Fumarate (28). A solution of 3-[[2-[2-[4-(benzyloxy)phenyl]-acetamido]ethyl]amino]-1-[2-[(*N*-methylcarbamoyl)methoxy]-phenoxy]propan-2-ol (prepared by method A: mp 162–164 °C; Anal. C, H, N) (1.04 g, 0.002 mol) in EtOH (25 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and the filtrate was evaporated to dryness. A solution of the residue in MeOH was added to a solution of fumaric acid in MeOH, and the precipitate was collected and recrystallized from MeOH: yield 0.2 g (18%); mp 168–170 °C.

3-[[2-(4-Acetamidobenzenesulfonamido)ethyl]amino]-1-phenoxypropan-2-ol Hydrochloride (47). A mixture of 4-acetamidobenzenesulfonyl chloride[13] (2.34 g, 0.01 mol) and $CHCl_3$ (25 ml) was added over 0.2 h to a stirred solution of 3-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenoxypropan-2-ol[10] (3.02 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in $CHCl_3$ (50 mL). The mixture was washed successively with 10% $NaHCO_3$ solution and H_2O and then dried (Na_2SO_4) and evaporated to dryness.

A solution of the residue in a mixture of ethanol (50 mL) and HOAc (1 mL) was hydrogenated over 30% Pd/C at room temperature and atmospheric pressure. The mixture was filtered, and filtrate was evaporated to dryness. The residue was dissolved in water (20 mL), and the solution was neutralized with $NaHCO_3$ and then extracted with EtOAc (3 × 20 mL). The combined extracts were dried and then acidified with ethereal HCl. The precipitated hydrochloride was collected and crystallized from $EtOH/H_2O$: yield 1.8 g (41%); mp 231–233 °C.

Pharmacology. β-Adrenoreceptor blocking potency was estimated in vivo by using the previously described cat preparation.[14] The results given in Tables I–V are the estimated dose, infused over a period of 30 min, that would cause a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The estimated degree (percent) of blockade of the vasodepressor response at that dose level is also given. Three to five dose levels of each compound were used to calculate these estimates. The relative potencies in these two systems give an indication of selectivity for β_1 (cardiac) as opposed to β_2 (vascular) receptors. Mean log ED_{50}'s were calculated for each compound on the basis of two or three tests, and the standard errors of the means were computed. On average, these mean values had an error of 30%. Previous data[14] have shown that the error in the percent inhibition of the depressor response at the ED_{50} value for inhibition of isoproterenol-induced tachycardia is less than 5%.

Acknowledgment. The authors thank J. Johnson and P. Mellish for their expert technical assistance, Dr. J. D. Fitzgerald and J. Carter for providing biological data, and C. J. Howarth for providing analytical data.

Registry No. **4**, 58027-28-4; **5**, 58027-75-1; **6**, 58027-66-0; **7**, 58027-62-6; **8**, 58027-90-0; **9**, 58027-89-7; **10**, 84051-23-0; **11**, 58027-88-6; **12**, 58027-39-7; **13**, 58027-41-1; **14**, 58027-40-0; **15**, 58027-60-7; **16**, 58027-72-8; **17**, 58027-38-6; **18**, 58027-44-4; **19**, 84051-24-1; **20**, 58027-21-7; **21**, 58027-22-8; **22**, 58027-56-8; **23**, 58027-30-8; **24**, 84051-25-2; **25**, 58027-27-3; **26**, 58027-33-1; **27**, 58027-87-5; **28**, 58027-86-4; **29**, 58027-31-9; **30**, 58027-32-0; **31**, 58027-36-4; **32**, 84051-26-3; **33**, 58027-23-9; **34**, 58027-29-5; **35**, 58027-25-1; **36**, 58027-24-0; **37**, 58027-53-5; **38**, 58027-11-5; **39**, 58027-69-3; **40**, 58027-20-6; **41**, 58027-94-4; **42**, 58027-80-8; **43**, 58827-22-8; **44**, 58827-85-3; **45**, 81253-57-8; **46**, 58827-83-1; **47**, 58827-21-7; **47** (free base), 84051-27-4; 1-(2-bromo-4-propionamidophenoxy)-2,3-epoxypropane, 58027-49-9; *N*-(2-aminoethyl)phenylacetamide, 15070-17-4; 3-chloro-1-(2-carbamoylphenoxy)propan-2-ol, 58027-55-7; *N*-(2-aminoethyl)isobutyramide, 53673-16-8; methanesulfonyl chloride, 124-63-0; 1-(2-aminophenoxy)-3-[*N*-benzyl-*N*-(2-isobutyramidoethyl)amino]propan-2-ol, 58027-73-9; *N*-[2-(benzylamino)ethyl]isobutyramide hydrochloride, 58027-76-2; 1-(2-nitrophenoxy)-2,3-epoxypropane, 21407-49-8; 1-[[2-[2-(2-nitrophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-77-3; 1-[[2-[2-(2-nitrophenyl)acetamido]ethyl]amino]-3-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-35-3; 3-[(2-aminoethyl)amino]-1-(2-cyanophenoxy)propan-2-ol, 58827-72-8; ethyl 4-acetamidomethylphenoxyacetate, 55458-50-9; 3-[[2-[2-[4-(benzyloxy)phenyl]acetamido]ethyl]amino]-1-[2-[(*N*-methylcarbamoyl)methoxy]phenoxy]propan-2-ol, 58027-46-6; 4-acetamidobenzenesulfonyl chloride, 121-60-8; 3-[*N*-(2-aminoethyl)-*N*-benzylamino]-1-phenoxy-2-propan-2-ol, 84051-28-5.

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Piperazinylimidazo[1,2-*a*]pyrazines with Selective Affinity for in Vitro α-Adrenergic Receptor Subtypes

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Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received April 28, 1982*

Regioselective syntheses of alkyl- and halogen-substituted piperazinylimidazo[1,2-*a*]pyrazines by novel oxidation–dehydration of [(β-hydroxyalkyl)amino]pyrazines are described. Lanthanide shift reagent studies allowed correction of literature assignments of NMR chemical shifts and coupling constants for the imidazo[1,2-*a*]pyrazine ring system (e.g., $J_{5,8} > J_{6,8}$). Equilibrium constants for displacement of specifically bound [^{3}H]clonidine and [^{3}H]prazosin from calf cerebral cortex homogenates in vitro are tabulated for reference and title compounds, and structure–affinity relationships for α_2- vs. α_1-adrenergic receptors are considered. Compound **2a**, 8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine, is equipotent with mianserin on the clonidine receptor (α_2) but ca. 70 times as selective as mianserin for this α_2-adrenergic receptor. Reduction of the imidazo ring (2,3-dihydro) lowers affinity for the α_2 receptor without affecting α_1-receptor affinity. Computer-assisted molecular modeling techniques are applied to the estimation of conformational energies of **2a** and its 5-position isomer in relation to the semirigid molecule mianserin.

