Synthesis and Pharmacological Examination of Benzofuran, Indan, and Tetralin Analogues of 3,4-(Methylenedioxy)amphetamine

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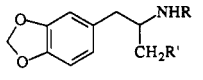
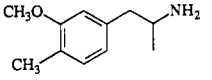
Benzofuran, indan and tetrahydronaphthalene analogs of 3,4-(methylenedioxy)amphetamine (MDA) were prepared in order to examine the role of the dioxole ring oxygen atoms of MDA in interacting with the serotonin and catecholamine uptake carriers. The series of compounds was evaluated for discriminative stimulus effects in rats trained to discriminate saline from the training drugs (*S*)-(+)-MBDB (**1c**), MMAI (**3**), and (*S*)-(+)-amphetamine and for the ability to inhibit the uptake of [^{3}H]serotonin, [^{3}H]dopamine, and [^{3}H]norepinephrine into crude synaptosome preparations. Behaviorally, the benzofuran and indan analogs **4–6** produced similar discriminative cues, whereas the tetralin derivative **7** did not fully substitute for the training drugs. The results in the *in vitro* pharmacology studies indicate that selectivity for 5-HT versus catecholamine uptake carriers may be modulated by the position and orientation of ring oxygen atoms. However, the nonoxygenated isostere **6** possessed high potency at all uptake sites examined. Enlargement of the saturated ring by one methylene unit to give the tetralin derivative resulted in a large (3–4-fold) reduction in activity at catecholamine sites.

For several years, our laboratory has been investigating the structure–activity relationships of compounds related to 3,4-(methylenedioxy)amphetamine (MDA) **1a** and 3,4-(methylenedioxy)methamphetamine (MDMA) **1b**. The latter compound became popular as a recreational drug known as "ecstasy" and has human psychopharmacology and animal pharmacology that differs significantly from the pharmacology of psychostimulants such as amphetamine, or hallucinogens such as LSD or the methoxylated amphetamines.[1–10] In particular, users of **1a** and **1b** have reported that these substances induce greatly enhanced feelings of "closeness" and communication with other individuals,[11] as well as a sense of calmness and physical and mental well-being.[12] It has been proposed that **1b** and similar compounds belong to a new pharmacological class, named entactogens.[4,5]



1a, R = R' = H
1b, R = CH_3, R' = H
1c, R = R' = CH_3



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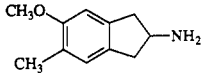

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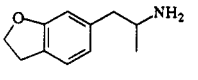
Our initial interest in **1b** and related compounds arose as a consequence of anecdotal reports by a number of psychiatrists that this material had potential as an adjunct to psychotherapy.[13–15] Nevertheless, any clinical evaluation of this claim was obstructed by the finding that **1b** produced the loss of serotonin axons and terminals in rodent[16,17] and nonhuman primate brain.[18,19] Therefore, our efforts were directed toward elucidating the structure–activity relationships of entactogens to determine whether the potentially useful psychopharmacological properties could be dissociated from the serotonergic neurotoxic effects.

It now seems fairly clear that the neurotoxic properties of **1a** and **1b** are related to their ability to induce the concomitant release of serotonin, by a mechanism mediated through the serotonin reuptake carrier, and neuronal catecholamines, through a similar mechanism.[20,21] These two effects also greatly stimulate dopamine biosynthesis and lead, in some way, to the neurotoxic events.

In the course of our studies, it became clear that changes in ring substitution patterns of the substituted amphetamines led to compounds with increased selectivity to affect serotonergic neurons.[22–24] As an example, **2** and its rigid analog **3** proved to be highly selective in inducing the release of neuronal serotonin, but almost inert in affecting neuronal catecholamines. These compounds also proved to lack completely any serotonergic neurotoxic properties, even when given in repeated doses over 4 days.[20,22]

We were interested to learn, therefore, what was unique about the dioxole ring of **1a** and **1b** that led it to possess the ability to interact both with the serotonin and the dopamine uptake carriers. It was decided to prepare the isomeric benzofuran derivatives **4** and **5**, where one of the



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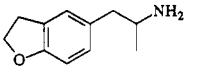

