Substituted (Pyrroloamino)pyridines: Potential Agents for the Treatment of Alzheimer's Disease

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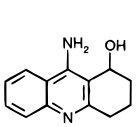
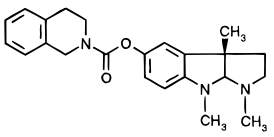
A novel series of substituted (pyrroloamino)pyridines was synthesized, and the compounds were evaluated for cholinomimetic-like properties *in vitro* (inhibition of [^{3}H]quinuclidinyl benzilate binding) and *in vivo* (reversal of scopolamine-induced dementia) as potential agents for the treatment of Alzheimer's disease. Compounds displaying significant activity were more broadly evaluated, which revealed the presence of a desirable adrenergic component of activity. The synthesis and structure−activity relationships for this series is presented, along with the biological profiles of selected compounds.

Introduction

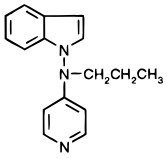
Alzheimer's disease (AD) is an age-related, chronic neuronal degenerative disorder occurring in middle or late life. The disease is characterized by a progressive dementia, which is associated with both severe disability in performing the activities of everyday life and a reduced life expectancy after onset of the disease. The well-known cholinergic hypothesis[1,2] of AD was based on accumulated evidence suggesting that enzymes involved in the synthesis and/or hydrolysis of acetylcholine were deficient in brains of AD patients. This breakdown of central cholinergic transmission resulted in efforts to treat AD with cholinomimetic agents that either augment the synthesis or inhibit the hydrolysis of acetylcholine. On the basis of this approach, the potent acetylcholinesterase inhibitors velnacrine[3] (HP 029) and HP 290,[4] discovered in our laboratories, were advanced for clinical evaluation.



velnacrine



HP 290



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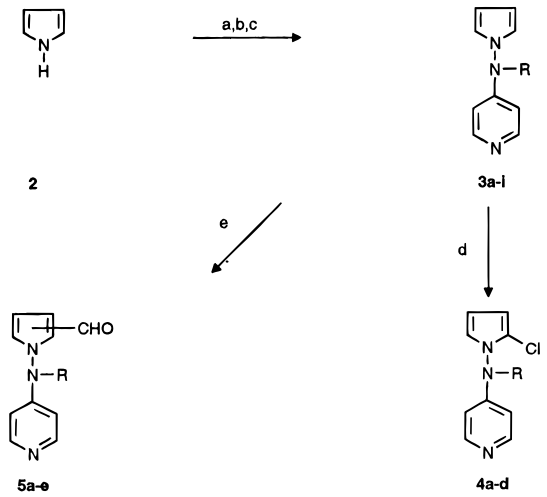
Neuropathological studies of brains from Alzheimer's patients and age-matched controls demonstrated that other neurotransmitters are also affected in the disease process, including catecholamines and particularly norepinephrine. In addition to cholinomimetic agents, a program was also initiated to discover compounds which would mitigate multiple biochemical deficits associated with AD[5] and thus possibly be more effective in a broader group of patients than pure cholinomimetics. As a class, the aminopyridines were known to enhance release of both acetylcholine and norepinephrine.[6] Since more lipophilic aminopyridine analogs had not been extensively investigated, the synthesis of a series of (pyrroloamino)pyridines was initiated. The compound **8a** emerged as an early lead from this program, and the biological profile of **8a** shows a unique combination of adrenergic and cholinomimetic-like properties. The structural features of **8a** led to investigation of more lipophilic analogs, which resulted in the synthesis and characterization of *N*-propyl-*N*-(4-pyridinyl)-1*H*-indol-1-amine (besipirdine, **1**).[7,8] The synthesis and structure−activity relationships of **8a** and related (pyrroloamino)-pyridine analogs constitute the subject of this paper, while **1** and related analogs are described in our companion paper.[9]

Scheme 1[a]



[a] (a) KOH, hydroxylamine *O*-sulfonic acid, DMF, 0−30 °C, 3 h; (b) 4-chloropyridine hydrochloride, NMP, 80 °C, 5 h; (c) NaH, R-X or dimethyl sulfate, DMF, 0−20 °C, 3 h; or acetic anhydride, 20 °C, 1 h; (d) NCS, THF, 5−20 °C, 20 h; (e) $POCl_3$, DMF, DCE, 0−80 °C, 3 h.

Chemistry

As shown in Scheme 1, pyrrole **(2)** was N-aminated with hydroxylamine *O*-sulfonic acid and subsequently condensed with 4-chloropyridine to afford pyrroloaminopyridine **3a** (R = H). Alkylation of **3a** with sodium hydride and dimethyl sulfate or an alkyl halide provided tertiary amines **3b**−**h**, and standard acylation afforded amide **3i** (Table 1). Chlorination of **3a**−**d** with *N*-chlorosuccinimide gave ((2-chloropyrrolo)amino)pyridines **4a**−**d**. The 2- and 3-pyrrolyl aldehydes **5a**−**e** were obtained by treatment of **3a,b,d** under Vilsmeier conditions and chromatographic separation of the isomeric aldehydes.

