g of 85% *m*-chloroperbenzoic acid (14.8 mmol). The mixture was stirred at room temperature for 18 h. An additional 50 mg of 85% *m*-chloroperbenzoic acid was added and the stirring was continued for 1 h. The solid was collected by filtration and was washed with $CHCl_3$. This procedure gave 0.386 g (74%) of **26** as a white powder: mp 245–247 °C; NMR (Me_2SO-d_6) δ 4.64 (d, 1 H, J = 14 Hz, CH_AH_BSO), 5.07 (d, 1 H, J = 14 Hz, CH_AH_BSO), 7.4–7.7 (m, 3 H, 7-, 8-, 9-H), 7.72 (s, 1 H, N=CH), 7.9 (dd, 1 H, J_o = 9 Hz, J_m = 2 Hz, 2-H), 8 (m, 1 H, 10-H), 8.12 (d, 1 H, J_m = 2 Hz, 4-H), 8.21 (d, 1 H, J_o = 9 Hz, 1-H), 12.5 (br s, 1 H, NH); *m/e* 353 (M^+). Anal. ($C_{17}H_{11}N_3O_4S$) C, H, N.

R_m Value Determination. The general procedure of Biagi et al.[19] was used, except that 7% (v/v) Dow Corning 200 (50 cSt) in hexane was used to coat the Analtech silica gel GF plates and 15, 20, 25, or 30% (v/v) CH_3CN in pH 7.0 (0.01 M) phosphate buffer was used as the mobile phase. R_m vs. percent (v/v) of CH_3CN curves were parallel for all compounds, but values in 25% (v/v) CH_3CN are reported because the 0% (v/v) extrapolated values would be too high for these lipophilic compounds and consequently much less accurate than values at a fixed percent (v/v) of CH_3CN.

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Piperazinylpyrazines with Central Serotoninmimetic Activity

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A series of 2-(1-piperazinyl)pyrazines was synthesized and evaluated for central serotonin-like activity. The most interesting member of the series, 6-chloro-2-(1-piperazinyl)pyrazine (**3a**), had pharmacological properties characteristic of potent central serotoninmimetic activity and only weak peripheral serotoninmimetic action. Structural similarities between **3a** and serotonin are discussed.

Evidence that serotonin plays an important role in the physiology of the normal mammalian central nervous system as well as in certain pathological states is increasing steadily.[1,2] A number of compounds of diverse structure have been reported recently[3-10] to enhance central serotonin function by selectively inhibiting reuptake of serotonin or by acting as serotonin agonists. Prior to these reports we had begun a search for substances which enhance central nervous system serotonin function because of their potential utility in the treatment of depression, obesity, and sleep disorders. Our approach utilized the mouse head twitch assay[11] as a measure of central serotoninmimetic activity and contraction of the isolated rat uterus[12] as a measure of unwanted peripheral serotoninmimetic activity.

Several other classes of aryl- and heteroarylpiperazines with central serotoninmimetic activity have been discovered during the course of this work, the most promising of which were the piperazinylpyrazines. One of these, 6-chloro-2-(1-piperazinyl)pyrazine (**3a**), notable for its selectivity for the central nervous system, was selected as a clinical candidate.

In this paper we describe the synthesis of selected piperazinylpyrazines and give evidence for their selective central serotoninmimetic action compared with quipazine.[3] Further details of potential advantages over other serotonin-like compounds of current interest (e.g., fenfluramine and quipazine) will be published elsewhere.

Chemistry. Most of the piperazinylpyrazines of Table I were synthesized readily by reaction of the appropriate chloropyrazine **1** with piperazine or an N-substituted derivative **2**. Formation of bis(pyrazinyl)piperazines **4** proved to be a troublesome side reaction when piperazine itself was used, since the bis products were frequently difficult to separate completely from **3**. In some cases, e.g., **3d** and **3j** (Table I), remaining traces of the bis products were removed through chromatography over neutral Al_2O_3. Formation of **4** was found to be repressed, but not eliminated, through use of excess piperazine or by conducting the reaction *neat* at the melting point of piperazine.

Intermediate chloropyrazines **1** required for synthesis of **3b,g,h,j,o,p** were prepared from the corresponding 2-pyrazinones **5** by treatment with $POCl_3$ or, in the case

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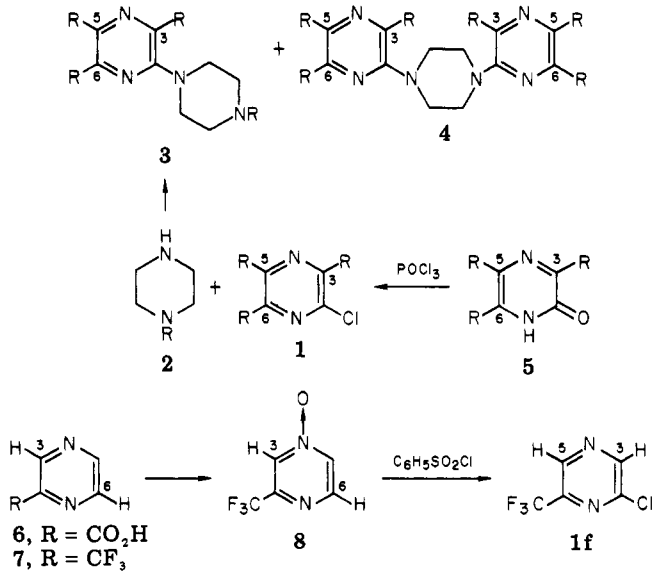
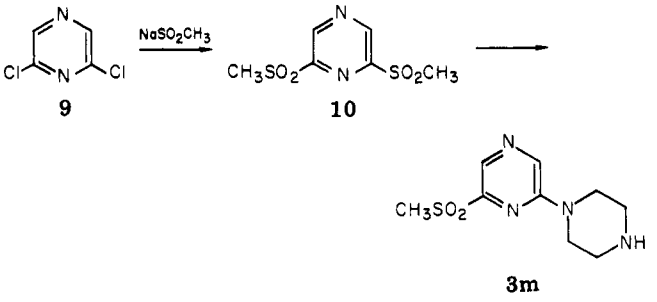


