inervated (Pavlov) gastric pouches, were food deprived with access to water 24 h prior to experiments. Following a 30-min basal collection period, the prostaglandin in the buffer/ethanol vehicle was administered into the pouch through a Thomas cannula. Thirty minutes later the gastric pouch was emptied and gastric secretion was stimulated by feeding 10–12 oz of canned dog food (Evanger's Dog and Cat Food Co., Inc., Wheeling, IL). Gastric juice samples were collected over a 4-h period at 30-min intervals. Total acid output (mequiv/30 min) was determined for each collection period by multiplying the volume of secretion (mL/30 min) and the acidity (mequiv/L). For new compounds, percent reduction of total acid output from control was calculated over each 4-h experiment for 2–5 doses and 2–7 dogs were used for each dose. Dose response curves and ED_{50} values were estimated by using linear regression and 95% confidence limits were determined by using Fieller's method.[24]

(24) Draper, N. R.; Smith, H. *Applied Regression Analysis*, 2nd ed.; John Wiley & Son: New York, 1981; pp 30–31.

Diarrheal Studies. Adult Charles River male rats weighing 210–230 g were individually housed and fasted with water available ad libitum for a 24-h prior to the test. The animals (N = 6–12) received logarithmically graded prostaglandin doses orally. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all or none basis for 8 h after drug treatment. The ED_{50} and 95% confidence intervals were calculated by logistic regression.

Acknowledgment. We thank J. Casler and C. Ponte for technical assistance in the antisecretory and diarrheal studies, M. Carniello for statistical analysis of the data, B. Rowell for resynthesis of **5g**, the group of E. Hajdu for spectral data, the group of E. Zielinski for microanalyses, and D. Weiman for typing the manuscript. We also thank Professors Paul A. Grieco and Anthony Barrett for helpful discussions and suggestions concerning the acid-catalyzed and oxidative reactions of **5d**.

Pyrroloisoquinoline Antidepressants. 3. A Focus on Serotonin

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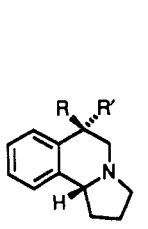
Received February 12, 1990

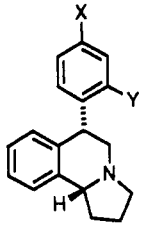
A collection of hexahydropyrroloisoquinoline derivatives (**1–22**), which represent a class of compounds that inhibit the neuronal uptake of dopamine (DA), norepinephrine (NE), and serotonin (5-HT), was investigated in vivo for serotonin-potentiating properties in the mouse head-twitch and rat serotonin syndrome assays. The *p*-methylthio compound **3b** (McN-5652-Z) was found to possess exceptional activity in these assays, and the activity was attributable almost exclusively to the (+)-6*S*,10b*R* enantiomer. Ten closely related analogues were synthesized, tested, and compared among themselves and with some previously prepared compounds, both in vivo and in vitro. Several trans diastereomers exhibited strong inhibition of 5-HT uptake and substantial potentiation of 5-HT, while the cis diastereomers (**3a**, **4a**, and **10a**) tested were virtually devoid of such activity. Although **3b** was only moderately selective in inhibiting the uptake of 5-HT vs NE, its 10-substituted analogues **4b**, **7b–9b** had improved 5-HT selectivity relative to NE, to the extent of 20–25 times (150–200 times relative to DA). Of these more selective compounds (in vitro), only **4b** and **7b** had substantial activity in vivo. Sulfoxide **11b** appeared to function as a prodrug of **3b** in vivo.

Drugs that potentiate the action of serotonin (5-HT) in the central nervous system (CNS) can be useful in a variety of therapeutic situations, including depression, obsessive–compulsive disorder, obesity, and alcohol abuse.[1] One approach to achieve this objective is the selective blockade of the uptake of serotonin into nerve cells. Over the years, such neuronal 5-HT uptake inhibitors have attracted considerable interest as antidepressants since they generally cause fewer side effects and are safer in overdosage than the more classical drugs, which generally function by potentiating central norepinephrine (NE) systems.[1b,2] Indeed, the recent favorable acceptance of fluoxetine, a selective 5-HT uptake inhibitor, serves to underscore the significance of this type of antidepressant.[3]

We have been investigating pyrroloisoquinoline derivatives for potential activity in the central nervous system.[4] This led to the discovery of a series of compounds, represented by prototype **1**, in which the trans diastereomers (**b** forms) are potent inhibitors of the uptake of biogenic amine neurotransmitters (Table I). Compound **2b** (McN-5707)[4a–c] was identified as a potential antidepressant from a drug-development perspective. During our extensive structure–activity study, we found that **3b** (McN-5652-Z) is an exceedingly potent inhibitor of the uptake of 5-HT into brain synaptosomes, although it is only