As shown in Scheme 2, 2-pyrrolyl aldehyde **5b** was reduced with $NaBH_4$ to give the primary alcohol **6**, and

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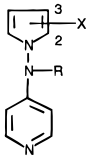
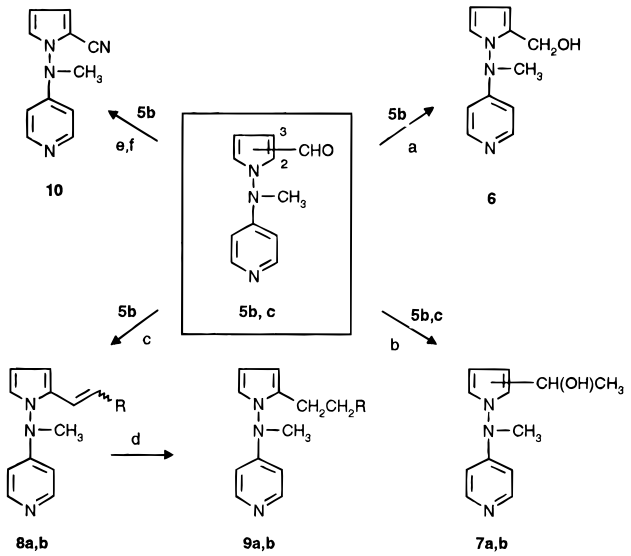
Table 1. Substituted (Pyrroloamino)pyridines[a]



compd	R	X	start. mat.	mp, °C	% yield[b]	recrystn[c] solvent	formula
3a	H	H	**2**	153−154	32	A	$C_9H_9N_3$
3b	CH_3	H	**3a**	226−227	55	B	$C_{10}H_{11}N_3$·HCl
3c	*n*-C_2H_5	H	**3a**	224−225	59	B	$C_{11}H_{13}N_3$·HCl
3d	*n*-C_3H_7	H	**3a**	232−233	58	B-C	$C_{12}H_{15}N_3$·HCl
3e	C_4H_9	H	**3a**	178−179	60	B	$C_{13}H_{17}N_3$·HCl
3f	$CH_2C_6H_5$	H	**3a**	210−211	43	D−C	$C_{12}H_{15}N_3$·HCl
3g	$CH_2CH{=}CH_2$	H	**3a**	218−219	59	B−C	$C_{12}H_{13}N_3$·HCl
3h	$CH_2C{\equiv}CH$	H	**3a**	230−231	57	B	$C_{12}H_{11}N_3$·HCl
3i	$COCH_3$	H	**3a**	220−222	80	E−C	$C_{11}H_{11}N_3O$·HCl
4a	H	2-Cl	**3a**	172−173	65	B−C	$C_9H_8ClN_3$·HCl
4b	CH_3	2-Cl	**3b**	230−231	23	B−C	$C_{10}H_{10}ClN_3$·HCl
4c	C_2H_5	2-Cl	**3c**	206−207	22	B−C	$C_{11}H_{12}ClN_3$·HCl
4d	*n*-C_3H_7	2-Cl	**3d**	210−211	19	B−C	$C_{12}H_{14}ClN_3$·HCl
5a	H	2-CHO	**3a**	165−166	23	B	$C_{10}H_9N_3O{\cdot}C_4H_4O_4$[d]
5b	CH_3	2-CHO	**3b**	118−119	58	B	$C_{11}H_{11}N_3O{\cdot}C_4H_4O_4$[d]
5c	CH_3	3-CHO	**3b**	139−140	11	B	$C_{11}H_{11}N_3O{\cdot}C_4H_4O_4$[d]
5d	*n*-C_3H_7	3-CHO	**3d**	144−146	28	B−C	$C_{13}H_{15}N_3O{\cdot}C_4H_4O_4$[d]
5e	*n*-C_3H_7	2-CHO	**3d**	95−97	25	B−C	$C_{13}H_{15}N_3O{\cdot}C_4H_4O_4$[d]
6	CH_3	2-CH_2OH	**5b**	150−151	77	B−F	$C_{11}H_{13}N_3O$
7a	CH_3	2-$CH(OH)CH_3$	**5b**	118−119	72	B−C	$C_{12}H_{15}N_3O{\cdot}C_4H_4O_4$[d]
7b	CH_3	3-$CH(OH)CH_3$	**5c**	95−96	55	C	$C_{12}H_{15}N_3O$
8a	CH_3	2-$CH{=}CH_2$	**5b**	87−88	22	B−C	$C_{12}H_{13}N_3{\cdot}C_4H_4O_4$[d]
8b	CH_3	2-$CH{=}CHC_6H_5$	**5b**	244−245	69	B−C	$C_{18}H_{17}N_3$·HCl
9a	CH_3	2-C_2H_5	**8a**	197−198	49	B−C	$C_{12}H_{15}N_3$·HCl
9b	CH_3	2-$(CH_2)_2C_6H_5$	**8b**	173−174	61	D−C	$C_{18}H_{19}N_3$·HCl
10	CH_3	2-CN	**5b**	251−252	71	B	$C_{11}H_{10}N_4$·HCl