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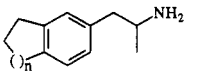

6, n = 1
7, n = 2

dioxole oxygen atoms has been replaced with a methylene unit, and to examine the pharmacology of these compounds. In addition, compound **6** was prepared to examine the effect of replacing both oxygen atoms of **1a** with methylene units, and **7** was prepared to study the effect of expanding the size of the fused ring. Thus, compounds **4–7** were synthesized and evaluated for their discriminative stimulus effects in rats trained to discriminate saline from the training drugs (*S*)-(+)-MBDB (**1c**), MMAI (**3**), and (*S*)-(+)-amphetamine. Also, the ability of the test compounds to inhibit the accumulation of [^{3}H]serotonin ([^{3}H]-5-HT), [^{3}H]dopamine ([^{3}H]DA), and [^{3}H]-

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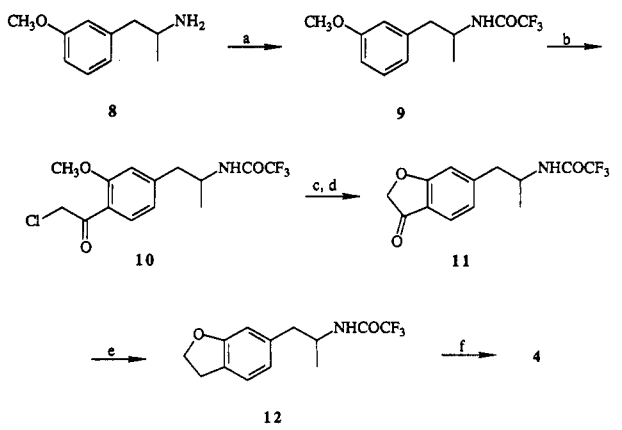
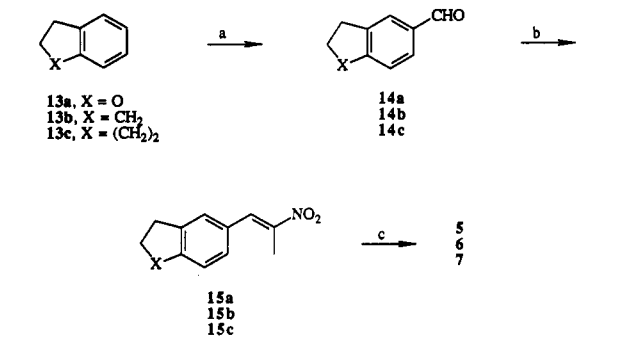
Scheme I[a]



[a] (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; (b) $ClCH_2COCl$, $AlCl_3$, DCE; (c) BBr_3, CH_2Cl_2; (d) NaOAc, MeOH; (e) H_2, PdOH/C, ethanol; (f) KOH, isopropyl alcohol reflux.

Scheme II[a]



[a] (a) Cl_2CHOCH_3, $SnCl_4$, CH_2Cl_2; (b) $CH_3CH_2NO_2$, NH_4OAc, reflux; (c) $LiAlH_4$, THF, reflux.

norepinephrine ([^{3}H]NE) into crude synaptosome preparations was examined.

Chemistry

Friedel–Crafts acylation of the *N*-trifluoroacetamide **9**, using chloroacetyl chloride and $AlCl_3$, gave **10** in good yield (Scheme I). Initial attempts to carry out this transformation using Toyoda's α-chloroacetylation procedure[25] resulted in very low yields. Demethylation of **10** with BBr_3, followed by cyclization under basic conditions according to a method described by Hammond,[26] produced **11** in modest yield. The benzofuranone was then reduced catalytically and *N*-deprotected to afford 6-(2-aminopropyl)-2,3-dihydrobenzofuran (**4**), which was isolated as its hydrochloride salt.

Compounds **5–7** were prepared in an identical manner by standard methods (Scheme II). The aldehydes **14a–c** were obtained by formylation using dichloromethyl methyl ether and $SnCl_4$ in dichloromethane. Condensation of the aldehydes with nitroethane gave the corresponding nitropropenes **15a–c**, which were reduced with $LiAlH_4$. The final compounds **5–7** were isolated as their hydrochloride salts.