of **1f**, from the *N*-oxide **8** with benzenesulfonyl chloride. This latter procedure yielded a single chloro isomer, the structure of which was shown to be **1f** by its H_3–H_5 ^1H NMR coupling constant of <1 Hz which is characteristic for 2,6-disubstituted pyrazines.[17,18] Reaction of pyrazine *N*-oxides with chlorinating agents of this type has been reported to give chlorination exclusively meta to the *N*-oxide function.[19] Assignment of structure **8** to the *N*-oxide formed upon oxidation of **7** with H_2O_2 in HOAc was based upon the anticipated upfield shifts[19] of H_6 (24 Hz) and H_3 (28 Hz) in the ^1H NMR of **8** relative to the chemical shift of H_6 and H_3, respectively, in **7**. The trifluoromethylpyrazine **7** was prepared by reaction of **6** with SF_4 in HF.

Substituted chloropyrazines were also obtained by displacement of one of the chlorine atoms of 2,6-dichloropyrazine with methoxide as reported by Cheeseman and Godwin[20] and by dimethylamine, methyl sulfinate, and methyl and phenyl mercaptide. Diazotization of 5-amino-2-chloropyrazine in concentrated H_2SO_4 afforded the corresponding 5-hydroxy derivative which was converted to 2,5-dichloropyrazine with $POCl_3$.[21] The 6-methylsulfonyl analogue **3m** (Table I) was prepared by



displacement of the methylsulfonyl from **10** with piperazine.

Biological Results and Discussion. The piperazinylpyrazines of Table I were examined (ip administration) for their ability to elicit head twitches in mice, a response characteristic of a serotoninmimetic action in the central nervous system. For example, serotonin given intracerebroventricularly is known[11] to produce head twitches in mice. Moreover, 5-hydroxytryptophan, the precursor of serotonin in vivo, is active orally in the same protocol.[11] These findings are consistent with the fact that 5-hydroxytryptophan, but not serotonin, crosses the blood–brain barrier. Elicitation of head twitches thus suggests a central serotoninmimetic action. Quipazine, a peripherally and centrally acting serotonin agonist, was included in the study for comparison.

As shown by the data in Table I, only the 6-Cl (**3a**) and 6-CH_3 (**3h**) derivatives produced a head twitch response in all of the mice at both dose levels. By comparison, quipazine was considerably less potent. Of the remaining 6-substituted compounds, only the OCH_3 (**3e**), CF_3 (**3f**), and SCH_3 (**3k**) analogues exhibited a high level of activity. The 6-unsubstituted analogue (**3d**) as well as other 6-substituted derivatives, i.e., CN (**3g**), C_6H_5S (**3l**), CH_3SO_2 (**3m**), $(CH_3)_2N$ (**3n**), and C_6H_5 (**3o**), did not produce head twitches at doses up to 30 mg/kg. These results indicate that the degree of central serotoninmimetic activity of the piperazinylpyrazines does not correlate solely with the electronic characteristics, e.g., σ_m, of the 6-substituents.

Whereas the 6-Cl (**3a**) and 6-CH_3 (**3h**) derivatives were found to be the most potent members of this series, the isomeric 5-Cl (**3b**), 3-Cl (**3c**), and 3-CH_3 (**3j**) analogues were considerably less effective in eliciting head twitches. Addition of a 3-CH_3 group, as in **3i** to the highly active 6-CH_3 derivative, led to a substantial decrease in activity. These results indicate that head shake activity does not correlate solely with lipophilicity.

Substitution on the piperazine nitrogen, as in **3s** and **4a**, or conversion of **3a** to the lactam **3r** eliminated activity. These results suggest that a basic NH may be required for serotoninmimetic activity.

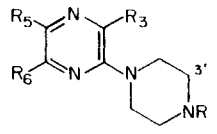
The finding that pretreatment with methergoline or cyproheptadine, but not with xylamidine, markedly antagonized the ability of **3a** to elicit head twitches (Table II) provides strong evidence for a central serotoninmimetic action by **3a**. Xylamidine was much less effective, partially but significantly antagonizing the action of **3a** only at the 60-min observation time. Both methergoline and cyproheptadine are well-known antagonists of serotonin which have been reported previously to be antagonists of 5-hydroxytryptophan-induced head twitches in rats,[22] whereas xylamidine is active peripherally as a serotonin antagonist but penetrates poorly into the central nervous system.[11,23] The dose (1 mg/kg) of xylamidine used in this experiment would be expected from the previous studies[11,23] to block nearly completely peripheral serotonin receptors.