Piperazinylpyrazines[1,2] and piperazinylquinoxalines[3,4] with selective actions on central nervous system neurons were the subjects of previous publications from these laboratories. From these studies, 6-chloro-2-(1-piperazinyl)pyrazine (MK0212, **1**) was selected for clinical study because of its serotoninmimetic properties. During in vitro receptor-binding studies of **1**, significant affinity

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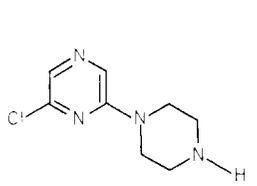

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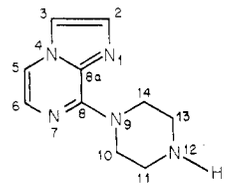


2a

for clonidine (α_2 adrenergic) and prazosin (α_1 adrenergic) receptor sites in calf cerebral cortex homogenates was discovered (Table III).

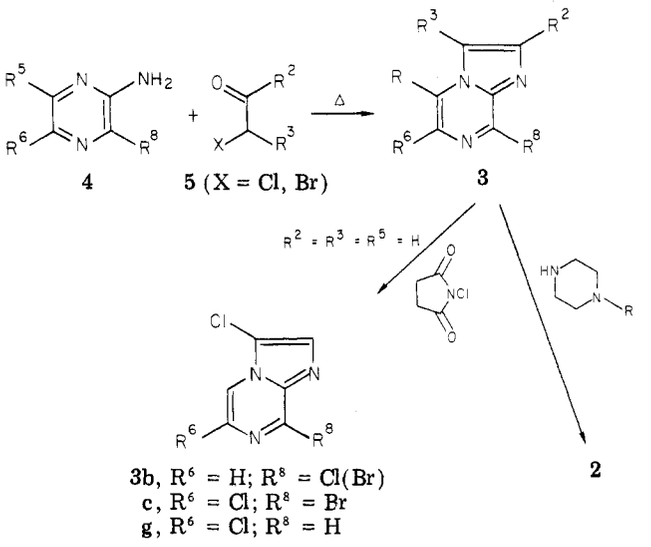
In the present study, the effects of an imidazo[1,2-*a*] fusion on the α-adrenergic receptor affinity of **1** were investigated. The parent imidazo[1,2-*a*]pyrazine (pK_a = 3.59)[5a] is a stronger base than either pyrazine (pK_a = 0.6)[5b] or 2-aminopyrazine (pK_a = 3.14).[5b] Thus, the effects of such a fusion are to introduce a weakly basic or hydrogen bonding site in a variable relationship to the piperazine side chain. Within this series of piperazinylimidazo[1,2-*a*]pyrazines,[6] compounds (e.g., **2a**) were found with interesting selectivity for α_1- and α_2-adrenergic receptors in vitro.

Chemistry. The parent imidazo[1,2-*a*]pyrazine was first completely characterized by DePompei and Paudler in 1975.[7] These workers synthesized the parent heterocycle by condensation of 2-aminopyrazine with chloroacetaldehyde and showed that electrophilic substitution with *N*-bromosuccinimide occurs at the 3-position. Prior to this work, a report of the synthesis of substituted derivatives by condensation of α-halo aldehydes and ketones with aminopyrazines had appeared.[8] In addition, the parent had been synthesized in low yield and its pK_a determined in 1965.[5b] We employed these findings in one approach to haloimidazopyrazine precursors **3** (Table I) of **2** (Scheme I).

In the present work, we also developed a new regiospecific synthesis of **3b** (R^3 = CH_3; R^6 = Cl; R^8 = Br) from 2,3-dichloropyrazine (**6**) according to Scheme II. No rigorous proof of the regiochemistry of condensation of aminopyrazines **4** with α-halocarbonyl compounds **5** (Scheme I) had been reported prior to this work. Reaction of **6** with 1-amino-2-propanol in refluxing dioxane gave **8**, which was chlorinated with *N*-chlorosuccinimide to give **9**. Oxidation of **9** to the corresponding ketone **10**, followed by dehydration–cyclization of **10** with trifluoroacetic anhydride and Cl, Br exchange (See Experimental, Method D), gave **3f**, identical with the product from condensation of 2-amino-3-bromo-5-chloropyrazine (**4f**) with 2-bromopropionaldehyde. This sequence establishes the regiochemistry of **3**, the regiospecificity of chlorination of **8** to **9**, and the greater ease of displacement of an 8-chloro substituent than a 6-chloro substituent in this ring system.[7a]

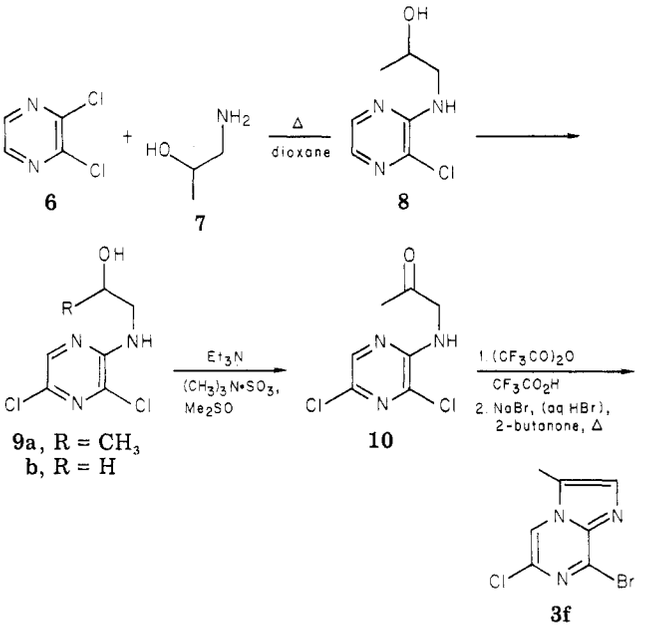
Intermediate **9b** served in a synthesis of the dihydro derivative (**2i**) of **2a** outlined in Scheme III. Reaction of **9b** with $SOCl_2$ gave **11**. The latter underwent selective displacement with piperazine at the 8-position, giving **2i**. The structure of **2i** was confirmed by its mass spectrum, which showed a molecular ion (1Cl) at *m/e* 239 with no loss of Cl or HCl, which is typical of an 8-chloro function

