NaBH_4$ (0.76 g, 20 mmol). After the vigorous evolution of gas had subsided, the reaction mixture was allowed to warm to room temperature and stirred overnight. EtOH was removed under reduced pressure and the residue partitioned between H_2O (100 mL) and Et_2O (100 mL). The aqueous extract was reextracted with three 100-mL portions of Et_2O, and the organic extracts were combined. After washing (saturated NaCl–H_2O) and drying (Na_2SO_4), the ether extracts were concentrated under reduced pressure. The crude base was converted to the hydrogen maleate salt with maleic acid in acetone and recrystallized (*i*-PrOH–Et_2O) to give 3.1 g (53%) of product, mp 126–128 °C dec.

Method C. 1-Methyl-4-(3-fluoro-2-pyridinyl)-1,2,5,6-tetrahydropyridine Hydrogen Maleate (3c). A solution of 2-bromo-3-fluoropyridine (1.76 g, 10 mmol) in Et_2O (10 mL) was added dropwise to a well-stirred mixture of *n*-BuLi in hexane (5.0 mL of a 2.18 M solution) and Et_2O (25 mL) at −55 to −60 °C. After addition was complete, the mixture was stirred at −55 °C for 30 min before adding a solution of 1-methyl-4-piperidone (1.13 g, 10 mmol) in Et_2O (15 mL) at −45 to −55 °C. The reaction mixture was allowed to warm to room temperature, poured onto ice (100 g), acidified with glacial HOAc, and extracted with Et_2O. The aqueous extract was made basic with 40% NaOH solution and then extracted with four 100-mL portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed (saturated NaCl–H_2O), dried (Na_2SO_4), filtered, and concentrated to give 2.0 g of crude alcohol as a viscous yellow oil.

$SOCl_2$ (20 mL) was added to the crude alcohol and the solution stirred at reflux for 3 h. After removal of excess $SOCl_2$ under reduced pressure, ice and 40% NaOH solution were added to the residue, and the product was extracted with four 100-mL portions

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(13) Eltze, M. *Eur. J. Pharmacol.* **1979**, *59*, 1.
(14) Unpublished results of D. Pettibone of these laboratories.

of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed (saturated NaCl–H_2O), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue over silica gel (E. Merck, 40–60-μm mesh, 250 g) and elution with 10% MeOH–90% $CHCl_3$ gave 0.75 g of pure olefin as an oil. The tetrahydropyridine base was converted to 0.75 g (24%) of the hydrogen maleate salt, mp 130–133 °C, with maleic acid in acetone–Et_2O.

Method D. 1-Methyl-4-(3-pyridinyl)-1,2,5,6-tetrahydropyridine Dihydrochloride (5). Crude alcohol obtained from the reaction of 3-pyridyl lithium (0.10 mol) with 1-methyl-4-piperidone (0.050 mol) by the procedure of method C was purified by flash chromatography over silica gel with 5% MeOH–95% $CHCl_3$ saturated with NH_3 as eluant to give 430 mg of the purified alcohol as an oil.

Dehydration of the alcohol was effected by stirring with 80% H_2SO_4 (10 mL) at 60 °C for 5 h. The cooled reaction mixture was diluted with H_2O, made basic with saturated Na_2CO_3 solution, and extracted with Et_2O. After washing (H_2O), the Et_2O extract was dried ($MgSO_4$), filtered, and concentrated to give a quantitative yield of the olefin. An analytical sample of the corresponding $2HCl·H_2O$ salt, mp 248–251 °C dec, was obtained upon recrystallization from *i*-PrOH.

Method E. 1-Methyl-4-(2-pyridinyl)piperidine Hydrogen Maleate (6). The free base of 1-methyl-4-(2-pyridinyl)-1,2,5,6-tetrahydropyridine (**3b**) was obtained from the corresponding hydrogen maleate salt (500 mg, 1.7 mmol) by stirring a solution of the salt in MeOH (150 mL) with Amberlite IRA-400 (basic) resin (3 g) for 15 min, filtering, and concentrating under reduced pressure. The residual oil was redissolved in EtOH (50 mL) and hydrogenated at room temperature and 1 atm pressure over a 10% Pd/C catalyst (150 mg) for 1 h until H_2 uptake ceased. After filtration and concentration, the residue was treated with maleic acid (180 mg) in acetone (20 mL) and the hydrogen maleate salt, mp 140–143 °C dec, was precipitated with Et_2O.