1a: R = Ph, R' = H
b: R = H, R' = Ph



2b: X = H, Y = Cl
3b: X = SMe, Y = H

(1) (a) Fuller, R. W. *J. Clin. Psychiatry* **1987**, *48* (Suppl), 5. (b) Asberg, M.; Eriksson, B.; Martensson, B.; Traskman-Bendz, L.; Wagner, A. *Ibid.* **1986**, *47* (Suppl), 23. (c) Fuller, R. W. *Ibid.* **1986**, *47* (Suppl.), 4. (d) Cohn, J. B.; Wilcox, C. *Ibid.* **1985**, *46*, 26. (e) Danish University Antidepressant Group *Psychopharmacology* **1986**, *90*, 131. (f) Asberg, M.; Thoren, P; Cronhelm, B. *Arch. Gen. Psychiatry* **1980**, *37*, 1281. (g) Turner, S. M.; Jacob, R. G.; Beidel, D. C.; Himmelroch, J. *J. Clin. Psychopharmacol.* **1985**, *5*, 207. (h) Blundell, J. E. *Neuropharmacology* **1984**, *23*, 1537. (i) Naranjo, C. A.; Sellers, E. M.; Lawrin, M. O. *J. Clin. Psychiatry* **1986**, *47* (*Suppl.*), 16. (j) Fuller, R. W. *Adv. Drug Res.* **1988**, *17*, 350. (k) For a monograph with a clinical emphasis: Gastpar, M.; Wakelin, J. S., Eds.; *Selective 5-HT Reuptake Inhibitors: Novel or Commonplace Agents*; Karger Press: Basel, 1988.
(2) Anon. *Scrip.* **1987**, October 14, No. 1248, 24.
(3) Anon. *Scrip* **1988**, August 19, No. 1336, 9.

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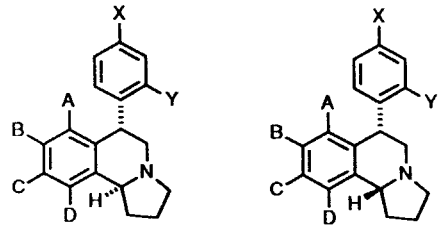
Table I. Chemical and Biological Data



a = cis (6α, 10bα) **b** = trans (6α, 10bβ)