Scheme I

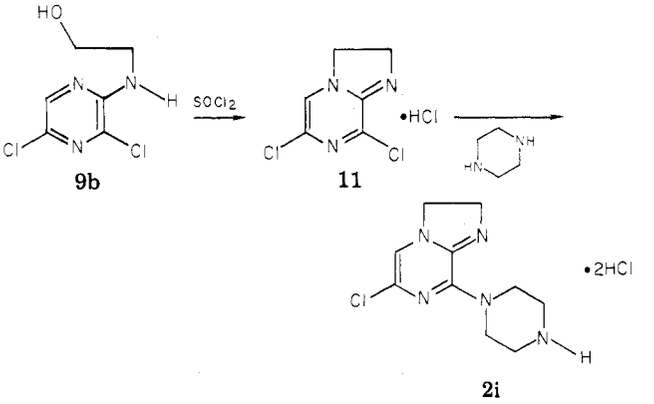


3b, R^6 = H; R^8 = Cl(Br)
c, R^6 = Cl; R^8 = Br
g, R^6 = Cl; R^8 = H

Scheme II



Scheme III



(e.g., **11**). Fragments at *m/e* 183 (1Cl) and 84 ($C_4H_8N_2$) correspond to losses of $CH_2CH_2N{=}CH_2$ and the piperazine side chain. In contrast, the mass spectrum of **11** shows, besides the molecular ion at *m/e* 189, a strong M − 1 peak and companion peaks at *m/e* 152, 154 of moderate intensity for loss of Cl at the 8-position. A very weak peak at

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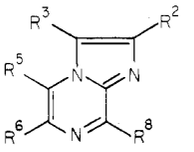
(8) Werbel, L. M.; Zamora, M. L. *J. Org. Chem.* **1965**, *2*, 287.

Table I. Haloimidazo[1,2-*a*]pyrazines

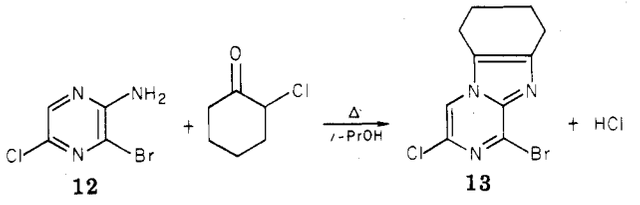


compd	R^2	R^3	R^5	R^6	R^8	formula	mp, °C	recrystn solvent	method	^{1}H NMR, δ
3a	H	H	H	H	Cl(Br)	*b*	178-180	sublimed		
3b	H	Cl	H	H	Cl(Br)	*b*	119-122	sublimed		
3c	H	Cl	H	Cl	Br	$C_6H_2BrCl_2N_3$	100-101	sublimed	B	H^5 7.70 H^2 8.00
3d	H	H	H	Cl	Br	$C_6H_3BrClN_3$	146-147	sublimed		H^2, H^3 7.92 H^5 8.30
3e[a]	H	H	H	C_6H_5	Br	$C_{12}H_8BrN_3 \cdot HBr$	290-293		F	
3f	H	CH_3	H	Cl	Br	$C_7H_5BrClN_3$	136-138	sublimed	E	H^2 δ 7.53 (1 H, s) H^5 δ 7.78 (1 H, s)
3g	H	Cl	H	Cl	H	$C_6H_3Cl_2N_3$	115-116	*i*-PrOH	C	H^8 δ 8.93 (1 H, d, J = 1.5 Hz) H^5 δ 8.17 (1 H, d, J = 1.5 Hz)
3h	H	H	Cl	H	H	$C_6H_4ClN_3$	95-95.5			H^2 δ 7.83 (1 H, s) H^8 δ 9.10 (1 H, s) H^6 δ 8.00 (1 H, s) H^2, H^3 δ 7.93 (2 H, AB, $J \approx 0$ Hz)
3i	2,3-dihydro		Cl	Cl		$C_6H_5Cl_2N_3 \cdot HCl$	290-300 dec	MeOH	A	see Exptl Sect
3k	$-(CH_2)_4-$		Cl	Cl(Br)		$C_{10}H_9Cl_2N_3$	142-157	sublimed		H^5 δ 7.75 (1 H, s)
3l[c]	2,3-dihydro		benzo	Cl		$C_{10}H_8ClN_3 \cdot HCl$	274-276			
3m	H	CH_3	H	Cl	Cl	$C_7H_5Cl_2N_3$	135-139	col chrom	D	see Exptl Sect
3n	H	H	H	Cl	H	$C_6H_4ClN_3$	137-138	sublimed	C	see Exptl Sect

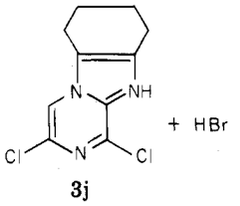
[a] Synthesized from methyl 3-amino-6-phenyl-2-pyrazinecarboxylate by method F. [b] Mixture of 8-Cl and 8-Br compounds. [c] The free base of this compound, mp 151-153 °C, is reported in the literature.[21]

m/e 129 for loss of $HC_5 = C_6Cl$ further indicates the relatively greater lability of 8-Cl vs. 6-Cl.

Condensation of aminopyrazine **12** with 2-chlorocyclo-



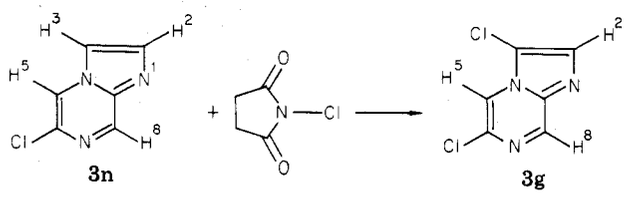
12 **13**



3j

hexanone afforded a mixture of mainly the dichloroimidazopyrazine **3j** and its bromo analogue **13** as evidenced by the high-resolution mass spectrum of the sublimate of the crude basic product, mp 142–157 °C. This result illustrates a general halogen scrambling that occurs in reactions of haloaminopyrazines with halo ketones.

The ^{1}H NMR spectra of intermediates **3** (Table I) have been analyzed with the aid of lanthanide shift reagents, and several discrepancies with literature assignments[7a] have been discovered.[7b] The ^{1}H NMR of intermediates **3n** and **3g** (see Experimental Section) showed more rapid



3n **3g**

broadening and downfield shift of the signals for H^2 and H^8 than for H^5 on successive addition of $Eu(DPM)_3$ (~0.1 equiv increments) as expected if the lanthanide complexes selectively at or near N^1. The H^2 signal at δ 7.92 for **3n** is thus unambigously assigned by virtue of its 0.5 Hz coupling to H^3 (AB pattern). It is clear from the spectrum that $J_{5,8}$ = 1.25 Hz. Consistent with the interpretation is the observation that the signals for H^5 and H^8 of **3g** are also doublets, $J \approx 1.5$ Hz. The doublet at δ 8.17 (Table I) is assigned to H^8 of **3g** on the basis of its conspicuously more rapid broadening and downfield shift on addition of increments of $Eu(DPM)_3$. The literature assignments of $J_{5,8} \approx 0$ and $J_{6,8} \approx 1.0$[7] are thus reversed.