The isolated rat uterus has been widely used for the study of serotoninmimetic substances and antagonists of serotonin.[12] As shown in Table III, **3a**, like serotonin, produced a contraction of the uterus. Since the contractile effects of both serotonin (0.01 μg/mL) and **3a** (10 μg/mL) were antagonized by the relatively selective serotonin antagonists hydroxindasol[24] (0.03 or 0.3 μg/mL) and methylsergide[25] (0.001 μg/mL), it can be concluded that **3a** possesses a serotonin-like action also on this tissue. Based on the EC_{50} values, **3a** was about 300 times less active than serotonin in this in vitro assay. However, since the dose–response curves were not parallel, it was not possible to determine their relative potencies exactly.

These studies suggest that **3a** is novel in that it produces significant central serotoninmimetic effects while exhibiting only relatively weak serotonin-like activity[26] in the isolated rat uterus. Further studies on the possible selectivity of **3a** for the central nervous system will be published elsewhere.[26]

Molecular Orbital and Strain Energy Calculation. Classical strain energy calculations[27] and CNDO molecular orbital techniques[28] aided by computer graphics[29] were employed to determine the minimum energy conformations of **3a**. These preferred conformations of **3a** were then

Table I. 2-(1-Piperazinyl)pyrazines—Physical Constants and Mouse Head-Twitch Activity



Compd	R	R_3	R_5	R_6	Formula[a]	Mp, °C	Recrystn solvent	Method	Yield, %	No. of mice exhibiting head twitch[b] 6 mg/kg[c]	30 mg/kg[c]
3a	H	H	H	Cl	$C_8H_{11}ClN_4 \cdot HCl$	350 dec	2 N HCl	A	50	5	5
3b	H	H	Cl	H	$C_8H_{11}ClN_4 \cdot HCl$	301–302 dec	EtOH-H_2O	A	48	0	3
3c	H	Cl	H	H	$C_8H_{11}ClN_4 \cdot HCl \cdot 0.25H_2O$	218–220 dec	MeOH-EtOH	E	50	0	0
3d	H	H	H	H	$C_8H_{12}N_4 \cdot HCl$	244–248 dec[d]	MeOH-EtOAc	D	25	0	2
3e	H	H	H	OMe	$C_9H_{14}N_4O \cdot 2HCl$	189–199 dec	MeOH	A	22	3	4
3f	H	H	H	CF_3	$C_9H_{11}F_3N_4 \cdot HCl$	292–294 dec	EtOH-H_2O	A	51	4	4
3g	H	H	H	CN	$C_9H_{11}N_5 \cdot AcOH \cdot 0.25H_2O$	130–131 dec	*i*-PrOH	A	25	0	0
3h	H	H	H	Me	$C_9H_{14}N_4 \cdot 2HCl$	242 dec[e]	EtOH-H_2O	D	46	5	5
3i	H	Me	H	Me	$C_{10}H_{16}N_4 \cdot 2HCl \cdot 0.25H_2O$	234–236 dec	EtOH-H_2O	D	66	0	1
3j	H	Me	H	H	$C_9H_{14}N_4 \cdot 2HCl$	225–240 dec[f]	*i*-PrOH	D	24	0	0
3k	H	H	H	MeS	$C_9H_{14}N_4S \cdot HCl$	269–270	EtOH-H_2O	A	49	4	4
3l	H	H	H	C_6H_5S	$C_{14}H_{16}N_4S \cdot HCl$	221–222	EtOH	A	54	1	2
3m	H	H	H	$MeSO_2$	$C_9H_{14}N_4O_2S \cdot HCl$	250 dec	EtOH-H_2O	C	16	0	1
3n	H	H	H	Me_2N	$C_{10}H_{17}N_5 \cdot 2HCl$	249–250 dec	EtOH-H_2O	D	39	0	0
3o	H	H	H	C_6H_5	$C_{14}H_{16}N_4 \cdot 1.5HCl$	305 dec	EtOH	A	49	1	0
3p	H	H	C_6H_5	H	$C_{14}H_{16}N_4 \cdot HCl$	306–314 dec	MeOH	E	67	0	0
3q	H	Cl	CO_2Me	NH_2	$C_{10}H_{14}ClN_5O_2 \cdot HCl$[g]	252–253	MeOH-EtOH	A	45	1	0
3r	(3'-one)	H	H	Cl	$C_8H_9ClN_4O$	192–193	H_2O	A	54	0	0
3s	$(CH_2)_3NMe_2$	H	H	Cl	$C_{13}H_{22}ClN_5 \cdot 2HCl \cdot 0.5H_2O$	284–285 dec	EtOH-H_2O	*h*	26	0	0
4a	$C_4H_2ClN_2$[i]	H	H	Cl	$C_{12}H_{12}Cl_2N_6$	193–194	$MeCO_2H$	B	43	0	1
Quipazine[j]										2	4

[a] C, H, and N analyses were within ±0.4% of the theoretical values except where indicated. [b] Five mice treated at each dose level. [c] Dose ip. Compound administered 60 min before observation for head twitches. [d] Lit.[13] mp 250–251.5 °C dec. [e] *p*-TosOH salt reported.[14] [f] HCl and *p*-TosOH salts reported.[14,15] [g] N: calcd, 22.73; found, 22.24. [h] Prepared by literature procedure.[16] [i] 6-Chloro-2-pyrazinyl. [j] Reference 3.