compd	X	Y	A	B	C	D	mol formula[a]	mp, °C (solv)[b]	% dp[c]	TBZ ED_{50},[d] mg/kg MA	TBZ ED_{50},[d] mg/kg ptosis	uptake inhibn: K_i,[e] nM DA	uptake inhibn: K_i,[e] nM NE	uptake inhibn: K_i,[e] nM 5HT	5HTP ED_{50},[f] mg/kg twitch	5HTP ED_{50},[f] mg/kg syndrome
1b	H	H	H	H	H	H	*g*	*g*	*g*	0.34	0.07	11.3	0.60	23.5	>25[h]	
2b	H	Cl	H	H	H	H	*g*	*g*	*g*	>60	0.17	27.4	1.6	9.7	>25[i]	>25
3a	SMe	H	H	H	H	H	*g*	*g*	*g*	>30	10.9	1740	127	16.6	~10	4.5% at 4
3b	SMe	H	H	H	H	H	*g*	*g*	*g*	>30	0.40	36.8	2.9	0.68	0.081	0.20[j]
(+)-3b	SMe	H	H	H	H	H	*g*	*g*				23.5	1.8	0.39	0.043	
(−)-3b	SMe	H	H	H	H	H	*g*	*g*				1450	280	58.4	~5	
4a	SMe	H	H	H	H	Cl	$C_{19}H_{20}ClNS$·HCl	150–153 (D/T)	>99	~1	I-3	10%	10%	~100	30% at 5	
4b	SMe	H	H	H	H	Cl	$C_{19}H_{20}ClNS$·HCl	258–262 (M/P)	>99	I-3	I-3	290	23.1	3.0	1.04	
5b	SMe	H	H	Cl	H	H	$C_{19}H_{20}ClNS$·HCl	249–252 (M/A)	~98	>3	>3	103	16.2	8.6	30% at 5	
6b	SMe	H	OMe	H	OMe	H	$C_{21}H_{25}NO_2S$·HCl	211–213 (EE/A)	>99			67%	55%	68%	~5	
7b	SMe	H	H	H	H	Me	$C_{20}H_{23}NS$·HBr	147–153 (D/T)	>99	>3	~1	57.7	11.5	2.4	0.16	
8b	SMe	H	H	H	H	Br	$C_{19}H_{20}BrNS$·HCl[k]	275–278 (M/A)	>99			652	93.8	4.1	>5	
9b	SMe	H	H	H	H	CN	$C_{20}H_{20}N_2S$·HCl[l]	277–280 (M/A)	>99			2800	390	14.7	>5	
10b	SEt	H	H	H	H	H	$C_{20}H_{23}NS$·HBr[m]	167–168 (P)	98.5	>10	~3	83.9	6.0	3.0	0.54	36% at 40
11a[n]	SOMe	H	H	H	H	H	$C_{19}H_{21}NOS$[l,o]	syrup	>99			2%	4%	12%	>5	
11b[n]	SOMe	H	H	H	H	H	$C_{19}H_{21}NOS$[l,p]	syrup	>99	>3	~2	6180	723	597	0.55	
12b	SO_2Me	H	H	H	H	H	*g*	*g*	*g*	I-30	30	2110	78.7	29.2	~5	1.5% at 4[h]
13b	H	SMe	H	H	H	H	*g*	*g*	*g*			187	4.5	12.7	30% at 5	
14b	H	OMe	H	H	H	H	*g*	*g*	*g*	~0.6	~0.3	278	3.3	3.2	0.81	5.2% at 4[h]
15b	$CONH_2$	H	H	H	H	H	*g*	*g*	*g*			84.5	90.2	19.1	~5	4.5[h]
16b	AcNH	H	H	H	H	H	*g*	*g*	*g*	0.04	0.04	43.7	58.8	15.6	0.31	1.37[q]
17b	CN	H	H	H	H	H	*g*	*g*	*g*			83.0	13.8	7.9	~3	15[h]
18b	Cl	H	H	H	Cl	H	*g*	*g*	*g*	37.4	4.0	3.2	3.2	2.9	30% at 2	22% at 5
19b[r]	Cl	H	H	H	H	H	*g*	*g*	*g*	0.39	0.14	0.99	0.68	1.76	0.76	52% at 5
20b	Cl	Cl	H	H	H	H	*g*	*g*	*g*			111	17.1	8.1	~5	
21b	C≡CH	H	H	H	H	H	*g*	*g*	*g*			2.6	0.94	1.01	~1	
22b	CF_3	H	H	H	H	H	*g*	*g*	*g*	>3	~2	128	10.6	4.8	0.55	5.8% at 4[h]
paroxetine												460	20	0.44	0.062	0.49
femoxetine										3.5	2.1	1035	120	9.1	3.3	11.4
fluoxetine												>2000	85	10.8	0.43	12.7
imipramine										0.58	0.98	>10000	12	42	>50	>25
citalopram												>10000	>1000	2.9	0.29	0.78

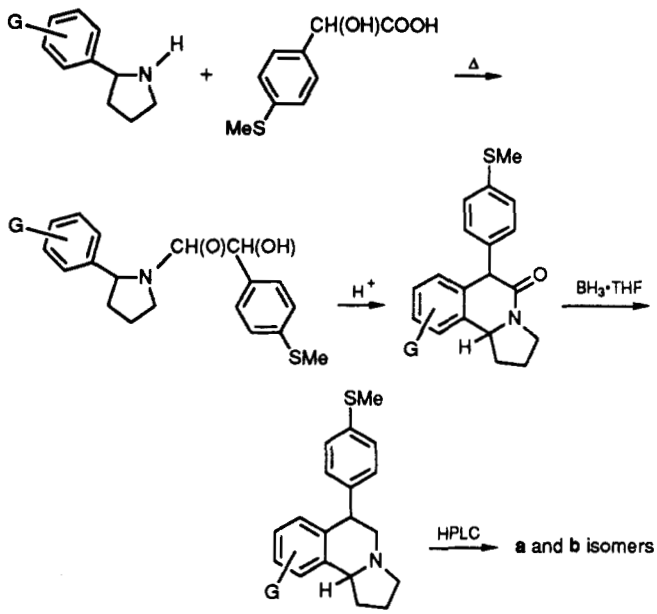
[a] The new compounds were characterized by IR, ^1H NMR, and elemental microanalyses. All compounds analyzed within ±0.4% for C, H, and N unless otherwise noted; some compounds were also analyzed for water (±0.4% unless otherwise indicated). Water composition was verified by Karl-Fisher analysis (unless otherwise noted) and solvent additives were verified by ^1H NMR analysis. [b] The recrystallization solvent is given in parentheses: M = methanol, P = 2-propanol, EE = ethyl ether, D = dichloromethane, A = acetonitrile, W = water, T = tetrahydrofuran. The syrups were obtained by evaporation of solvent (ethyl acetate/methanol) from HPLC fractions. All mp data are corrected. [c] Diastereomeric purity, presented as percent major diastereomer, was generally determined by GLC on an SE-30 or OV-17 column (assuming a detector response ratio of 1.0 between the isomers) and occasionally evaluated by TLC and ^1H NMR. [d] Tetrabenazine (TBZ) antagonism measured in mice, via intraperitoneal administration unless noted otherwise (ref 4a). Data for two parameters, motor activity (MA) and ptosis, are presented. For relatively inactive compounds, the maximum dose tested, which may have been limited by toxicity, is presented. Thus, for example, a compound that is weakly active (≥10% and <30% antagonism) at 30 mg/kg is represented as ">30" and a compound that is inactive (<10% antagonism) at 30 mg/kg is represented as "I-30". [e] Inhibition of monamine uptake measured in rat brain synaptosomes (ref 4a). K_i values are reported unless