Intermediates **3** were reacted with piperazine (e.g., method E) to give the desired piperazinylimidazo[1,2-*a*]-pyrazines (Table II). In general, the reactivity of the halogen in **3** was 8 > 5 ≫ 6 as previously reported.[7a]

In Vitro Receptor Binding Studies. Compounds that displace specifically bound [^{3}H]clonidine from cerebral cortical homogenates (high-affinity sites)[9] are defined as ligands for α_2-adrenergic receptors. Agents that block the agonist effects of clonidine at these receptors, such as mianserin,[10,11] have potential as nonclassical antidepressants. Compounds that displace [^{3}H]prazosin from the same homogenates are defined as α_1-adrenergic ligands.[12]

Pharmacological consequences of α_1- and α_2-adrenergic receptor binding depend on a number of factors, including tissue selectivity, whether an agonist or antagonist response is elicited, and whether the binding is to pre- or postsynaptic receptors. For example, the action of clonidine-like

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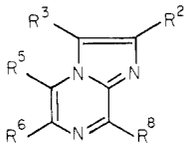
Table II. Physicochemical Data for Piperazinylimidazo[1,2-*a*]pyrazines



compd	R^2	R^3	R^5	R^6	R^8	formula	mp, °C	recrystn solvent	yield, %
2a	H	H	H	H	P[b]	$C_{10}H_{13}N_5 \cdot 2HCl$	273-276		
2b	H	Cl	H	H	P	$C_{10}H_{12}ClN_5 \cdot HCl$	dec	EtOH	69
2c	H	Cl	H	Cl	P	$C_{10}H_{11}Cl_2N_5 \cdot HCl$	>350 dec	EtOH-H_2O	94
2d	H	H	H	Cl	P	$C_{10}H_{12}ClN_5 \cdot 2HCl$	>350 dec	EtOH	88
2e	H	H	H	C_6H_5	P				
2f[a]	H	CH_3	H	Cl	P	$C_{11}H_{14}ClN_5 \cdot 2HCl$	317-318		86
2g	H	Cl	H	P	H	$C_{10}H_{12}ClN_5 \cdot 2HCl \cdot 0.5H_2O$	dec	EtOH	34
2h	H	H	P	H	H	$C_{10}H_{13}N_5 \cdot C_4H_4O_4 \cdot 0.5H_2O$	236-236.5 dec	EtOH, H_2O	44
2i[c]	2,3-dihydro		H	Cl	P	$C_{10}H_{14}ClN_5 \cdot 2HCl \cdot {}^1/_6C_2H_5OH$	315 dec		89
2j	H	H	H	Cl	NCH_3-P	$C_{11}H_{14}ClN_5 \cdot HCl \cdot 0.5H_2O$	298 dec		
2k	-$(CH_2)_4$-		H	Cl	P	$C_{14}H_{18}ClN_5 \cdot 2HCl$	320-322 dec	EtOH	36
2l	2,3-dihydro		benzo		P	$C_{14}H_{17}N_5 \cdot 2HCl$	320-321 dec		

[a] Method E. [b] P = piperazin-1-yl. [c] Method A.

Table III. Receptor-Binding Data for Piperazinylimidazo[1,2-*a*]pyrazines

						α_1: [^{3}H]prazosin			α_2: [^{3}H]clonidine			K_D (α_1)/ K_D (α_2)
compd	R^2	R^3	R^5	R^6	R^8	K_D, nM	$-\Delta G$, kcal/mol	$\Delta\Delta G_n$,[b] kcal/mol	K_D, nM	$-\Delta G$, kcal/mol	$\Delta\Delta G_n$,[b] kcal/mol	
MK-212 (1)						2 400 ± 500			150 ± 10			16
Mianserin						43 ± 7			19 ± 1			2.3
2a	H	H	H	H	P	3 100 ± 200	7.49		19 ± 1	10.50		160
2b	H	Cl	H	H	P	2 780 ± 90	7.55	−0.06 (a)	290 ± 20	8.89	1.61 (a)	9.6
2c	H	Cl	H	Cl	P	410 ± 50	8.68	0.30 (d)	1 000 ± 200	8.16	1.43 (d)	0.4
								−1.13 (b)			0.73 (b)	
2d	H	H	H	Cl	P	250 ± 20	8.98	−1.49 (a)	88 ± 6	9.59	0.91 (a)	2.8
2e	H	H	H	C_6H_5	P	360 ± 20	8.76		1 800 ± 200	7.81		0.20
2f	H	CH_3	H	Cl	P	160 ± 10	9.24		250 ± 20	8.98		0.64
2g	H	Cl	H	P	H	6 800 ± 400	7.03		18 900 ± 800	6.42		0.36
2h	H	H	P	H	H	51 000 ± 4000	5.84		28 100 ± 900	6.19		1.8
2i	2,3-dihydro		H	Cl	P	3 000 ± 200	7.51		1 600 ± 100	7.88		1.9
2j	H	H	H	Cl	NCH_3-P	380 ± 80	8.73		144 ± 6	9.30		2.6
2k	-$(CH_2)_4$-		H	Cl	P	200 ± 20	9.11		1 500 ± 300	7.92		0.13
2l	2,3-dihydro		benzo		P	1 300 ± 100	8.00		1 800 ± 100	7.81		0.72

[a] ± SD. [b] The difference in free energies of binding between a compound and a reference compound designated by check letter in parentheses.

antihypertensives[13] depends on α_2/α_1 selectivity, as well as selectivity for the central vs. peripheral neurons. The present work is another example of how selectivity for α_1- and α_2-adrenergic receptors can be studied in vitro.

Receptor binding data, represented by displacement of [^{3}H]clonidine (α_2) and [^{3}H]prazosin (α_1) from calf neocortical membrane homogenates in vitro, are listed for reference compounds MK-212 (**1**) and mianserin and for compounds **2a–l** in Table III. Compounds **2** ranged from 10 times (**2a**) to less than $^1/_{100}$ (**2k**) as selective as **1** for the α_2 receptors. Compound **2a**, 8-(1-piperazinyl)imidazo-[1,2-*a*]pyrazine, is approximately 70 times more selective than mianserin for the α_2 receptor.