[a] All compounds exhibited IR, MS, and ^{1}H-NMR spectra consistent with the structure, and elemental analyses (C,H,N) were within ±0.4%. [b] Isolated yield; yields were not optimized. [c] A = benzene; B = 2-propanol; C = ethyl ether; D = absolute ethanol; E = methanol; F = petroleum ether. [d] Acid maleate salt.

Scheme 2[a]



[a] (a) $NaBH_4$, *i*-C_3H_7OH, 20 °C, 20 h; (b) CH_3MgBr, THF, 5−20 °C, 3 h; (c) *n*-BuLi, $CH_3P(C_6H_5)_3Br$ or $C_6H_5CH_2P(C_6H_5)_3Cl$, DCM, 0 °C, 1 h; (d) 10% Pd/C, H_2, C_2H_5OH, 20 °C, 1 h; (e) H_2NOH−HCl, pyridine, 20 °C, 1 h; (f) benzenesulfonyl chloride, 90 °C, 0.5 h.

addition of methylmagnesium bromide to **5b** or the 3-pyrrolyl aldehyde **5c** provided secondary alcohols **7a,b**, respectively. Wittig olefination of **5b** with *n*-butyllithium and methyltriphenylphosphonium bromide or benzyltriphenylphosphonium chloride afforded alkenes **8a**,**b**, which were catalytically reduced to alkanes **9a**,**b**. Conversion of **5b** to the oxime derivative and subsequent dehydration with benzenesulfonyl chloride gave the ((2-cyanopyrrolo)amino)pyridine **10**.

Biological Results and Discussion

One goal of our research was the discovery of agents which would mitigate multiple biochemical deficits associated with AD, and compounds displaying a combination of cholinomimetic and adrenergic properties were considered highly desirable. As shown in Table 2, the majority of the compounds from this series displayed moderate to weak affinities for central muscarinic binding sites as evidenced by inhibition of [^{3}H]-quinuclidinyl benzilate ([^{3}H]QNB) binding *in vitro*.[10] Zinc and other heavy metals or sulfhydryl reagents were shown to increase the affinity of [^{3}H]QNB binding sites for cholinergic agonists (e.g. oxotremorine).[11] In our laboratory a muscarinic agonist-like profile for a compound is associated with a ratio of [^{3}H]QNB IC_{50} values equal to or greater than 3 obtained in the absence (−Zn) and presence (+Zn) of zinc.[12] As shown in Table 2, the enhancement in binding affinity observed in the presence of zinc suggested that many of these compounds might be cholinergic agonists. Most of these compounds were also active *in vivo* with respect to antagonizing scopolamine-induced deficits in the scopolamine dementia dark avoidance paradigm (SDDA).[13] However, only compounds **7b** and **8a** significantly antagonized tetrabenazine-induced ptosis (TBZ),[14] which is a property associated with many clinically efficacious antidepressants that augment central adrenergic mechanisms. These compounds represented early leads in our search

Table 2. Biological Data for Substituted (Pyrroloamino)pyridines[a]