Footnotes for Table I (Continued)

activity was fairly weak, in which case values for percent inhibition at 100 nM are given. [f]Two serotonin potentiation assays were employed: potentiation of mouse head twitches on administration of a subthreshold dose of L-5-hydrotryptophan, followed by test compound; and production of a serotonin syndrome caused by 5HTP in rats, reflective of central serotonin activation. Both tests involved subcutaneous administration of test compound, unless noted otherwise. In cases of weak activity, percent potentiation at a certain dose (mg/kg) is given. The symbol ">" before an entry signifies a virtual absence of activity (relative to control) at that dose. 95% confidence limits are given in the supplementary material. [g]Compound was characterized previously in the preceding paper of this series (ref 4a). [h]Oral administration of test compounds. [i]Central serotonin antagonist with an ID_{50} value of 7.3 mg/kg ip (ref 4a). [j]ED_{50} = 1.6 mg/kg po. [k]Contains 0.05 mol of water. [l]Contains 0.5 mol of water. [m]Contains 0.2 mol of water. [n]Mixture of diastereomers by virtue of the stereogenic sulfoxide sulfur atom. Probably a 1:1 mixture (see the Experimental Section). Separation was not possible. [o]Contains 0.125 mol of ethyl acetate. [p]Contains 0.2 mol of ethyl acetate. [q]ED_{50} value of ~4 mg/kg po. [r]3,4-Dichlorophenyl derivative.

INITIAL TABLE WIDTH IS ROTATED

Scheme I



moderately selective relative to inhibition of NE uptake.[4a] However, subsequent examination of **3b** in vivo revealed that it is a very strong serotonergic agent, even on oral administration, with reasonably good selectivity and a long duration of action.[4d] Thus, we sought to synthesize and test analogues with minor structural changes to assess the range of this special activity. This paper reports the neurochemical and pharmacological evaluation of 10 new pyrroloisoquinoline derivatives and approximately 10 previously synthesized compounds in tests predictive of central serotonergic enhancement.

Results and Discussion

Chemical Synthesis. Most of the new methylthio compounds (**4a** and **4b–8b**) were prepared from 4-(methylthio)mandelic acid and the appropriate 2-arylpyrrolidine, according to the previously described procedure (Table I; Scheme I).[4a] Nitrile **9b** was obtained by reaction of aryl bromide **8b** with CuCN.[4a] Ethylthio derivative **10b** was obtained by treating the corresponding bromo compound with NaSEt in dimethylformamide at reflux. Sulfoxides **11a** and **11b** were synthesized by oxidation of each corresponding sulfide **3a** or **3b** with sodium metaperiodate. Each sulfoxide was characterized as an oily free base since we were not able to identify any suitable crystalline salt (out of 15 acids tried); each sample was a 1:1 mixture of diastereomers by virtue of the stereogenic sulfur atom. The other pyrroloisoquinolines in Table I were prepared earlier.[4a]

Biological Testing. In our extensive structure–activity study, we reported results for a variety of pyrroloisoquinoline compounds in the tetrabenazine (TBZ) antagonism assay in vivo and in inhibition of the neuronal uptake of dopamine (DA), norepinephrine, and serotonin in vitro.[4a] Compound **3b** (trans isomer) stood out from the many because it was particularly potent in inhibiting the uptake

(4) (a) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433. (b) Maryanoff, B. E.; Shank, R. P.; Gardocki, J. F. *Drugs Future* **1986**, *11*, 18. (c) Shank, R. P.; Gardocki, J. F.; Schneider, C. R.; Vaught, J. L.; Setler, P. E.; Maryanoff, B. E.; McComsey, D. F. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 74. (d) Shank, R. P.; Vaught, J. L.; Pelley, K. A.; Setler, P. E.; McComsey, D. F.; Maryanoff, B. E. *Ibid.* **1988**, *247*, 1032.