Introduction of a 3-Cl substituent (**2b**) reduces α_2 affinity nearly 15-fold relative to **2a** without a significant effect on α_1 affinity. A 6-Cl substituent (**2d**), on the other hand, reduces α_2 affinity (5×) and increases α_1 affinity (10×). Insufficient examples exist to attempt a quantitative correlation of binding with substituent parameters. The general pattern of 3- or 6-substitution favoring α_1 while disfavoring α_2 binding is, however, clear from the data for the 8-piperazinyl series **2a–f**. All of the substituents studied would exert a significant steric effect and tend to increase lipid solubility.

Analysis of the free energies of binding (kcal/mol, see Table III) for the α_2 receptor show that for introduction of a 3-Cl substituent (**2a** → **2b**, $\Delta\Delta G$ = 1.61 kcal/mol; **2d** → **2c**, $\Delta\Delta G$ = 1.43 kcal/mol) the free energy change is independent of the presence of a 6-Cl substituent. The converse is also true, i.e., **2a** → **2d** ($\Delta\Delta G$ = 0.91 kcal/mol) and **2b** → **2c** ($\Delta\Delta G$ = 0.73 kcal/mol). These results point to an apparent independence of interaction of 3-Cl and 6-Cl substituents at the α_2 receptor and suggest that a Free–Wilson analysis[14] of the SAR might be possible when more examples are prepared in this series. A similar analysis for the α_1 receptor is not as satisfactory.

Moving the imidazo fusion to the d face (**2g**) or f face (**2h**) markedly lowers α_1 and α_2 affinities. These effects may stem from the steric effect of N_1 on the rotational freedom of the 8-piperazinyl substituent, an effect that tilts the plane of the 4C atoms of the piperazine ring with reference to that of the imidazo ring system. Such a tilted geometry is rigidly enforced with respect to the piperazine

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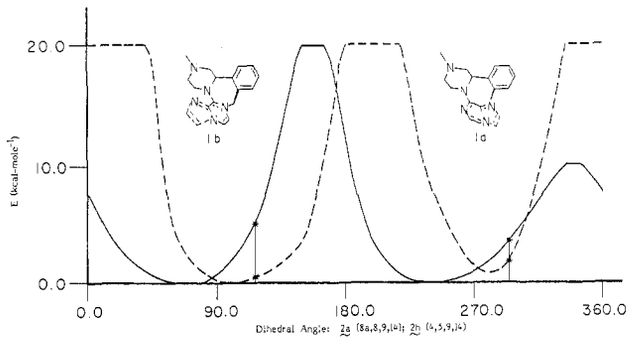

Figure 1. Conformational energies of **2a** (—) and **2h** (---) relative to mianserin geometry.

ring and N-bound benzene ring in the known α_2-antagonist mianserin. The Merck molecular modeling system[15] (MMMS) was used to superimpose the geometry of **2a** with the X-ray structure reported[16] for mianserin (Figure 1; Ia,b). Dihedral (8a, 8, 9, 14) angles of −31.2° (**Ia**) and −152.2° (**Ib**) were required to obtain optimal matches for these molecules.[17]

Conformational energies, computed by classical mechanical methods (Program CONF, see Experimental Section), are plotted as a function of the dihedral angle (8a, 8, 9, 14) in Figure 1. The conformer Ia of **2a** (solid curve) was found to be ca. 1.8 kcal/mol lower in energy than Ib. For comparison, a similar plot (Figure 1, dashed curve) for the conformations of the 5-isomer of **2a** (**2h**) shows that the opposite conformer, i.e., the one analogous to Ib, is the lower in energy by 1.4 kcal/mol. Thus, the lack of affinity of **2h** for both types of α receptors may be due to its preference to exist in a low affinity conformation and the high barrier to its conversion to a conformer analogous to Ia. The lack of affinity of the 6-piperazinyl compound **2g** could then be ascribed to the lack of a steric factor to enforce the tilted conformation, which is expected to be electronically less stable than the untilted geometry.[18]

The 2,3-dihydro analogue (**2i**) of **2a** has markedly less affinity for the α_2-adrenergic receptor but essentially identical α_1-receptor affinity, suggesting that the imidazo fusion of **2a** may contribute π binding to the former receptor. Our original hypothesis that the locus of the five-membered ring nitrogen (N_1) of analogues **2** might contribute to receptor binding via hydrogen bonding does not aid in explaining the receptor-binding data. The expected increase in basicity of N-1 in the dihydro analogue **2i** compared to **2a** may be another explanation for lower affinity for the α_2 receptors.

In conclusion, a novel series of piperazinylimidazo[1,2-*a*]pyrazines with selective affinity for α_1- and α_2-adrenergic receptors was described. Computer-assisted molecular modeling techniques were used to describe possible preferred conformations for receptor binding. Some new methods for regioselective synthesis of the heterocyclic ring systems were reported. NMR assignments were made with the aid of paramagnetic shift reagent studies, and literature NMR assignments for the imidazo[1,2-*a*]pyrazine ring system were corrected. Further details of the pharmacology of some of the described compounds **2** will be published elsewhere.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus with open capillaries and are uncorrected. Microanalytical results on new compounds are indicated by atomic symbols and are within ±0.4% of theoretical values unless otherwise noted. NMR spectra were recorded on Varian T-60 or EM-390 spectrometers in $CDCl_3$–Me_4Si unless otherwise specified. Mass spectra were determined at an ionizing voltage of 70 eV on an AEI MS-902 double-focusing mass spectrometer. CONF, a modification of Boyd's Molbld2 molecular mechanics energy minimization program[15] which assumes rigid rotation, i.e., no stretching or bending functions, was used to compute the conformational energies of **2a** and **2h**. The program COMPARE[15] was used to superimpose **2a** and **2h** with mianserin.

Receptor-Binding Assay. Assays for the competitive binding of selected compounds to central α-adrenergic receptors employed radiolabeled clonidine or radiolabeled prazosin, which were obtained from New England Nuclear and Amersham, respectively. [^{3}H]Clonidine (specific activity 22.2–23.8 Ci/mmol) was stored in ethanol/water (7:2) at 0 °C, and [^{3}H]prazosin (specific activity 33 Ci/mmol) was stored in a solution of diethylamine in ethanol at 0 °C. The radiochemical purity of these ligands was periodically checked by TLC.

Binding assays were conducted with frozen sections of calf cerebral cortex (−70 °C). A Brinkmann Polytron PT-10, at setting 6 for 10 s, was used to homogenize the frozen tissue in 20 vol (w/v) of ice-cold 50 nM pH 7.7 Tris-HCl buffer. The resultant homogenate was centrifuged twice at 48000*g* (Sorvall SS-34 rotor, 2000 rpm, RC-5 centrifuge) for 10 min at 40 °C, with rehomogenization of the intermediate pellet in 20 vol of fresh buffer. This final pellet was resuspended in 50 vol of ice-cold buffer.