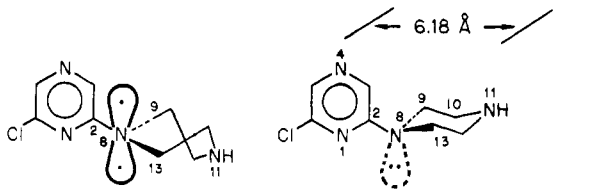
Table II. Effect of Pretreatment with Methergoline, Cyproheptadine, or Xylamidine on Head Twitches Elicited in Mice by 6-Chloro-2-(1-piperazinyl)pyrazine Hydrochloride (3a)

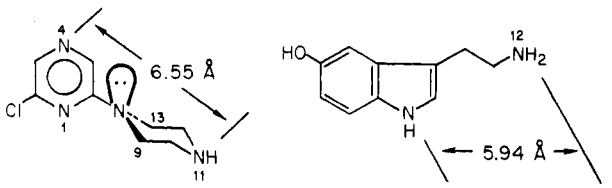
Pretreatment[a] (mg/kg ip)	Treatment (mg/kg ip)	No. of head twitches (six mice/2 min)[b] 30 min	60 min
Vehicle	Vehicle	2.4 ± 2.9	2.4 ± 1.8
Methergoline (1)	Vehicle	0.6 ± 0.5	1.2 ± 1.6
Vehicle	3a (10)	23.8 ± 5.8[c]	29.6 ± 8.0[c]
Methergoline (1)	3a (10)	0.6 ± 0.9[d]	0.8 ± 1.3[d]
Vehicle	Vehicle	1.6 ± 1.7	1.2 ± 1.1
Vehicle	3a (10)	22.6 ± 7.1[c]	26.8 ± 5.5[c]
Xylamidine (1)	3a (10)	15.4 ± 9.0[c]	13.8 ± 8.0[c,d]
Xylamidine (1)	Vehicle	4.6 ± 2.6	3.2 ± 3.3
Cyproheptadine (1)	3a (10)	3.2 ± 4.0[d]	5.2 ± 3.7[c,d]
Cyproheptadine (1)	Vehicle	1.4 ± 1.1	2.8 ± 2.8

[a] One hour prior to treatment; all doses refer to the free base. [b] $X \pm SD$ of five groups of six mice/group for each treatment; the mice were observed under blind conditions 30 and 60 min after treatment. [c] $p < 0.05$ (two-tailed, t test) vs. vehicle + vehicle. [d] $p < 0.05$ (two-tailed, t test) vs. vehicle + 3a.

compared with serotonin in order to determine those structural features of **3a** which might interact with serotonin receptors.

In one approach, strain energies of various conformers of **3a** with N_8 constrained to either sp^2 or sp^3 hybridization[30] were minimized and CNDO binding energies calculated with the strain-minimized coordinates. In the case of sp^2 geometry, strain energy calculations yielded the chair-like structure **11a**, in which the electron





pair of N_8 is perpendicular to (unconjugated with) the π orbitals of the pyrazine ring, with a minimum strain energy of 15.8 kcal/mol. For sp^3 geometry, a minimum strain energy of 18.2 kcal/mol was calculated for the chair conformation **11b** in which the pyrazine ring occupies an equatorial relationship to the piperazine ring and the N_8 electron pair is not in conjugation with the pyrazine π orbitals. CNDO calculations indicated the molecular binding energy of **11b** (−7286 kcal/mol) to be approximately 14 kcal/mol greater (more negative) than for **11a** (−7272 kcal/mol), suggesting that sp^3 hybridization is the lower energy state.

Strain minimization of a rotamer **11c** of **11b** (strain energy = 18.2 kcal/mol) (obtained by rotation of the piperazine ring of **11b** 180° around the 2,8 bond) resulted in major distortions of the piperazine ring and led to a decrease of 1.5 kcal/mol in strain energy and a decrease of approximately 2.2 kcal/mol in binding energy.

In a second approach, coordinates were generated for the sp^2 structure **11a** and the sp^3 chair structure **11c** using bond lengths and angles from the first approach but substituting pyrazine ring parameters from the X-ray structure of pyrazine[31] (see the Experimental Section). Strain and binding energies of these (nonstrain minimized) structures were then studied as a function of the degree of rotation around the 2,8 bond. The results are summarized in Figure 1 for sp^2 hybridization at N-8 and in Figure 2 for sp^3 hybridization at this center.

Table III. Relative Activities of Serotonin and 6-Chloro-2-(1-piperazinyl)pyrazine Hydrochloride (3a) on the Isolated Rat Uterus

Compd	Concn, μg/mL	Grams of tension developed	% of maximal tension developed
Serotonin	0.00050	0.22 ± 0.07[a]	7
	0.00075	1.23 ± 0.42	37
	0.001	2.32 ± 0.30	70
	0.005	2.67 ± 0.41	80
	0.01	3.08 ± 0.45	92
	0.05	3.18 ± 0.45	95
	0.10	3.20 ± 0.45	96
	EC_{50} = 0.0083 (0.0074-0.0097)[b]		
Methacholine	1.0	3.33 ± 0.48	100
3a	0.1	0.0	0
	0.5	0.27 ± 0.10	10
	1.0	0.40 ± 0.12	15
	5.0	2.12 ± 0.17	80
	10.0	2.28 ± 0.17	86
	20.0	2.42 ± 0.22	91
	EC_{50} = 2.411 (2.106-2.765)[b]		
Methacholine	1.0	2.65 ± 0.34	100

[a] $X \pm$ SEM of six tissues. [b] 95% confidence limits in parentheses.