of serotonin, with a K_i value of 0.68 nM. This activity is almost completely borne by the (+)-6*S*,10b*R* enantiomer, as the eudysmic ratio is ca. 150 (Table I). Although the selectivity for 5-HT vs NE was modest in experiments in vitro, we discovered that **3b** is *extremely potent* in antagonizing head twitches in mice induced by L-5-hydroxytryptophan (5HTP), a metabolic precursor of serotonin, and in antagonizing the 5HTP-induced serotonin syndrome in rats (subcutaneous administration). Indeed, in the mouse head-twitch assay this compound possesses an ED_{50} value of *0.08* mg/kg, which shows that it is approximately equipotent to paroxetine and 5 times more potent than fluoxetine. In the serotonin syndrome test, **3b** has an ED_{50} value of *0.20* mg/kg, which shows that it is approximately twice as potent as paroxetine, 60 times more potent than fluoxetine, and 4 times more potent than citalopram. In the head-twitch test, the active enantiomer (+)-**3b** has an ED_{50} of *0.04* mg/kg, making it twice as potent as **3b** (comparison of the ED_{50} values for the two enantiomers gives a eudysmic ratio of ca. 120). The fact that **3b** did not exhibit the motor activity (MA) component of the TBZ test suggests that its activity in vivo may be substantially characterized by central serotonin potentiation (e.g., cf. TBZ data for **3b** with that for **1b** or **19b**).[5] This aspect can be appreciated from the in-depth study of **3b** that we have delineated elsewhere.[4d]

The structural prototype **1b** (McN-4612-Z) and the other compound of interest to us from a development perspective, **2b**,[4b,c] did not function as serotonin potentiators (Table I), even though they show a reasonable level of inhibition of 5-HT uptake (23.5 and 9.7 nM, respectively). Other chloro-substituted compounds, namely **18b–20b**, are moderately active as serotonin potentiators in vivo, in approximate correspondence to their K_i values for inhibition of 5-HT uptake, in the range of 1–10 nM. Similarly, trifluoromethyl derivative **22b** is moderately active in vitro and in vivo (mouse head-twitch test). Perhaps, different pyrroloisoquinoline structures are distributed differently in the CNS of animals, such that the in vitro potency observed is not necessarily reflective of the ultimate biological response in vivo.

Compounds more closely related to **3b** gave mixed results, with no better serotonin agonism being encountered in our limited exploration. *o*-Methylthio compound **13b** is a much weaker 5-HT uptake inhibitor than **3b** and is weak in vivo as well. The *o*-methoxy (**14b**), *p*-ethylthio (**10b**), *p*-cyano (**17b**), *p*-ethynyl (**21b**) derivatives show some serotonin potentiation, but these compounds are much weaker than **3b**. Given the results here and elsewhere,[4a] it appears that one needs a narrowly defined para substituent, with just the right electron-releasing and steric properties, for strong inhibition of 5-HT uptake and extraordinarily strong potentiation of 5-HT in vivo.

Some analogues of **3b** substituted on the fused benzene ring were also tested. Monochloro substitution, as in **4b** and **5b**, causes an attenuation of activity relative to **3b**. However, it is clear that the chloro substituent is better placed at the 10-position than at the 8-position. Cis isomer **4a** is devoid of activity, as expected from our earlier studies.[4a] Although the K_i values for **6b–9b** in the in vitro 5-HT uptake test do not show an improvement in potency over that for **3b**, there is a clear improvement in selectivity. While **3b** is only 4-fold selective for 5-HT over NE, **4b**, **8b**, and **9b** are 8-, 23-, and 26-fold selective, respectively. For some 10-substituted compounds there is also a modest increase in selectivity for 5-HT vs DA. Unfortunately, **8b** and **9b** are virtually inactive as 5-HT potentiators in vivo, which is particularly surprising for **8b** (10-bromo) because of its close resemblance to reasonably active **4b** (10-chloro) and **7b** (10-methyl). So, substitution of the 10-position of **3b** is much better tolerated in the in vitro 5-HT assay as opposed to the in vivo head-twitch assay.

Interestingly, although sulfone **12b** is just weakly active in vitro and in vivo, sulfoxide **11b** is quite active in vivo in comparison to its poor showing in vitro (Table I). It is conceivable that **11b** is functioning predominantly as a prodrug for **3b**, as has been observed for some other sulfoxide-containing drugs.[6] Sulfoxide **11a** is essentially devoid of activity.