Standard displacement assays were run with either 0.20 nM [^{3}H]clonidine or 0.14 nM [^{3}H]prazosin. Triplicate assays tubes contained ^{3}H-labeled ligand, 100 μL of various concentrations of the compound being investigated, 1 mL of tissue homogenate, and 50 mM pH 7.7, Tris-HCl buffer to a final volume of 2 mL. The reaction was initiated by the addition of tissue, and incubation continued for 30 min at 25 °C, at which time it was terminated by rapid filtration through Whatman GF/B glass-fiber filters under vacuum. Each filter was immediately rinsed with 3 × 5 mL aliquots of ice-cold buffer. The filters were removed into 10 mL of PCS (Amersham) and counted on either a Packard Model 2425 or Packard Model 460C scintillation spectrophotometer at approximately 35% efficiency.

Specific binding was defined as the difference between samples with and without 1 μM clonidine or 1 μM prazosin for [^{3}H]clonidine and [^{3}H]prazosin assays, respectively.

Data from binding assays were plotted as log concentration vs. percent inhibition and analyzed by nonlinear least-squares techniques in which 100% maximal inhibition was assumed at high test compound concentrations. The IC_{50} values obtained from such data treatment were used to calculate apparent inhibition constants from the following formula

$$K_i = \frac{IC_{50}}{1 + [C]/K_D}$$

where [C] is the concentration of radioligand employed in the binding assay and K_D is its receptor dissociation constant (K_D = 0.48 nM for [^{3}H]clonidine and 0.14 nM for [^{3}H]prazosin). The change in Gibbs free energy on binding to the receptor was calculated from the measured dissociation constant by $\Delta G = RT \ln K_D$.

Method A. 2,3-Dihydro-6,8-dichloroimidazo[1,2-*a*]pyrazine Hydrochloride (3i). Step A. 2,3-Dichloropyrazine (25.0 g, 0.168 mol) and ethanolamine (25 mL) were refluxed for 7 h under N_2 in 100 mL of dioxane. The mixture was cooled, and the upper layer was separated and concentrated under vacuum. The residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3. The CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and concentrated to an orange oil, which was distilled

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(16) Van Rij, C.; Feil, D. *Tetrahedron* **1973**, *29*, 1891.
(17) The program MATCH, which iteratively minimizes the distances between specified atoms of dissimilar structures by a global or least-squares technique, is part of MMMS.
(18) While the attached piperazine N may be pyramidal, its lone pair of electrons is expected to prefer overlap with the π-electron system of imidazo[1,2-*a*]pyrazine: Parr, W. J. E.; Wasylishen, R. E. *J. Mol. Struct.* **1977**, *38*, 272. Hehre, W. J.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 1496.

to give 22.7 g (78%) of 2-chloro-3-[(2-hydroxyethyl)amino]-pyrazine, bp 133 °C (0.3 mm). The oil gradually crystallized, mp 54–55 °C (n-C_4H_9Cl).

Step B. An 18 g (0.10 mol) sample of the product from step A was added to a solution of *N*-chlorosuccinimide (15.5 g, 0.12 mol) in 200 mL of $CHCl_3$. The solution was refluxed for 1.5 h on the steam bath, cooled, and washed repeatedly with water. The $CHCl_3$ was dried (Na_2SO_4), filtered, and concentrated to an oil, which was distilled to give 18 g (87%) of 2,6-dichloro-3-[(2-hydroxyethyl)amino]pyrazine, bp 145 °C (0.5 mm).

If the reaction mixture was percolated through a dry column of activity III alumina, elution with $CHCl_3$ gave 20 g (93%) of a crystalline complex of 2,6-dichloro-3-[(2-hydroxyethyl)-amino]pyrazine (**9b**) with succinimide: mp 106.5–107.5 °C; ^{1}H NMR δ 7.9 (1 H, s), 3.77 (4 H complex), 2.77 (4 H, s).

Step C. The product from step B (9.5 g, 45.5 mmol) was treated neat with 20 mL of $SOCl_2$ in 25 mL of $CHCl_3$, and the mixture was stirred (mild exotherm) and then heated briefly on the steam bath ($CaCl_2$ drying tube) until a light yellow precipitate formed. The solid was collected and washed with ether to give 10 g (46%) of 2,3-dihydro-6,8-dichloroimidazo[1,2-*a*]pyrazine hydrochloride (**3i**): mp 290–300 °C dec after recrystallization from MeOH; ^{1}H NMR (CF_3CO_2D) δ 6.93 (1 H, s), 3.68 (4 H, A_2B_2).

Method B. 8-Bromo-3,6-dichloroimidazo[1,2-*a*]pyrazine (3c). 8-Bromo-6-chloroimidazo[1,2-*a*]pyrazine (4.6 g, 20 mmol) and *N*-chlorosuccinimide (3.2 g, 24 mmol) were combined in 30 mL of $CHCl_3$, and the mixture was refluxed for 2.5 h on the steam bath. The mixture was cooled and washed with two 20-mL portions of dilute aqueous $NaHSO_3$. The $CHCl_3$ layer was separated, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to a gum, which was chromatographed on activity III alumina. Elution with toluene–n-C_4H_9Cl gave fractions containing 4.8 g (90%) of white solid, mp 99–101 °C. Vacuum sublimation gave pure 8-bromo-3,6-dichloroimidazo[1,2-*a*]pyrazine (**3c**), mp 100–101 °C.

Method C. 3,6-Dichloroimidazo[1,2-*a*]pyrazine (3g). Step A. 6-Chloroimidazo[1,2-*a*]pyrazine (3n). A 20-g (15.3 mL, 0.101 mol) sample of bromoacetaldehyde diethyl acetal and 4 mL 40% aqueous HBr were combined and refluxed vigorously under N_2 (bath 120 °C) for 1.5 h. The mixture was cooled and poured into a suspension of 40 g of $NaHCO_3$ in 200 mL of i-C_3H_7OH. After CO_2 evolution had ceased, the mixture was filtered, and the filtrate was treated with 7.75 g (59.6 mmol) of 2-amino-5-chloropyrazine.[19] The resulting mixture was refluxed for 2 h. Thin-layer chromatography (silica gel GF, 5% MeOH–$CHCl_3$; sample spotted in $CHCl_3$ saturated with aqueous NH_3) showed a single spot, R_f = 0.44 [slightly greater than the starting material, which gave a rose color with Dragendorf reagent (a reaction characteristic of all imidazo[1,2-*a*]pyrazines studied but negative for all aminopyrazines studied)]. The mixture was treated with 10 mL of 40% aqueous HBr and concentrated under vacuum. The residue was triturated with fresh i-PrOH, reconcentrated to remove water, and filtered to give the crude HBr salt of the product. This salt was partitioned between saturated aqueous $NaCO_3$ and $CHCl_3$, the $CHCl_3$ extracts were combined, dried (Na_2SO_4), and filtered, and the filtrate was concentrated to give 6.5 g of crude free base. Sublimation under vacuum gave 6.2 g (68%) of yellow crystalline 6-chloroimidazo[1,2-*a*]pyrazine (**3n**): mp 137–138 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (1 H, m, H^8), 8.30 (1 H, d, J = 1.25 Hz, H^5), 7.92 (1 H, d, J = 0.5 Hz, H^2), 7.83 (1 H, d, J = 0.5 Hz, H^8).