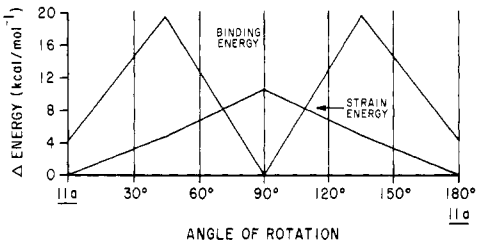


Figure 1. Calculated binding and strain energies of **11a** as a function of rotation around the 2,8 bond.

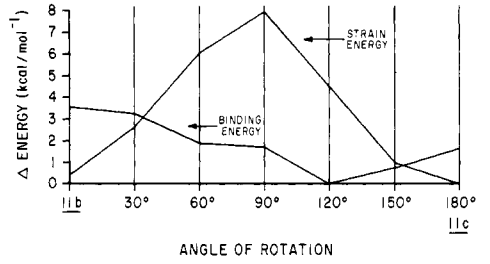


Figure 2. Calculated binding and strain energies of **11c** as a function of rotation around the 2,8 bond.

For sp^2 hybridized N-8 (Figure 1), the conformation with the N-8 lone pair conjugated with the pyrazine ring (θ = 90°) is electronically the most stable (minimum binding energy) but also the most strained (maximum strain energy). The conformation with the N-8 lone pair orthogonal to the pyrazine orbitals is only slightly less stable electronically (+4 kcal/mol binding energy) but is significantly less strained (ca. 10 kcal/mol), while intermediate conformations show a steep rise in strain energy. Since CNDO underemphasizes nonbonded repulsions,[32] **11a** may actually be the total energy minimum.

Table IV. Structural Comparison of 11b and 11c with Serotonin

Structure	Calcd N_1 charge[a]	Calcd N_4 charge[a]	Calcd N_4-N_{11} distance, Å	Calcd N_1-N_{11} distance, Å
11b	−0.1310	−0.0917	6.18	5.25
11c	−0.1395	−0.0867	6.55	4.83
Serotonin (12)	−0.108			5.94[b]

[a] Net atomic charge (esu). [b] Calcd N_1-N_{12} distance.

For sp^3 hybridized N-8 (Figure 2), the binding energy varies only slightly with rotation about the 2,8 bond, but strain energy is at a maximum again at $\theta = 90°$. In agreement with the first approach, the binding energy is 14 kcal/mol more negative and the strain energy only 2 kcal/mol higher for sp^3 than for sp^2 geometry. Again, we favor the deconjugated structures **11b,c** as the best representations of the total energy minimum.

Results of our CNDO calculations on strain minimized serotonin agree qualitatively with the INDO result of Kang and Cho[33] but differ significantly from the extended Hückel results of Kier.[34] Standard bond lengths and angles were used in both of these calculations.

As shown in Table IV, the net atomic charge of the indole nitrogen of serotonin (−0.1081 esu) compared more favorably with the N_4 charge densities of **11b** or **11c** than the corresponding N_1 charge densities. N_4–N_{11} interatomic distances of 6.18 and 6.55 Å, respectively, for **11b** and **11c**, in contrast to the N_1–N_{11} separations, also approximate the N_1–N_{12} interatomic distance of 5.94 Å calculated for serotonin.

The results of these calculations suggest that sp^3-hybridized **3a** is lower in energy, that the various energy minima for sp^3-hybridized **3a** are readily equilibrated at ambient conditions, and that one of these, **11b**, is most similar to serotonin in geometry and charge localization at basic N atoms. The possibility that the structure **11b** is relevant to the geometry of serotonin receptors is under continuing study.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus using open capillaries and are uncorrected. Microanalytical results on all new compounds are indicated by the atom symbols and are within ±0.4% of the theoretical values. NMR spectra were recorded on a Varian T-60 spectrophotometer in $CDCl_3$–Me_4Si unless otherwise specified. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Infrared spectra were recorded on Perkin-Elmer grating spectrophotometers. TLC was performed on silica gel GF plates and components were visualized by I_2 exposure, short or long wavelength UV fluorescence properties, or by spraying with Dragendorff reagent (available from Quantum Industries). Gas–liquid chromatography was performed on a Hewlett-Packard 5710 gas chromatograph equipped with flow-matched 6 ft × 0.25 in. stainless steel columns with 5% stationary phase on 60–80 mesh acid-washed dimethylchlorosilane-treated Chromosorb W and thermal conductivity detectors [Hewlett-Packard columns A (OV17) and B (OV210)]. Yields were not optimized and refer to the amount of the analytical sample.

2-Piperazinylpyrazines. Method A. 6-Chloro-2-(1-piperazinyl)pyrazine Hydrochloride (3a). A solution of 298 g of technical 2,6-dichloropyrazine (2.0 mol) and 400 g of piperazine (4.64 mol) in 3 L of CH_3CN was stirred and heated on the steam bath to an internal temperature of 70 °C. After an exotherm to 80 °C had subsided, the mixture was stirred and heated 2 h on the steam bath.