Pharmacology

The racemic compounds **4–7** were evaluated for their ability to substitute for **1c** ((*S*)-MBDB)[4,8] and **3** (MMAI)[22] in a two-lever drug-discrimination assay. In addition, **6** was tested in rats trained to discriminate (*S*)-amphetamine from saline.

The ability of the test compounds to inhibit synaptosomal [^{3}H]-5-HT, [^{3}H]DA, and [^{3}H]NE accumulation was used to determine whether any of the compounds interact with monoamine neurotransmitter uptake carriers and/or release mechanisms. Also, **1a** was included in these assays to provide a point of comparison to previous work from this laboratory.[23] It should be noted that this assay, as performed, cannot distinguish whether these compounds interfere with accumulation by blockade of the monoamine uptake transporters, or whether they cause the release of neuronal stores of vesicular or nonvesicular neurotransmitter.

Results and Discussion

The results of the drug-discrimination studies are shown in Table I and II. Benzofurans **4** and **5** fully substituted in (*S*)-**1c**-trained and **3**-trained rats with ED_{50}s not significantly higher than those of the training drugs and potencies comparable to one another. Both **4** and **5** were potent in producing disruption in (*S*)-amphetamine-trained and LSD-trained rats, and neither compound substituted in (*S*)-amphetamine-trained or LSD-trained rats which were not disrupted (data not shown). These results indicate that, behaviorally, **4** and **5** resemble (*S*)-**1c** and **3**, and have neither amphetamine-like nor LSD-like properties. Furthermore, these data indicate that the position of the oxygen atom in relation to the alkylamine side chain is not particularly significant in producing **1c**- or **3**-like behavioral responses. Thus, both **4** and **5** might be expected to exhibit human psychopharmacology similar to one another, to **1c** and **3**, and, possibly, to the related entactogens **1a** and **1b**. This prediction is based on our previous observations that both **1a** and **1b** fully substitute for the training drug **1c**.[8,27] Since **4** and **5** also substitute for **1c**, it seems highly likely that these compounds must produce a behavioral cue similar to that produced by **1a** and **1b**.

Aminoindan **6** was found to substitute fully in (*S*)-**1c** trained rats and was approximately 5 times more potent than the training drug in eliciting this discriminative cue (Table II). In **3**-trained rats, however, 80% of the animals were disrupted and ED_{50} values could not be determined, although all of the rats which were not disrupted at the 1 mg/kg dose selected the drug lever. While **6** did not substitute for (*S*)-amphetamine, it did produce disruption at higher doses in those animals. The aminotetralin analog **7** did not substitute for **3** or (*S*)-amphetamine, and only substituted in 63% of the (*S*)-**1c**-trained rats, with 26% disruption at the 1 mg/kg dosage level (data not shown).

Interpretation of these data is problematic since both **1c** and **3** are known to be 5-HT releasing agents which fully substitute for one another in drug-discrimination assays.[22] Therefore, **6**, which substitutes for **1c**, would be expected to also substitute for **3**, assuming that both training drugs produce similar discriminative cues. However, **6** caused disruption in a large percentage of **3**-trained rats, indicating that the behavioral effects of **1c** and **3** may actually be slightly different. The explanation for this discrepancy may lie in the fact that **3** is *highly* selective for affecting serotonin uptake/release, and its behavioral cue probably reflects a more "purely serotoneric" response. In moving from **3** to **1c** to **1a**, an increased ability to affect catecholamine uptake/release is observed, and behavioral responses may reflect this change in the ratio of catecholamine to 5-HT effect. It is our hypothesis that **6**,