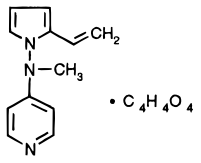
compd	QNB[b] IC_{50} (μM) −Zn	QNB[b] IC_{50} (μM) +Zn	ratio −Zn/+Zn	TBZ[c] ED_{50} (mg/kg, ip)	SDDA[d] A, NA, or NT, mg/kg, sc (% response)
3a	184 (98−343)	43 (33−55)	4.3	>20	A (4/8) 0.31 (21), 0.63 (21), 2.5 (47), 5.0 (36)
3b	70 (54−90)	13 (7−21)	5.4	>20	A (1/6) 5.0 (29)
3c	120 (91−152)	9.5 (4.7−18.8)	12	>20	NA
3d	21.5 (11.6−39.6)	6.5 (4.8−8.7)	3.3	>20	A (3/6) 0.16 (33), 0.63 (27), 2.5 (27)
3e	12.5 (6.7−23)	4.0 (1.4−11)	3.1	>20	A (1/6) 0.63 (20)
3f	13.5 (8.2−20.2)	3.5 (2.1−4.6)	3.9	>20	A (1/6) 0.16 (20)
3g	27 (22−34)	6.9 (5.9−8.2)	3.9	>20	A (2/6) 0.16 (20), 0.63 (20)
3h	76.4 (40−147)	9.0 (4−20)	8.5	>20	A (4/6) 0.02 (20), 0.04 (27), 0.16 (47), 0.31 (27)
3i	>1000	NT			NT
4a	76.2 (56−104)	13 (7.6−20)	5.9	>20	NA
4b	43 (34−56)	6.9 (4.8−10)	6.2	>20	NA
4c	33 (25−45)	5.4 (2.3−13)	6.1	>20	A (3/6) 0.63 (20), 1.25 (36), 2.5 (27)
4d	8.6 (4.2−17.4)	2.6 (2.0−3.3)	3.3	>20	A (1/6) 2.5 (27)
5a	721 (567−916)	86 (52−142)	8.4	>20	A (4/6) 0.16 (20), 0.31 (27), 0.63 (43), 1.25 (20)
5b	52 (34−78)	24 (15−38)	2.2	>20	A (6/6) 0.16 (50), 0.31 (53), 0.63 (27), 1.25 (60), 2.5 (50), 5.0 (31)
5c	185 (110−311)	33 (25−40)	5.6	>20	A (4/6) 0.31 (20), 0.63 (33), 1.25 (29), 5.0 (47)
5d	138 (91−208)	11 (8.7−14)	12.5	>20	NT
5e	51 (30−88)	14 (5.7−33)	3.6	>20	NA
6	39 (20−74)	26 (13−51)	1.5	>20	NT
7a	173 (101−296)	23 (18−29)	7.5	>20	NA
7b	24 (12−48)	11 (6.1−19)	2.2	10 (9.4−12)	A (3/6) 0.16 (20), 0.31 (20), 1.25 (27)
8a	18 (14−23)	8.8 (5.1−15)	2.0	8.3 (7.8−9.0)	A (6/6) 0.16 (27), 0.31 (33), 0.63 (33), 1.25 (33), 2.5 (27), 5.0 (20)
8b	17 (8.2−33)	1.6 (0.53−46)	10.6	>20	A (2/6) 2.5 (20), 5.0 (33)
9a	22 (17−29)	6.4 (4.9−8.3)	3.4	>20	A (2/6) 0.63 (20), 5.0 (27)
9b	8.1 (6.5−9.9)	3.0 (1.3−5.9)	2.7	>20	A (1/6) 0.31 (33)
10	295 (181−480)	24 (16−35)	12.3	>20	A (2/6) 1.25 (40), 5.0 (20)
1	3.0 (1.9−4.6)	0.94 (0.56−1.6)	3.2	3.1 (2.9−3.4)	A (5/6) 0.02 (24), 0.04 (30), 0.08 (33), 0.16 (27), 0.63 (40)
oxotremorine	2.7 (2.2−3.7)	0.66 (0.43−1.0)	4.2		
amitriptyline	0.3 (0.29−0.32)			1.5 (1.0−2.1)	

[a] IC_{50} and ED_{50} values are corrected for the percentage of base compound in the case of salts. Numbers in parentheses are 95% confidence limits unless otherwise noted. [b] Inhibition of [^{3}H]quinuclidinyl benzilate (QNB) binding, rat forebrain membranes, in the absence (−Zn) and presence (+Zn) of zinc. [c] Prevention of tetrabenazine-induced (TBZ) ptosis by intraperitoneal compound administration in mice. [d] Antagonism of scopolamine-induced behavioral deficits in mice in the scopolamine dementia dark avoidance (SDDA) paradigm. A cutoff was defined for the scopolamine−vehicle group as the value for the animal with the second longest latency time. Results are reported as active (A), not active (NA) or not tested (NT) with the number of active (≥20% response) dosages versus the total number of dosages evaluated in parentheses. For active compounds, the second line of data represents the active doses (mg/kg, sc) with the percent response (i.e. the percent of animals in the scopolamine−drug group with latencies greater than the cutoff time) in parentheses.

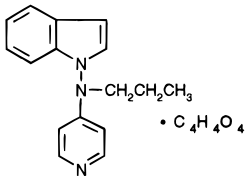
for agents with broader biochemical profiles, and **8a** was selected for further evaluation.

The biological profile of **8a** is summarized in Table 3 and compared with compound **1**, which was selected from a later series. *In vitro* both **8a** and **1** displayed affinity for central α_2-adrenergic receptors as evidenced by inhibition of [^{3}H]clonidine[15] and [^{3}H]yohimbine[16] binding, and both compounds were comparatively weaker with respect to affinity for α_1-adrenergic binding sites as evidenced by inhibition of [^{3}H]WB4101 binding.[17] With respect to biogenic amine uptake, **8a** was a considerably weaker inhibitor of norepinephrine,[18] dopamine,[18] and serotonin[19] uptake than **1**. Although **8a** has affinity for central muscarinic receptors as