Step B. The product from step A (3.07 g, 20 mmol) was refluxed with *N*-chlorosuccinimide (2.8 g, 21 mmol) in 50 mL of $CHCl_3$ for 1 h. The mixture was cooled and filtered to give the crude product, which was recrystallized from 2-propanol to give 2.7 g (72%) of 3,6-dichloroimidazo[1,2-*a*]pyrazine (**3g**), mp 115–116 °C.

Method D. 3-Methyl-6-chloro-8-bromoimidazo[1,2-*a*]pyrazine (3f). Step A. 2-[(2-Hydroxy-1-propyl)amino]-3,5-dichloropyrazine (9). 2-[(2-Hydroxy-1-propyl)amino]-3-chloropyrazine (**8**) (bp 136 °C, 0.7 torr, synthesized by a procedure analogous to method A, 10 g, 53 mmol) was added to a solution of 8 g (60 mmol) of *N*-chlorosuccinimide in 50 mL of $CHCl_3$. The mixture was refluxed for 2 h on the steam bath, cooled, and washed with water, and the $CHCl_3$ layer was percolated through a dry column of activity III alumina. Continued elution with $CHCl_3$ gave fractions containing 10.6 g (85%) of an orange syrup, which crystallized from n-C_4H_9Cl to give light yellow prisms of 2-[(2-hydroxy-1-propyl)amino]-3,5-dichloropyrazine (**9**), mp 76–77 °C. Anal. Calcd for $C_7H_9Cl_2N_3O$: C, 37.86; H, 4.09; N, 18.92. Found: C, 37.85; H, 4.07; N, 19.29.

Step B. 2-[(2-Oxo-1-propyl)amino]-3,5-dichloropyrazine (10). The alcohol (**9**) from step A (11.3 g, 51 mmol) was dissolved in 33 mL each of triethylamine and Me_2SO, and the mixture was treated with 10 g (72 mmol) of trimethylamine–sulfur trioxide complex. The resulting mixture was stirred for 16 h at room temperature and partitioned between ice–water and $CHCl_3$. The $CHCl_3$ extracts were separated, combined, dried (Na_2SO_4), and filtered, and the filtrate was concentrated. The oily residue was chromatographed on a dry column of silica gel. Elution with $CHCl_3$ gave fractions containing an oil, which crystallized twice from cyclohexane to give 4.6 g (41%) of pure **10**: mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (1 H, s), 5.92 (1 H exchangeable), 4.27 (1 H, d, J = 5 Hz), 2.27 (3 H, s).

Step C. 3-Methyl-6,8-dichloroimidazo[1,2-*a*]pyrazine (3m). The product from step B (4.0 g, 18 mmol) was dissolved in 10 mL of CF_3CO_2H under N_2, and the solution was treated with trifluoroacetic anhydride (6 mL) added through the top of the reflux condenser. After stirring for 5 h at room temperature, the mixture was concentrated under vacuum, and the residue was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and percolated through a dry column of silica gel. Continued elution with $CHCl_3$ gave fractions containing 3.4 g (93%) of 3-methyl-6,6-dichloroimidazo[1,2-*a*]pyrazine (**3m**): mp 135–139 °C; ^{1}H NMR δ 7.83 (1 H, s), 7.60 (1 H, s), 2.53 (3 H, s).

Step D. 3-Methyl-6-chloro-8-bromoimidazo[1,2-*a*]pyrazine (3f). A mixture of the product from step C (400 mg, 2.0 mmol), sodium bromide (400 mg), and 5 N aqueous HBr (5 μL) in 3 mL of 2-butanone was refluxed for 18 h under N_2. The mixture was concentrated under vacuum, and the residue was sublimed (110 °C, 0.5 torr) to give 332 mg (67%) of 3-methyl-6-chloro-8-bromoimidazo[1,2-*a*]pyrazine (**3f**), mp 138 °C, mmp with **3f**, prepared from 3-bromo-5-chloro-2-aminopyrazine by a method analogous to method B, undepressed: ^{1}H NMR δ 7.83 (1 H, s), 7.55 (1 H, s), 2.52 (3 H, s).

Method E. 3-Methyl-6-chloro-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine Dihydrochloride (2f). Step A. 3-Methyl-6-chloro-8-bromoimidazo[1,2-*a*]pyrazine (3f). 2-Bromopropionaldehyde diethyl acetal (7 g, 0.035 mol), 40% aqueous HBr (2 mL), and water (2 mL) were refluxed for 30 min (bath 110 °C) under N_2. The mixture was cooled and poured into a stirred suspension of $NaHCO_3$ (16 g) in 100 mL of i-PrOH. After CO_2 evolution had ceased, the suspension was filtered, the filtrate was treated with 3-bromo-5-chloro-2-aminopyrazine[20] (4.17 g, 20.0 mmol), and the mixture was refluxed for 20 h. The mixture was concentrated, and the crude HBr salt (3.5 g, mp >325 °C) was collected and partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and filtered, and the filtrate was concentrated under vacuum to give 1.8 g (37%) of crude product, which was sublimed to give pure 3-methyl-6-chloro-8-bromoimidazo[1,2-*a*]pyrazine (**3f**), mp 136–138 °C.

Step B. The product from step A (1.5 g, 6.1 mmol) and piperazine (1.5 g) were dissolved in 5 mL of CF_3CH_2OH at room temperature for 5 h, during which a thick, white precipitate separated. The mixture was concentrated, and the residue was partitioned between aqueous Na_2CO_3 and $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and filtered, and the filtrate was percolated through a dry column of silica gel. Elution with 4% CH_3OH–$CHCl_3$ gave fractions containing pure free base, which was converted to the HCl salt in ethanol. White crystals (1.7 g, 86%) of pure 3-methyl-6-chloro-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine dihydrochloride (**2f**), mp 317–318 °C dec, separated. The product was identical by TLC (silica gel, 9:1 $CHCl_3$ saturated with aqueous NH_3/CH_3OH) and ^{1}H NMR with that obtained from **3f** synthesized in method D: ^{1}H NMR (CF_3CO_2D) δ 7.86

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(1 H, s), 7.72 (1 H, s, broad), 4.00 (4 H, A_2B_2), 2.63 (3 H, broad s).