Two other compounds with moderate activity in both 5HTP tests are carboxamide **15b** and acetamide **16b** (Table I). The latter compound is also exceedingly potent in the TBZ assay, probably one of the most potent antagonists ever seen.[4a]

Conclusion

Potent inhibition of 5-HT uptake by the neuronal carrier can be realized by a variety of pyrroloisoquinoline structures, many of which demonstrate potent inhibition of uptake for norepinephrine and dopamine as well.[4a,7] At this time, we can recognize certain structural features that lead to powerful uptake inhibition of these biogenic monoamines; however, a full appreciation of which features can lead to good selectivity for 5-HT over NE and DA has not yet materialized.[7] In this respect, each series will probably exhibit its own subtle peculiarities. Nevertheless, the parent *p*-methylthio derivative **3b** displays moderate in vitro selectivity for inhibition of 5-HT uptake (out of a wide range of compounds[4a]). In vivo, **3b** appears to manifest even greater selectivity, such that **3b** is one of the most potent agents ever reported in the mouse 5HTP head-twitch assay (ED_{50} of 0.08 mg/kg ip). From probing structure–activity relationships, we have found that this *p*-methylthio substitution is somewhat special and that substitution of the 10-position of **3b** with a Cl (**4b**) or a Me (**7b**) group results in a substantial enhancement of selectivity for 5-HT in vitro, while retaining a reasonable level of in vivo potency.

Experimental Section

General Procedures. The general methods and techniques employed have been adequately represented in our previous full paper.[4a,9] Melting points are corrected. ^1H NMR spectra were recorded at 90 MHz, unless noted otherwise. Preparative HPLC was performed on a Waters Prep 500 instrument on a silica gel column.

2-(2-Chlorophenyl)- and 2-(2-Bromophenyl)pyrrolidine. Ethyl 2-halobenzoate (1.0 equiv), *N*-vinylpyrrolidin-2-one (1.1

(5) Maj, J.; Rogoz, Z.; Skuza, G. *J. Pharm. Pharmacol.* **1983**, *35*, 128 and references cited therein.

(6) For sulindac and sulfinpyrazone, see: (a) Duggan, D. E.; Kwan, K. C. *Drug Metab. Rev.* **1979**, *9*, 21. (b) Duggan, D. E.; Hooke, K. F.; Hwang, S. S. *Drug Metab. Dispos.* **1980**, *8*, 241. (c) Renwick, A. G.; Strong, H. A.; George, C. F. *Biochem. Pharmacol.* **1986**, *35*, 64 and references cited therein.

(7) (a) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (b) Bogeso, K. P.; Hyttel, J.; Christensen, A. V.; Arnt, J. *Innovative Approaches in Drug Research*; Elsevier: Amsterdam, 1986. (c) Smith, D. F. *Neurosci. Biobehav. Rev.* **1986**, *10*, 37. (d) Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. *J. Med. Chem.* **1988**, *31*, 185.

(8) Corne, S. J.; Pickering, R. W.; Warner, B. T. *Br. J. Pharmacol.* **1963**, *20*, 106.

(9) For an improved, stereoselective synthesis of **3b** and an enantiospecific synthesis of (+)-**3b**, see: Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567.

equiv), and sodium hydride (1.2 equiv, 60% oil dispersion) were reacted as previously described.[4a] Acid hydrolysis and workup (Kugelrohr distillation, 100–150 °C, 0.05 Torr) gave 2-(2-chlorophenyl)-1-pyrroline (39.8 g, 42%) or 2-(2-bromophenyl)-1-pyrroline (116.2 g, 56%) as amber oils. Reduction with sodium borohydride provided oily 2-(2-chlorophenyl)pyrrolidine (34.4 g, 86%) or 2-(2-bromophenyl)pyrrolidine (105.4 g, 97%). [^{1}H NMR of the chloro compound ($CDCl_3$) δ 1.3–2.6 (m, 5 H, includes NH), 2.8–3.3 (m, 2 H), 4.4 (t, 1 H, J = 7.5 Hz, H2), 7.0–7.8 (m, 4 H, aromatic).] A hydrochloride salt of the bromo compounds, prepared with ethereal HCl, was recrystallized from methanol/acetonitrile to furnish white crystals: mp 191–193 °C; IR ν_{max} 1413, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.8–2.7 (m, 4 H), 3.1–4.0 (m, 2 H), 4.7–5.2 (m, 1 H), 7.0–8.0 (m, 4 H, aromatic), 9.70 (br s, 1 H, NH), 10.50 (br s, 1 H, NH). Anal. ($C_{10}H_{12}BrN$·HCl) C, H, N.