Table 3. Biological Profiles of **8a** and **1**



8a



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	IC_{50} (μM)[a]	
in vitro assays	**8a**	**1**
Receptor Binding: Adrenergic		
[^{3}H]clonidine (α_2, cortex)[b]	0.21 (0.08−0.59)	0.33 (0.22−0.51)
[^{3}H]yohimbine (α_2, cortex)[b]	0.95 (0.58−1.6)	0.25 (0.18−0.33)
[^{3}H]WB4101 (α_1, whole brain)[c]	5.9 (3.4−10)	10 (6.4−17)
Biogenic Amine Uptake[d]		
[^{3}H]norepinephrine (whole brain)	14 (1−20)	0.43 (0.29−1.7)
[^{3}H]dopamine (striatum)	>20	0.41 (0.23−0.73)
[^{3}H]serotonin (whole brain)	>20	2.6 (1.4−5.0)
Receptor Binding: Cholinergic		
[^{3}H]QNB (muscarinic, forebrain)[e]	18 (14−23)	3.0 (1.9−4.6)
$+Zn^{2+}$	8.8 (5.1−15)	0.94 (0.56−1.6)
[^{3}H]pirenzepine (M_1, cortex)[b]	5.1 (2.5−10)	1.3 (1.0−1.8)
AChE Inhibition		
acetylthiocholine (striatum)[f]	>100	>100

in vivo assays	**8a**	**1**
TBZ[g] ED_{50} (mg/kg, ip)	8.3 (7.8−9.0)	3.1 (2.9−3.4)
SDDA[h] (mg/kg, sc)	active at 0.16, 0.31, 0.63, 1.25, 2.5, 5.0	active at 0.02, 0.04, 0.08, 0.16, 0.63

[a] IC_{50} and ED_{50} values are corrected for the percentage of base compound in the case of salts. Numbers in parentheses are 95% confidence limits. Compounds **8a** and **1** were evaluated as maleate salts. [b] Rat cortical membranes. [c] Rat whole brain minus cerebella. [d] Rat brain synaptosomes. [e] Inhibition of [^{3}H]quinuclidinyl benzilate (QNB) binding, rat forebrain membranes. [f] Acetylcholinesterase (AChE) inhibition (rat striatum) using acetylthiocholine as substrate. [g] Prevention of tetrabenazine-induced (TBZ) ptosis (mice). [h] Scopolamine dementia dark avoidance (SDDA) paradigm (mice).

evidenced by inhibition of [^{3}H]QNB and [^{3}H]pirenzepine[20] binding, the compound was less potent than **1**. Neither **8a** nor **1** significantly inhibited striatal acetylcholinesterase (AChE).[21] *In vivo*, both **8a** and **1** were active with respect to reversing scopolamine-induced deficits in the SDDA paradigm and both compounds enhanced adrenergic mechanisms as evidenced by prevention of tetrabenazine-induced ptosis. However, **1** displayed a broader, more robust profile with respect to adrenergic and cholinomimetic-like effects than **8a**, and **1**[22] was advanced to clinical trials.

Conclusions

A series of (pyrroloamino)pyridine analogs was synthesized and evaluated as potential agents for the treatment of Alzheimer's disease. Compound **8a** was selected for further evaluation. The compound displayed affinity for central α_2-adrenergic and muscarinic receptors but was weakly active with respect to inhibition of biogenic amine uptake. Compound **8a** does not inhibit acetylcholinesterase but is active *in vivo* with respect to antagonizing scopolamine-induced deficits in the SDDA paradigm, suggesting potential utility for Alzheimer's disease. In addition, **8a** augments adrenergic mechanisms as suggested by weak *in vitro* inhibition of norepinephrine uptake and *in vivo* prevention of tetrabenazine-induced ptosis.

Experimental Section

All structures are supported by their IR (Perkin-Elmer 547), MS (Finnigan 4000 GC−MS equipped with an INCOS data system), and ^{1}H-NMR (Varian XL-200) spectra. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. HPLC separations were performed on a Waters Prep LC/System 500A using a Prep Pak-500/Silica cartridge. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

***N*-Aminopyrrole**. To a solution of pyrrole (10.7 g, 0.16 mol, **2**) in 150 mL of DMF at 0 °C was added milled KOH (40 g, 0.8 mol), followed by hydroxylamine *O*-sulfonic acid (20 g, 0.18 mol) added portionwise over 30 min. After stirring at ambient temperature for 1 h, the mixture was filtered, and the filtrate was poured into 1 L of ice−water and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. The resultant oil was eluted on a silica gel column with dichloromethane (DCM) via HPLC to give *N*-aminopyrrole as a clear oil: 5 g (38%); ^{1}H-NMR ($CDCl_3$) δ 6.20 (t, 2H, J = 8 Hz), 6.70 (t, 2H, J = 8 Hz), 8.30 (broad s, 2H); IR ($CHCl_3$) 3325 cm^{-1}, NH_2; EI-MS *m/e* 82. Anal. ($C_4H_6N_2$) C, H, N.