Method F. 6-Phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine (2e). Step A. 3-Amino-6-phenyl-2-pyrazinecarboxylic Acid. A solution of methyl 3-amino-6-phenylpyrazine-2-carboxylate[22] (4.6 g, 0.02 mol) and 10 mL of 5 N NaOH in 200 mL of CH_3OH was stirred for 1 h at room temperature and then diluted with 1 L of water and adjusted to pH 2 with 6 N HCl. The 3-amino-6-phenyl-2-pyrazinecarboxylic acid precipitated, collected, and dried by suction to give 3.8 g (88%) of a yellow solid, mp 189–191 °C (dec). Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.09; H, 4.13; N, 19.55.

Step B. 2-Amino-3-bromo-5-phenylpyrazine. To a vigorously stirred suspension of the product from step A (3.5 g, 0.016 mol) and sodium acetate trihydrate (4.5 g, 0.033 mol) in 30 mL of glacial HOAc at room temperature was added dropwise a solution of bromine (2.8 g, 0.91 mL, 0.018 mol) in 10 mL of glacial HOAc. The mixture was stirred for 18 h at room temperature and poured into 200 mL of H_2O, and the tan solid, 2-amino-3-bromo-5-phenylpyrazine (3.7 g, 91%), was collected by suction and dried in vacuo, mp 146–147 °C. Anal. Calcd for $C_{10}H_8BrN_3$: C, 48.02; H, 3.22; N, 16.80. Found: C, 48.25; H, 3.13; N, 16.83.

Step C. 8-Bromo-6-phenylimidazo[1,2-*a*]pyrazine (3e) Hydrobromide. Condensation of the product from step B with bromoacetaldehyde by a procedure analogous to method C (step A) afforded the crystalline 8-bromo-6-phenylimidazo[1,2-*a*]pyrazine hydrobromide in 73% yield, mp 290–293 °C. Anal. Calcd for $C_{12}H_8BrN_3$·HBr: C, 40.59; H, 2.55; N, 11.84. Found: C, 40.99; H, 2.58; N, 11.46.

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Step D. 6-Phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine Hydrochloride (2e). Treatment of the product from step C with excess piperazine by a procedure analogous to method E (step B) gave 6-phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine hydrochloride (**2e**) as colorless crystals from EtOH in 60% yield, mp >300 °C. Anal. Calcd for $C_{16}H_{17}N_5$·HCl: C, 60.85; H, 5.74; N, 22.18. Found: C, 60.57; H, 5.70; N, 21.89.

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Registry No. **1**, 64022-27-1; **2a**, 76537-28-5; **2a** (base), 76537-53-6; **2b**, 76551-54-7; **2b** (base), 84065-99-6; **2d**, 76537-24-1; **2d** (base), 77111-80-9; **2e**, 84066-00-2; **2e** (base), 84066-01-3; **2f**, 84066-02-4; **2f** (base), 84066-03-5; **2g**, 84066-04-6; **2g** (base), 76537-52-5; **2h**, 84066-05-7; **2i**, 84066-06-8; **2i** (base), 84066-07-9; **2j**, 76537-29-6; **2j** (base), 84073-46-1; **2k**, 76537-25-2; **2k** (base), 84066-08-0; **2l**, 84066-09-1; **2l** (base), 84066-10-4; **3a** (R^8 = Cl), 69214-33-1; **3a** (R^8 = Br), 69214-34-2; **3b** (R^8 = Cl), 76537-30-9; **3b** (R^8 = Br), 76537-31-0; **3c**, 76537-33-2; **3e**, 84066-12-6; **3f**, 84066-11-5; **3g**, 76537-32-1; **3h**, 63744-41-2; **3i**, 84066-13-7; **3k** (R^8 = Cl), 84066-14-8; **3k** (R^8 = Br), 76537-20-7; **3l**, 84066-15-9; **3m**, 84066-16-0; **3n**, 76537-23-0; **8**, 76537-36-5; **9a**, 84066-17-1; **9b**, 84066-18-2; **10**, 84066-19-3; 2-chloro-3-[(2-hydroxyethyl)amino]-pyrazine, 84066-20-6; **3d**, 76537-19-4; methyl 3-amino-6-phenylpyrazine-2-carboxylate, 1503-42-0; 3-amino-6-phenyl-2-pyrazinecarboxylic acid, 84066-21-7; 2-amino-3-bromo-5-phenylpyrazine, 67602-05-5; 2,3-dichloropyrazine, 4858-85-9; 3-bromo-5-chloro-2-aminopyrazine, 76537-18-3; 2-bromopropionaldehyde diethyl acetal, 3400-55-3; ethanolamine, 141-43-5; *N*-chlorosuccinimide, 128-09-6; 2-amino-5-chloropyrazine, 33332-29-5; piperazine, 110-85-0; bromoacetaldehyde, 17157-48-1; bromoacetaldehyde diethyl acetal, 2032-35-1.

Synthesis of (7*R*)-7*H*-Indolo[3,4-*gh*][1,4]benzoxazines, a New Class of *D*-Heteroergolines with Dopamine Agonist Activity

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Synthesis of several members of the 9-oxaergoline ring system is presented. Both the C/D cis and the C/D trans isomers of 4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine were prepared, and the C/D trans isomer was resolved into its optical isomers. The enantiomer having the highest affinity for the [^{3}H]apomorphine binding site, (−)-*trans*-6-ethyl-9-oxaergoline[9] [(−)-**6b**], was shown to have the same absolute configuration as the natural ergolines, namely, 6a*R*,10a*R*. In vivo and in vitro pharmacological evaluation shows these 9-oxaergolines to possess potent dopamine agonist properties.

Parkinsonism is a condition associated with reduced dopamine function and may be characterized by a decrease of transmission at dopamine D_2 receptors.[1] Levodopa, particularly in combination with a decarboxylase inhibitor (i.e., Sinemet), is the established drug of choice for the treatment of this condition. Recently, direct-acting dopamine agonists of the ergoline class, such as bromocriptine,[2] lisuride,[3-5] and pergolide,[6] have been reported to improve the condition of patients who have developed oscillation phenomena or have become partially refractory to levodopa. In addition, the anti-parkinson effect of these direct agonists may be synergistic with levodopa and Sinemet. This class of direct-acting agents has become increasingly attractive with the advent of peripherally selective dopamine antagonists capable of reducing side effects associated with receptor activation.

In this report we describe the pharmacological profile of a new class of heteroergolines, the 4,6,6a,8,9,10a-hexa-

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