Synthesis of *cis*- and *trans*-10-Chloro-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline (4a and 4b). Following the previously described general procedure,[4a] 4-methylthiomandelic acid[4a] (20.0 g, 0.101 mol) was reacted with 2-(2-chlorophenyl)pyrrolidine (19.3 g, 0.106 mol), and the resulting amido alcohols (21.4 g, 59%, two diastereomers) were cyclized with polyphosphoric acid to give a mixture of lactams (18.4 g, 95%), which was reduced with borane–THF to yield **4a** and **4b** (15.9 g, 88%, **4a**/**4b** = 13:1 by GLC). Base-induced epimerization[4a,10] (25% aqueous NaOH/DMSO, 30 min at reflux) provided product enriched in **4b** (14.6 g, 92%, **4a**/**4b** = 2:1, GLC). The isomers were separated by preparative HPLC (hexane/ethyl acetate, 3:1) to furnish 4.50 g of **4a** and 3.56 g of slower eluting **4b**. Cis isomer **4a** was converted to an HCl salt and twice recrystallized from THF to give beige crystals (3.36 g): mp 150–153 °C; IR ν_{max} 1449, 788 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5–2.3 (m, 3 H), 2.45 (s, 3 H), 2.7–4.0 (m, 6 H), 4.20 (dd, 1 H, J = 6.6, 10.5 Hz, H6), 5.15 (dd, 1 H, J = 7.5, 8.4 Hz, H10b), 6.55 (d, 1 H, J = 7.5 Hz, H7), 6.8–7.4 (m, 6 H, aromatic). Anal. ($C_{19}H_{20}ClNS$·HCl) C, H, N. Trans isomer **4b** was converted to the HCl salt and twice recrystallized from 2-propanol to yield beige crystals (2.23 g): mp 258–262 °C; IR ν_{max} 1444, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.7–2.4 (m, 2 H), 2.45 (s, 3 H), 2.9–4.1 (m, 6 H), 4.6–5.0 (m, 2 H, H6 and H10b), 6.55 (d, 1 H, J = 7.5 Hz, H7), 6.9–7.4 (m, 6 H, aromatic). Anal. ($C_{19}H_{20}ClNS$·HCl) C, H, N.

Synthesis of *trans*-1,2,3,5,6,10b-Hexahydro-6-[4-(methylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline-10-carbonitrile (9b). Pure *trans*-10-bromo-1,2,3,5,6,10b-hexahydro-6-[4-(methylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline (**8b**;[11] 3.81 g, 0.010 mol) was reacted with CuCN (1.59 g, 0.018 mol) and tetrakis(triphenylphosphine)palladium(0) (0.235 g, 0.0002 mol) in degassed DMF (50 mL) at 120 °C, as previously described,[12] to furnish **9b** (2.16 g, 66%) as a brown oil after preparative HPLC purification (ethyl acetate/methanol, 19:1). The hydrochloride salt, prepared by using ethereal HCl, was recrystallized twice from methanol/acetonitrile to yield white crystals (1.53 g, 41%): mp 277–280 °C; IR ν_{max} 2227 (C≡N), 1497, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 1.7–2.4 (m, 4 H), 2.50 (s, 3 H), 2.9–4.1 (m, 5 H, includes 0.5 mol of H_2O), 4.7–5.2 (m, 2 H, H6 and H10b), 6.9–7.5 (m, 6 H, aromatic), 7.60 (d, 1 H, H9). Anal. ($C_{20}H_{20}N_2S$·HCl·0.5H_2O) C, H, N, H_2O.

Synthesis of *trans*-6-[4-(Ethylthio)phenyl]-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (10b). A solution of sodium hydride (5.3 g, 0.11 mol, 50% oil dispersion) in dimethylformamide (300 mL) was treated cautiously with ethyl mercaptan (6.90 g, 0.11 mol) under argon at room temperature and stirred for 5 min. A solution of the 6-(4-fluorophenyl)-hexahydropyrroloisoquinoline[4a] corresponding to **10b** (15.0 g, 0.056 mol) in dimethylformamide (100 mL) was added and the mixture was refluxed for 4 h, cooled, treated with water, and extracted with methylene chloride (2 × 150 mL). The combined organic phase was washed with 5% NaOH (3 × 150 mL) and brine, dried (K_2CO_3), and concentrated in vacuo to a crude oil (15.9 g, mixture of cis and trans diastereomers). Purification via preparative HPLC (ethyl acetate/hexane, 4:1) afforded 1.8 g (ca. 10%) of oily **10b**, which was purified as an HBr salt (from 2-propanol) to afford pale green crystals (0.96 g): mp 167–168 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.30 (t, 3 H), 2.2 (m, 3 H), 2.8 (m, 1 H), 2.91 (q, 2 H), 3.0–3.1 (m, 2 H), 3.6 (m, 1 H), 4.0 (m, 1 H), 4.74 (dd, 1 H, J = 4.1, 11.8 Hz, H6), 4.9 (m, 1 H, H10b), 6.75 (d, 1 H, H7), 7.1–7.4 (m, 7 H, aromatic). Anal. ($C_{20}H_{23}NS$·HBr·0.2H_2O) C, H, N, H_2O.