The mixture was cooled and concentrated under vacuum and the residue partitioned between 1 L of 2 N NaOH and 1 L of C_6H_6. The aqueous layer was extracted with two additional 1-L portions of C_6H_6 and the combined extracts were washed with two 300-mL portions of 2 N NaOH. The extracts were dried (Na_2SO_4) and concentrated under vacuum to give 310 g of crude product which was dissolved in 1 L of hot 2 N HCl. The hot mixture was filtered to remove insoluble *N,N'*-bis(6-chloro-2-pyrazinyl)piperazine (**4a**) and the filtrate cooled to give 214 g (46%, dry weight) of nearly colorless needles of 6-chloro-2-(1-piperazinyl)pyrazine hydrochloride: mp 350 °C dec; homogeneous on TLC (9:1 $CHCl_3$ saturated with aqueous NH_3–MeOH); UV (H_2O) λ_{max} 250.5 nm (ϵ 15 900), 334.5 (6620). Anal. ($C_8H_{11}ClN_4$·HCl) C, H, N, Cl.

Method B. *N,N'*-Bis(6-chloro-2-pyrazinyl)piperazine (4a). A mixture of 60 g of technical 2,6-dichloropyrazine (0.40 mol), 17.2 g of anhydrous piperazine (0.20 mol), and 42.5 g of Na_2CO_3 (0.37 mol) in 100 mL of CH_3CN was refluxed under N_2 for 18 h. The hot mixture was diluted to 400 mL with cold water, mixed with 100 mL of EtOAc, and filtered to give 40 g of crude product which was recrystallized from 250 mL of glacial AcOH to afford 26.7 g (43%) of light yellow *N,N'*-bis(6-chloro-2-pyrazinyl)-piperazine: mp 193–194 °C; homogeneous on TLC (9:1 $CHCl_3$ saturated with aqueous NH_3–MeOH). Anal. ($C_{12}H_{12}Cl_2N_6$) C, H, N, Cl.

Method C. 6-Methylsulfonyl-2-(1-piperazinyl)pyrazine Hydrochloride (3m). A mixture of 3.54 g of 2,6-bis(methylsulfonyl)pyrazine (0.015 mol) and 3.55 g of anhydrous piperazine (0.041 mol) in 25 mL of CH_3CN was stirred 30 min at room temperature and then refluxed 15 min under N_2. The cooled mixture was concentrated under vacuum and the residue partitioned between $CHCl_3$ and H_2O. The combined $CHCl_3$ extracts were washed with two 10-mL portions of 2 N NaOH and 20 mL of saturated Na_2CO_3 and dried (Na_2SO_4). The $CHCl_3$ extract was concentrated under vacuum and the residue chromatographed on silica gel. Elution with 10% MeOH–$CHCl_3$ gave fractions free of a yellow, more polar impurity which were combined and concentrated under vacuum to an oil. Treatment of the oil with EtOH–HCl in *i*-PrOH gave 0.7 g of the crude hydrochloride which was recrystallized from EtOH–H_2O to give yellow plates of 6-methylsulfonyl-2-(1-piperazinyl)pyrazine hydrochloride: decomposition without melting at 250 °C. Anal. ($C_9H_{14}N_4O_2S$·HCl) C, H, N.

Method D. 2-(1-Piperazinyl)pyrazine Hydrochloride (3d). A vigorously stirred mixture of 33.4 g (0.292 mol) of 2-chloropyrazine and 36.1 g (0.419 mol) of anhydrous piperazine was heated cautiously to 140 °C in an oil bath. After the initial vigorous reaction had subsided, heating was continued for 1 h at 140 °C. The cooled reaction mixture was ground to a powder and slurried with 250 mL of water. Filtration removed 10.1 g of the bis condensation product. The filtrate was made strongly basic with 10% NaOH and the crude product extracted into three 150-mL portions of $CHCl_3$. After drying (Na_2SO_4), filtering, and concentrating under reduced pressure, the residual oil, 22.6 g, was chromatographed over 450 g of neutral alumina. The bis condensation product was removed by elution with 2.4 L of C_6H_6 and the desired product eluted with 6 L of $CHCl_3$. The $CHCl_3$ fractions containing product were combined and concentrated under reduced pressure to an oil which was converted with EtOH–HCl to 14.5 g (24.9%) of the monohydrochloride contaminated with a small amount of the dihydrochloride: mp (225 °C shrinks) 245–248 °C dec. Recrystallization from MeOH–EtOAc containing pyridine gave the pure monohydrochloride, mp 244–248 °C dec. Anal. ($C_8H_{12}N_4$·HCl) C, H, N.

Method E. 5-Phenyl-2-(1-piperazinyl)pyrazine Hydrochloride (3p). After stirring a mixture of 5.58 g (0.029 mol) of 2-chloro-5-phenylpyrazine,[17] 7.56 g of anhydrous piperazine, and 60 mL of *n*-BuOH at reflux for 24 h and cooling, solvent was removed from reduced pressure. The residue was diluted with Na_2CO_3 solution and the product extracted into three 100-mL portions of $CHCl_3$. After drying the $CHCl_3$ extracts (Na_2SO_4), filtering, and concentrating, the residue was converted to the HCl salt with EtOH–HCl in hot EtOH. Recrystallization from MeOH containing pyridine (to convert the dihydrochloride to the monohydrochloride) gave 5.4 g (67.3%) of 5-phenyl-2-(1-piperazi-

nyl)pyrazine hydrochloride, mp 306–314 °C dec. Anal. ($C_{14}H_{16}N_4$·HCl) C, H, N.