4-(1*H*-Pyrrol-1-ylamino)pyridine (3a). To 150 mL of *N*-methyl-2-pyrrolidinone were added *N*-aminopyrrole (18 g, 0.22 mol) and 4-chloropyridine hydrochloride (17 g, 0.14 mol), and the mixture was stirred at 80 °C for 5 h. After cooling, the mixture was poured into 300 mL of water, basified with Na_2CO_3, and extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the resultant oil eluted on a silica gel column with ethyl acetate via HPLC to give 12 g of a light tan solid, mp 150 °C. A sample was recrystallized from benzene to give **3a** as light tan crystals: mp 153−154 °C; ^{1}H-NMR ($CDCl_3$) δ 6.20 (t, 2H, J = 8 Hz), 6.30 (d, 2H, J = 10 Hz), 6.70 (t, 2H, J = 8 Hz), 8.30 (d, 2H, J = 10 Hz), 8.40 (broad s, 1H); IR ($CHCl_3$) 3270 cm^{-1}, NH; EI-MS *m/e* 159. Properties of **3a** are included in Table 1.

4-[*N*-Methyl-*N*-(1*H*-pyrrol-1-yl)amino]pyridine Hydro-

chloride (3b). To a suspension of NaH (50% oil dispersion, 1.5 g, 0.030 mol) in 5 mL of DMF at 0 °C, was added a solution of **3a** (4g, 0.025 mol) in 10 mL of DMF. After warming to 50 °C for 30 min, the solution was cooled to 0 °C, and a solution of dimethyl sulfate (3.8 g, 0.03 mol) in 5 mL of DMF was slowly added. After 30 min, the mixture was stirred with 300 mL of ice−water and extracted with DCM (3 × 100 mL). The organic extract was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to give 4 g of a yellow oil, which was eluted on a silica gel column with ethyl acetate via HPLC to afford 3.5 g of a yellow oil. The oil was dissolved in 2-propanol and converted to the hydrochloride salt by addition of ethereal HCl to give **3b** as white crystals: 3.1 g; mp 226−227 °C; ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 3H), 6.30 (t, 2H, J = 3 Hz), 6.60 (broad s, 2H), 6.75 (t, 2H, J = 3 Hz), 8.30 (broad s, 2H), 15.80 (broad s, 1H); EI-MS *m/e* 174. Properties of **3b**, and of **3c**−**h** prepared in a similar manner using the appropriate alkylhalide, are included in Table 1.

***N*-(4-Pyridinyl)-*N*-(1*H*-pyrrol-1-yl)acetamide Hydrochloride (3i)**. A solution of **3a** (4 g, 0.025 mol) in 25 mL of acetic anhydride was stirred at ambient temperature for 1 h and then evaporated *in vacuo* to an oil. This oil was stirred with water, basified with Na_2CO_3, and extracted with DCM (3 × 100 mL). The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to a solid (6 g), which was purified by flash chromatography (silica, 20% EtOAc/DCM) to give 5 g of a white solid, mp 103−105 °C. This solid was converted to the hydrochloride salt and recrystallized from methanol−ether (1:10) to give 4.8 g of **3i** as a white solid: mp 220−222 °C dec; ^{1}H-NMR (DMSO-d_6) δ 2.04 (s, 3H), 6.35 (t, 2H, J = 3 Hz), 7.24 (t, 2H, J = 3 Hz), 7.48 (d, 2H, J = 4 Hz), 8.80 (d, 2H, J = 4 Hz); IR (KBr) 1660 cm^{-1}, C(=O)N; EI-MS *m/e* 201. Properties of **3i** are included in Table 1.

4-[*N*-(2-Chloro-1*H*-pyrrol-1-yl)-*N*-methylamino]pyridine Hydrochloride (4b). To a solution of **3b** (7.7 g, 0.044 mol) in 300 mL of THF at 5 °C was added *N*-chlorosuccinimide (6.1 g, 0.046 mol). After stirring at ambient temperature for 60 h, the mixture was stirred with an aqueous solution of $NaHSO_3$ and extracted with ether (3 × 100 mL), and the organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to give a brown oil, 9.5 g. The oil was purified by HPLC (silica, EtOAc) to give 4.4 g (48%) of a yellow oil, which was eluted by column chromatography (alumina, ether) to provide 2.4 g of an oil. This oil was converted to the hydrochloride salt in 2-propanol, diluting with ether to give **4b** as white crystals: 2.5 g; mp 230−231 °C; ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 3H), 6.30−6.50 (m, 3H), 6.80 (s, 1H), 7.20 (broad s, 1H), 8.40 (broad s, 2H), 16.40 (broad s, 1H); EI-MS *m/e* 207. Properties of **4b**, and of **4a,c,d** prepared in a similar manner, are included in Table 1.