1-(*tert*-Butoxycarbonyl)-4-piperidone. A solution of 4-piperidone hydrochloride hydrate (3.1 g, 20 mmol) and Et_3N (2.02 g, 20 mmol) in DMF (25 mL) was stirred for 30 min at room temperature and then cooled to 0 °C while a solution of di-*tert*-butyl dicarbonate (4.37 g, 20 mmol) in DMF (10 mL) was added over 15 min. After addition was complete, the reaction mixture was stirred at room temperature for 18 h. Solvent was removed under reduced pressure and the residue partitioned between EtOAc–H_2O. The EtOAc layer was dried ($MgSO_4$), filtered, and concentrated to give 1-(*tert*-butoxycarbonyl)-4-piperidone (2.5 g, 63%), mp 68–69 °C. Anal. ($C_{10}H_{17}NO_3$) C, H, N.

2-Bromo-3-fluoropyridine. A solution of $NaNO_2$ (3.08 g, 44.6 mmol) in H_2O (6 mL) was added dropwise over 30 min to a well-stirred solution of 3-amino-2-bromopyridine[15] (6.92 g, 40 mmol) in concentrated HCl (25 mL) and H_2O (30 mL) at −5 °C. The solution was stirred at −5 to 0 °C for an additional 30 min and then HPF_6 (20 mL of a 60 wt % solution in H_2O) was added while the temperature was maintained at 0 °C. After 1 h at 0 °C, the diazonium salt was removed by filtration, washed successively with cold H_2O, cold *i*-PrOH, and Et_2O, and then dried under reduced pressure at room temperature for 2 h. The diazonium salt was decomposed by adding it in portions to 30 mL of mineral oil stirred at 90–100 °C. After addition was complete, the cooled reaction mixture was made basic with saturated Na_2CO_3 solution, saturated with solid K_2CO_3, and the product was extracted into four 100-mL portions of Et_2O. The ether extracts were combined, washed (saturated NaCl–H_2O), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography over silica gel (E. Merck, 40–60-μm mesh, 250 g) and elution with a 10% EtOAc–90% hexane solvent mixture afforded 2-bromo-3-fluoropyridine (1.05 g, 15%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.25–7.35 (m), 7.45 (t of d), 8.25 (d); ^{19}F NMR ($CDCl_3$) δ 112.0 (d, d, J = 4, 8 Hz).

Radioligand Binding. Procedures for determination of the extent of competitive binding of selected compounds to calf cerebral cortex α-adrenergic binding sites have been described previously.[16] The radioligands [^3H]clonidine (specific activity 22.2–23.8 Ci/mmol) and [^3H]pyrazosin (specific activity 33 Ci/mmol) used in the present studies were obtained from New England Nuclear and Amersham, respectively.

Rat Vas Deferens. Rat vas deferens were extirpated from Sprague–Dawley rats (250–350 g) and prepared for field stimulation as described elsewhere.[17] pA_2 values were estimated on the basis of one or two concentrations of antagonists and a minimum of three tissues for each concentration[18] or by Schild plot analysis[19] using a minimum of three concentrations of antagonists and at least three tissues for each concentration. Clonidine and methoxamine were used as α_2- and α_1-adrenergic agonists, respectively, according to protocols described previously.[17]

Tetrabenazine Antagonism. Groups of Carworth Farm female mice (CF-1 strain), 18–22 g, were administered tetrabenazine (45 mg/kg ip) 15 min after administration of the test compounds (10 per treatment group) and observed 30 min later for ptosis. Ptosis was graded on the basis of at least 50% closure of the eyelids. ED_{50} and standard deviation values were determined by probit analysis according to the method of Miller and Tainter.[20]

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Registry No. **2** (X = H, R = BOC), 90606-75-0; **2** (X = F, R = Me), 90606-76-1; **2** (X = H, R = Me), 75446-42-3; **3** (X = H, R = BOC), 90606-77-2; **3a**, 50461-51-3; **3a** hydrogen fumarate, 90606-78-3; **3b**, 90606-79-4; **3b** hydrogen maleate, 90606-80-7; **3c**, 90606-81-8; **3c** hydrogen maleate, 90606-82-9; **3d** hydrogen maleate, 90606-84-1; **3e** sesqui hydrogen tartrate, 90606-86-3; **4** hydrogen maleate, 90606-88-5; **5**, 90606-89-6; **5**·2HCl, 90606-90-9; **6**, 85237-63-4; **6** hydrogen maleate, 90606-91-0; 2-bromopyridine, 109-04-6; 1-methyl-4-piperidone, 1445-73-4; 3-pyridyl lithium, 60573-68-4; 1-*tert*-butoxycarbonyl-4-piperidone, 79099-07-3; 1-methyl-4-(2-pyridinyl)pyridinium methyl sulfate, 74801-37-9; 2-bromo-3-fluoropyridine, 40273-45-8; 4-piperidone hydrochloride, 41979-39-9; 3-amino-2-bromopyridine, 39856-58-1.

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