Intermediates. 2-Trifluoromethylpyrazine (7). A stainless steel pressure tube reactor (300-mL capacity) was charged with 50 g of 2-pyrazinecarboxylic acid (0.404 mol), 50 mL of HF, 108 g of SF_4 (1.0 mol), and 1 drop of mercury. The tube was electrically heated with rocking for 6 h at 150 °C. The mixture was cooled, vented, and, after 3 days, quenched on ice and filtered. The filtrate was adjusted to pH 6 with NaOH and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed (H_2O), dried (Na_2SO_4), and distilled at atmospheric pressure to give a fraction, bp 118 °C, representing 20 g (68%) of 2-trifluoromethylpyrazine: homogeneous on GLC (columns A and B; 70 °C); ^{19}F NMR ($\delta_{CF_3} - \delta_{FCl_3}$) 67.6 ppm. Anal. ($C_5H_3F_3N_2$) C, H, N.

2-Trifluoromethylpyrazine 4-Oxide (8). A mixture of 15.9 g of 2-trifluoromethylpyrazine (0.107 mol), 30 mL of glacial AcOH, and 20 mL of 30% H_2O_2 was stirred 72 h at 70 °C. After quenching on ice and extracting with six volumes of C_6H_6, the combined C_6H_6 extract was washed (H_2O), dried (Na_2SO_4), and distilled to give C_6H_6 and some unchanged starting material. The distillation residue was crystallized from hexane to give 7.6 g (89% based on recovered starting material) of 2-trifluoromethylpyrazine 4-oxide: mp 57–59 °C; ^{19}F NMR ($\delta_{CF_3} - \delta_{FCl_3}$) 68.8 ppm. Anal. ($C_5H_3F_3N_2O$) C, H, N.

2-Chloro-6-trifluoromethylpyrazine (1f). A stirred mixture of 3.28 g of 2-trifluoromethylpyrazine 4-oxide (0.020 mol) and 5 mL of benzenesulfonyl chloride was heated 4 h at 100 °C in a sealed vessel. The resulting mixture was fractionally distilled to give 1.6 g (44%) of 2-chloro-6-trifluoromethylpyrazine: bp 135 °C; GLC shows >99% one component (columns A and B). Anal. ($C_5H_2ClF_3N_2$) C, H, N.

6-Methylthio-2-chloropyrazine. A solution of 5.5 g of commercial $NaOCH_3$ in 200 mL of DMF under N_2 was saturated with CH_3SH. Technical 2,6-dichloropyrazine (15.9 g) was added to the resulting stirred suspension through a gooch tubing. After 1 h the mixture was heated on the steam bath to expel CH_3SH and then concentrated under vacuum. The oily residue was partitioned between C_6H_6 and H_2O, and the C_6H_6 extract was washed (H_2O), dried (Na_2SO_4), and concentrated under vacuum to an oil. The crude product was dissolved in 100 mL of *i*-PrOH and treated with 10 mL of 6 N EtOH–HCl. The mixture was cooled 2 h at 0 °C and filtered and the filtrate concentrated under vacuum. The residual yellow solid was partitioned between Na_2CO_3 solution and C_6H_6. C_6H_6 extract was dried (Na_2SO_4) and concentrated under vacuum to an oil which was distilled to give 8 g (50%) of 6-methylthio-2-chloropyrazine: bp 105 °C (20 mm); ^1H NMR δ 2.57 (CH_3). Anal. ($C_5H_5ClN_2S$) C, H, N.

6-Phenylthio-2-chloropyrazine. A stirred mixture of 15.9 g of technical 2,6-dichloropyrazine and 11 g of C_6H_5SH (0.10 mol) in 200 mL of DMF was treated under N_2 with 5 g of ca. 50% NaH–Nujol emulsion through a gooch tubing. The resulting mixture was stirred 3 h at room temperature and concentrated under vacuum, and the remaining oil was partitioned between C_6H_6 and H_2O. The C_6H_6 extract was dried (Na_2SO_4) and concentrated under vacuum to an oil which was chromatographed on 200 g of silica gel. Elution with hexane and then $CHCl_3$ gave 20.5 g (92%) of a light yellow oil, a sample of which was distilled, bp 121–122 °C (0.2 mm), to give an analytical sample of 6-phenylthio-2-chloropyrazine. Anal. ($C_{10}H_7ClN_2S$) C, H, N.

6-(*N*,*N*-Dimethylamino)-2-chloropyrazine. A cooled, stirred solution of 49.9 g of technical 2,6-dichloropyrazine (0.33 mol) in 250 mL of *i*-PrOH was treated with a stream of Me_2NH until 36 g (0.8 mol) had been absorbed (mild exotherm). The mixture was maintained at 35–40 °C for 2 h and then stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 extract was washed (saturated NaCl), dried (Na_2SO_4), and concentrated under vacuum to an oily solid which was recrystallized several times from *i*-PrOH–H_2O to give 16.1 g (31%) of 6-(*N*,*N*-dimethylamino)-2-chloropyrazine: mp 44–45 °C. Anal. ($C_6H_8ClN_3$) C, H, N.