1-[*N*-Methyl-*N*-(4-pyridinyl)amino]pyrrole-2-carboxaldehyde Maleate (5b) and 1-[*N*-Methyl-*N*-(4-pyridinyl)-amino]pyrrole-3-carboxaldehyde Maleate (5c). To cold DMF (7 g, 0.096 mol) was slowly added $POCl_3$ (14.7 g, 0.096 mol), and the resultant clear complex was stirred 1 h at ambient temperature and then dissolved in 25 mL of dichloroethane (DCE). To this was slowly added a solution of **3b** (15 g, 0.087 mol) in 25 mL of DCE. After stirring 12 h at 95 °C, the mixture was cooled, and a solution of sodium acetate trihydrate (60 g, 0.44 mol) in 200 mL of water was slowly added. The mixture was stirred 1 h at 95 °C, cooled, stirred with 500 mL of water, and then basified with Na_2CO_3 solution. An oil separated and was extracted with DCM (3 × 100 mL). The organic phase was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to give a brown oil, 18 g. The oil was purified by HPLC (silica, EtOAc) to afford 10.2 g of the 2-carboxaldehyde as a light brown solid, mp 71−74 °C. A 2.5 g portion of the solid was converted to the maleate salt and recrystallized from 2-propanol to give 3.4 g of **5b** as white crystals: mp 118−119 °C; ^{1}H-NMR ($CDCl_3$) δ 3.65 (s, 3H), 6.30 (s, 2H), 6.40−6.60 (m, 3H), 7.15 (broad s, 2H), 8.20 (d, 2H, J = 4 Hz), 9.58 (s, 1H), 16.35 (broad s, 2H); IR ($CHCl_3$) 1640 cm^{-1}, CHO; EI-MS *m/e* 201. Further elution afforded 2.0 g of the 3-carboxaldehyde as a light brown oil. This oil was converted to the maleate salt and recrystallized from 2-propanol to give 1.9 g of **5c** as white crystals: mp 139−140 °C; ^{1}H-NMR ($CDCl_3$) δ 3.76 (s, 3H), 6.35 (s, 2H), 6.70 (d, 2H, J = 3 Hz), 6.88 (d, 2H, J = 1 Hz), 7.50 (d, 1H, J = 1 Hz), 8.50 (d, 2H, J = 3 Hz), 9.87 (s, 1H), 13.20 (broad s, 2H); IR ($CHCl_3$) 1640 cm^{-1}, CHO; EI-MS *m/e* 201. Properties of **5b,c**, and **5a,d,e** prepared in a similar manner, are included in Table 1.

1-[*N*-Methyl-*N*-(4-pyridinyl)amino]-1*H*-pyrrole-2-methanol (6). To a solution of **5b** (8 g, 0.04 mol) in 100 mL of 2-propanol was added $NaBH_4$ (3g, 0.08 mol). After stirring for 2 h at ambient temperature, water was added, and the mixture was extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to give 7.6 g of a pale yellow oil, which was purified by HPLC (silica, 5% MeOH/EtOAc) to afford 6.2 g of a pale yellow solid, mp 145−148 °C. A 4 g portion of this solid was recrystallized from 2-propanol/petroleum ether (1:10) to give 2.3 g of **6** as white crystals: mp 150−151 °C; ^{1}H-NMR ($CDCl_3$) δ 2.68 (broad s, 1H), 3.46 (s, 3H), 4.40 (dd, 2H, J = 4, 8 Hz), 6.20 (d, 2H, J = 2 Hz), 6.22 (m, 2H), 6.67 (m, 1H), 8.23 (d, 2H, J = 2 Hz); IR ($CHCl_3$) 3240 cm^{-1}, OH; EI-MS *m/e* 203. Properties of **6** are included in Table 1.

1-{1-[*N*-Methyl-*N*-(4-pyridinyl)amino]pyrrol-2-yl}-ethanol Maleate (7a). To a cooled solution of **5b** (3g, 0.015 mol) in 50 mL of THF was slowly added CH_3MgBr (3.2 M in ether, 5.1 mL, 0.0164 mol). After stirring for 2 h at ambient temperature, the mixture was stirred with 300 mL of NH_4Cl solution and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to give 3.4 g of a yellow oil. This oil was purified by HPLC (silica, 5% MeOH/DCM) to afford 3.0 g of a clear oil, which was converted to the maleate salt and recrystallized from 2-propanol/ether (1:10) to give 3.6 g of **7a** as white crystals: mp 118−119 °C; ^{1}H-NMR (DMSO-d_6) δ 1.35 (d, 3H, J = 3 Hz), 3.60 (s, 3H), 4.30 (m, 1H), 6.08 (s, 2H), 6.10−6.22 (m, 2H), 6.52 (d, 2H, J = 2 Hz), 6.95 (t, 1H, J = 2 Hz), 8.42 (d, 2H, J = 2 Hz); IR (KBr) 3240 cm^{-1}, OH; EI-MS *m/e* 217. Properties of **7a**, and of **7b** prepared in a similar manner, are included in Table 1.