Synthesis of *cis*- and *trans*-1,2,3,5,6,10b-Hexahydro-6-[4-(methylsulfinyl)phenyl]pyrrolo[2,1-*a*]isoquinoline (11a and 11b). Sulfide **3b** (12.5 g, 0.04 mol) was added to a mixture of sodium metaperiodate (18.1 g, 0.09 mol) in methanol (300 mL), water (100 mL), and tetrahydrofuran (40 mL). The mixture was stirred at room temperature for 2 days, filtered, and evaporated in vacuo to a semisolid. This material was redissolved in methylene chloride, washed with 3 N NaOH, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a semisolid (9.04 g), which was purified via preparative HPLC (ethyl acetate/methanol, 4:1) to give **11b** as a light brown oil (2.86 g, 23%): IR ($CHCl_3$) ν_{max} 1045 (S=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, 50:50 mixture of diastereomers) δ 1.75–2.0 (m, 3 H), 2.39 (m, 1 H), 2.56 (m, 1 H), 2.690/2.695 (pair of s, 3 H, 50:50 mixture of diastereomers by comparison of intensity for the two signals), 2.9–3.1 (m, 3 H), 3.46 (m, 1 H, H10b), 4.23 (dd, 1 H, J = 4.3, 4.3 Hz, H6), 6.84 (d, 1 H, H7), 7.0–7.5 (m, 7 H, aromatic). Anal. ($C_{19}H_{21}NOS$·0.5H_2O·0.2$C_4H_8O_2$) C, H, N, H_2O. Cis isomer **11a** was synthesized in the same manner by using **3a** (15.30 g, 0.05 mol) and sodium metaperiodate (19.28 g, 0.09 mol) to give 12.29 g of crude oil, which was purified via preparative HPLC to give an oily product (5.21 g, 42%): IR ($CHCl_3$) ν_{max} 1086 (S=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, presumed to be a 50:50 mixture of diastereomers) δ 1.7–2.0 (m, 3 H), 2.3–2.7 (m, 3 H), 2.71 (s, 3 H), 3.12 (m, 1 H), 3.44 (m, 1 H), 3.65 (m, 1 H, H10b), 4.44 (dd, 1 H, J = 6.4, 10.2 Hz, H6), 6.76 (d, 1 H, H7), 7.0–7.6 (m, 7 H, aromatic). Anal. ($C_{19}H_{21}NOS$·0.5H_2O·0.1$C_4H_8O_2$) C, H, N, H_2O.

Head-Twitch Assay. Head-twitch behavior in mice is mediated by the activation of central serotonergic systems. The method used here is a minor modification of that reported by Corne et al.[8]

Adult, male, Swiss CD-1 mice (Charles River) weighing 19–24 g were employed. Ten mice per dose were injected with the test compound by the subcutaneous route and, after 30 min, were injected intraperitoneally with a subthreshold dose of L-5-hydroxytryptophan (50 mg/kg, 10 mL/kg). The mice were placed in glass bell jars (two mice/jar) for acclimation. After 15 min, the mice were observed for the presence or absence of the head-twitch response over a 2-min period. The data (number of mice in each group exhibiting the response) were reported as either percent of total or as an ED_{50} (dose estimated to cause response in 50% of the animals), determined by probit analyses. At least three doses were used to construct a dose–response curve.

Serotonin Syndrome Assay. There is a behavior syndrome in rodents that is mediated by activation of central serotonergic systems. This syndrome is a complex of various stereotyped behaviors, the nature of which depends on the species and the intensity of the syndrome. This method, described elsewhere in detail,[4c] serves to quantify this activity, which is induced by L-5-hydroxytryptophan.

Briefly, each test compound, or vehicle, was administered subcutaneously (2 mL/kg) to rats in groups of 10. After 30 min, a dose of L-5-hydroxytryptophan (100 mg/kg, 10 mL/kg) approximating the ED_{10} was given intraperitoneally. After 20 min, each rat was placed into a clear plastic observation chamber, and 10 min later each was observed over a 2-min period for the presence of six characteristic behaviors.[4c] Scoring was conducted as described previously.[4c] When dose–response curves were generated, they were based on four to six doses and 10 rats per dose.

Acknowledgment. We thank Kathleen Pelley and James Schupsky for technical assistance with the biological experiments.

Supplementary Material Available: A table of 95% confidence limits for the 5HTP ED_{50} values in Table I (1 page). Ordering information is given on any current masthead page.

(10) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.

(11) Prepared from 4-(methylthio)mandelic acid and 2-(2-bromophenyl)pyrrolidine according to the procedure described for **4b**.[4a]

(12) Prepared by following the procedure used for 4-(*trans*-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-6-yl)benzonitrile in ref 4a.