2,6-Bis(methylsulfonyl)pyrazine (10). A solution of 5.35 g of technical 2,6-dichloropyrazine (0.036 mol) in 150 mL of DMF was vacuum distilled to remove 50 mL of DMF and then treated with 8.0 g of sodium methylsulfinate (0.078 mol) with stirring under N_2. The mixture was heated for 20 min at 100 °C and then stirred overnight while cooling to room temperature. The cooled mixture was concentrated under vacuum and the residue crystallized twice from H_2O to give 4.5 g (53%) of 2,6-bis(methylsulfonyl)pyrazine: mp 186–188 °C; IR 1130, 1310 cm^{-1}; ^1H NMR δ 3.45 (s, CH_3). Anal. ($C_6H_8N_2O_4S_2$) C, H, N.

Table V. Input Coordinates to the COORD Program for 11c

ijkl	r_{rl}	θ_{jkl}	ϕ_{ijkl}
1,2,3	(1.334)[a]	(1.378)[a]	(122.4)[a]
1,2,3,4	1.334	122.4	0
2,3,4,5	1.334	115.1	0
3,4,5,6	1.378	122.4	0
4,5,6,7	1.722	118.8	180
4,3,2,8	1.421	118.8	180
3,2,8,9	1.488	114.6	114.6
3,2,8,13	1.488	114.6	245.4
2,8,9,10	1.534	110.74	−172.21
8,9,10,11	1.482	111.23	−55.56
2,8,13,12	1.534	110.74	172.21

[a] The first line values are $r_{1,2}$, $r_{2,3}$, $\theta_{1,2,3}$.

Biological Methods. Head Twitch. Mice, CF Carworth females weighing 18–22 g, were injected intraperitoneally with the test compounds at two dose levels, 6 and 30 mg/kg. Five mice were used at each dose level for each compound. One hour after injection, the mice were observed for 2 min by an investigator who was not aware of the compound under investigation. The number of mice exhibiting one or more head twitches during the observation period was recorded.

Experiments were also carried out to ascertain the effect of pretreatment with serotonin antagonists on the ability of the 6-chloro derivative **3a** to elicit the head-twitch response. In this procedure the animals were pretreated with methergoline, cyproheptadine, xylamidine, or vehicle 1 h before treatment with **3a**·HCl or vehicle. The mice were observed under random and blind conditions for twitching of the head. Variability of the test procedure was reduced by using six mice for each of the various treatment groups and recording the total number of head twitches occurring during a 2-min observation period for all six mice receiving the same treatment. In other words, to achieve an N of 5 for a particular group, a total of 30 mice received that treatment. The same number of animals in each of the treatment groups of an individual experiment was always tested concurrently.

Methergoline was dissolved in 2.5% ascorbic acid while all other compounds were dissolved or suspended in 1% methylcellulose and injected ip using a volume of 0.1 mL/10 g of body weight. Cyproheptadine hydrochloride was obtained from Merck Sharp & Dohme, West Point, Pa.; methergoline from Farmitalia, Milan, Italy; and xylamidine tosylate from Wellcome Research Laboratories, Beckenham, England.

Isolated Uterus. Uterine horns were removed from Charles River rats (150–200 g of body weight) treated subcutaneously 24 h earlier with 0.16 mg of diethylstilbestrol. The horns were suspended in De Jalon's solution,[35] maintained at 37 °C, and oxygenated by bubbling 95% O_2–5% CO_2 through the solution. The uterine horns were placed under an initial tension of 1 g. Maximal isometric contractions were obtained with methylcholine (1 μg/mL) prior to determination of a dose–response effect for serotonin or **3a**. The dose–response studies were done in a cumulative fashion; i.e., after the uterus had contracted maximally to a given concentration of agonist, additional drug was added to the bath to achieve the next higher concentration without an intervening washout. **3a**·HCl and serotonin were each tested on six separate tissues. Data are expressed as percent of the maximum response obtained with methacholine. EC_{50} and 95% confidence limit values were estimated.[36]

A separate study was preformed to ascertain the effect of two serotonin antagonists, hydroxindasol and methylsergide, on the contractile response to maximal stimulating doses of serotonin (0.01 μg/mL) or **3a**·HCl (10 μg/mL). Each agonist was studied on three separate uterine horns. The concentrations of serotonin creatinine sulfate (Regis Chemical Co.), methylsergide maleate (Sandoz), hydroxindasol hydrochloride (Merck), methylcholine chloride (Merck), and **3a**·HCl are expressed as the base (Table V).

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Novel Anxiolytic Agents Derived from α-Amino-α-phenyl-*o*-tolyl-4*H*-triazoles and -imidazoles[1]

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Several new α-amino-α-phenyl-*o*-tolyltriazoles and -imidazoles have been prepared in one step by means of a novel reductive rearrangement of the corresponding benzodiazepines with hydrazine hydrate. These new triazoles were found to have moderate sedative and muscle relaxing activity in mice (i.e., these compounds depressed the traction and dish reflexes at higher doses than did diazepam) but were very potent antagonists of the clonic convulsions induced in mice by the administration of pentylenetetrazole. Furthermore, they antagonized the lethality induced by thiosemicarbazide. While these new compounds were very active in mice, most were inactive in rats. These results are discussed with reference to the metabolism of compound **13**.

A recent report attributed potent muscle relaxant and anticonvulsant activity to a series of new triazoles, **1a**, which may be considered to be ring-opened analogues of the corresponding triazolobenzodiazepines, **2**, wherein the

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