***N*-(2-Ethenyl-1*H*-pyrrol-1-yl)-*N*-methyl-4-pyridinamine Maleate (8a)**. To *n*-BuLi (2.1 M in hexane, 25 mL, 0.052 mol), diluted with 50 mL of ether and cooled with an ice-bath, was slowly added methyltriphenylphosphonium bromide (18 g, 0.050 mol), followed by addition of a solution of **5b** (8 g, 0.040 mol) in 100 mL of ether. After stirring with cooling for 1 h, water was added, and the aqueous layer was extracted with DCM (2 × 100 mL). The combined organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to a brown oil, which was purified by HPLC (silica, EtOAc) to give a yellow oil, 5.4 g. The oil was converted to the maleate salt and recrystallized from 2-propanol/ether (1:10) to give **8a** as white crystals: 2.7 g; mp 87−88 °C; ^{1}H-NMR (DMSO-d_6) δ 3.55 (s, 3H), 5.05 (d, 1H, J = 3 Hz), 5.50 (d, 1H, J = 3 Hz), 6.08 (s, 2H), 6.28 (t, 1H, J = 2 Hz), 6.35 (d, 1H, J = 2 Hz), 6.57 (d, 2H, J = 3 Hz, broad s, 1H), 7.07 (s, 1H), 8.45 (d, 2H, J = 2 Hz), 14.20 (broad s, 2H); EI-MS *m/e* 199. Properties of **8a**, and **8b** prepared in a similar manner, are included in Table 1.

***N*-(2-Ethyl-1*H*-pyrrol-1-yl)-*N*-methyl-4-pyridinamine Hydrochloride (9a)**. A solution of **8a** (5.2 g, 0.026 mol) in 250 mL of ethanol containing PtO_2 (350 mg) was hydrogenated in a Parr apparatus at 50 psi for 3 h at ambient temperature. After filtering, the solvent was evaporated *in vacuo* to a yellow oil (5 g), which was purified by flash chromatography (silica, 25% DCM/EtOAc) to give 3.9 g of a pale yellow oil. This oil was converted to the hydrochloride salt and recrystallized from 2-propanol/ether (1:10) to afford 3.0 g of **9a** as white crystals: mp 197−198 °C; ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 6 Hz), 2.25−2.35 (m, 2H), 3.64 (s, 3H), 6.00 (m, 3H), 6.28 (dd, 1H, J = 4, 2 Hz), 6.64 (d, 1H, J = 2 Hz), 8.20 (broad s, 1H), 8.50

(broad s, 1H), 16.35 (broad s, 1H); EI-MS *m/e* 201. Properties of **9a**, and **9b** prepared in a similar manner, are included in Table 1.

***N*-(2-Cyano-1*H*-pyrrol-1-yl)-*N*-methyl-4-pyridinamine Hydrochloride (10)**. To a solution of **5b** (9.5 g, 0.047 mol) in 50 mL of pyridine was added $H_2N-OH\cdot HCl$ (10 g, 0.14 mol). After stirring at ambient temperature for 1 h, the solvent was evaporated *in vacuo*, and the residue was stirred with water and extracted with ether (3 × 100 mL). The ether layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to a yellow oil (13 g), which was purified by HPLC (silica, EtOAc) to give 9.2 g of an isomeric mixture of oximes: IR ($CHCl_3$) 3240, NOH, 1640 cm^{-1}, C═N; EI-MS *m/e* 216.

To a solution of the oximes (4.3 g, 0.024 mol) in 50 mL of ether was added pyridine (2g, 0.024 mol) followed by benzenesulfonyl chloride (4.2 g, 0.024 mol). After warming on a steam bath to dryness (30 min), the residue was cooled, stirred with water, basified with Na_2CO_3, and extracted with ethyl acetate (2 × 100 mL). The organic extract was washed with water and saturated NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* to a brown waxy residue (4 g), which was purified by HPLC (silica, EtOAc) to give a white solid, 3.2 g, mp 88−90 °C. This material was converted to the hydrochloride salt and recrystallized from 2-propanol to give **10** as white crystals: 3.3 g; mp 251−252 °C; ^{1}H-NMR (DMSO-d_6) δ 3.75 (s, 3H), 6.48 (t, 1H, J = 3 Hz), 6.85 (broad s, 2H), 7.06−7.15 (m, 1H), 7.32 (d, 1H, J = 3 Hz), 8.55 (d, 1H, J = 3 Hz); IR (KBr) 2250 cm^{-1}; C≡N; EI-MS *m/e* 198. Properties of **10** are included in Table 1.

Biological Methods. Procedural details for *in vitro* displacement of [^{3}H]quinuclidinyl benzilate (QNB),[12] [^{3}H]clonidine,[15] [^{3}H]yohimbine,[16] [^{3}H]WB4101,[17] and [^{3}H]pirenzepine[20] binding; *in vitro* inhibition of biogenic amine uptake;[18,19] *in vitro* inhibition of acetylcholinesterase[21] (AChE); and *in vivo* prevention of tetrabenazine (TBZ) induced ptosis[14] and reversal of scopolamine-induced dementia dark avoidance[13] (SDDA) were previously reported.

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