Table I. Drug Discrimination Data in *S*-1c-Trained or 3-Trained Rats

drug	dose mg/kg	dose μmol/kg	N[a]	D[b]	%SDL[c]	ED_{50} (95% CI)[f] mg/kg	ED_{50} (95% CI)[f] μmol/kg
			S-1c-Trained				
1c						0.79[d]	3.25[d]
4	0.108	0.5	7	2	0		
	0.215	1.0	10	3	14	0.40	1.68
	0.429	2.0	10	3	57	(0.23–0.57)	(1.06–2.66)
	0.643	3.0	12	4	88		
	0.857	4.0	11	5	100		
5	0.215	1.0	10	2	25		
	0.429	2.0	11	5	50	0.37	1.72
	0.643	3.0	10	3	71	(0.24–0.57)	(1.13–2.64)
	0.857	4.0	10	4	100		
			3-Trained				
3						0.56[e]	2.63[e]
4	0.108	0.5	8	6	0		
	0.214	1.0	12	6	17	0.31	1.44
	0.429	2.0	12	6	83	(0.19–0.49)	(0.91–2.29)
	0.643	3.0	12	5	100		
	0.857	4.0	12	2	90		
	1.286	6.0	8	6	100		
5	0.108	0.5	8	3	0		
	0.215	1.0	11	8	33	0.48	2.23
	0.429	2.0	12	6	50	(0.31–0.74)	(1.44–3.43)
	0.643	3.0	12	4	75		
	0.857	4.0	11	4	86		
	1.286	6.0	8	5	100		

[a] Number of animals tested. [b] Number of animals disrupted (50 presses not completed in 5 min). [c] Percentage of nondisrupted animals selecting drug lever. [d] ED_{50} values included for comparison, taken from Nichols et al.[21] [e] ED_{50} values taken from Johnson et al.[22] [f] The ED_{50} values for substitution were calculated according to the method of Litchfield and Wilcoxon (see Experimental Section).

Table II. Drug-Discrimination Data from *S*-1c-Trained, 3-Trained, and (*S*)-Amphetamine-Trained Rats

drug	dose mg/kg	dose μmol/kg	N[a]	D[b]	%SDL[c]	ED_{50} (95% CI)[h] mg/kg	ED_{50} (95% CI)[h] μmol/kg
			S-1c-Trained				
1						0.79[d]	3.25[d]
6	0.125	0.4	14	3	9		
	0.250	0.8	15	5	70	0.20	0.62
	0.500	1.6	15	3	100	(0.15–0.26)	(0.48–0.82)
	1.000	3.2	9	2	100		
			3-Trained				
3						0.56[e]	2.63[e]
6	0.125	0.4	10	2	13		
	0.250	0.8	11	5	17	[g]	[g]
	0.500	1.6	12	6	83		
	1.000	3.2	10	8	100		
			(*S*)-amphetamine-Trained				
(*S*)-amphetamine						0.31[f]	1.68[f]
6	0.125	0.4	15	2	0		
	0.250	0.8	14	2	0	NS	NS
	0.500	1.6	15	7	0		
	1.000	3.2	10	6	0		

[a] Number of animals tested. [b] Number of animals disrupted. [c] Percentage of nondisrupted animals selecting drug lever. [d] ED_{50} values included for comparison, taken from Nichols et al.[21] [e] ED_{50} values taken from Johnson et al.[22] [f] ED_{50} values taken from OBerlender and Nichols.[7] [g] Because %D > 50, ED_{50} values were not determined—see Experimental Section. [h] The ED_{50} values for substitution were calculated according to the method of Litchfield and Wilcoxon (see Experimental Section).

which possesses a significant catecholaminergic component, behaviorally lies closer to the **1a** end of a spectrum of behavioral effects than it does to the pure serotonin releasing, or **3**, end. Thus, the compounds in this series can be ranked in order of their ratio of catecholamine/5-HT effect such that **1a** > **6** > **1c** > **3**. These ratios of effects may significantly alter the behavioral pharmacology, since we have recently shown that 5-HT-releasing agents can markedly potentiate the effects of an indirectly-acting dopaminergic drug.[28]

The *in vitro* pharmacology showed clear differences among the ability of the compounds to inhibit synaptosomal accumulation of [^{3}H]5-HT, [^{3}H]DA, and [^{3}H]NE (Table III). While compounds **5**–**7** exhibited IC_{50}s for 5-HT accumulation in the 100 nm range, compounds **1a** and **4** had some 3-fold lower activity in this assay. In the catecholamine assays, **1a** and **4** showed a 3-fold higher potency at inhibiting uptake, relative to compounds **5** and **7**.

These results clearly support our hypothesis that serotonin/catecholamine selectivity can be controlled by the position and orientation of ring oxygen atoms. In an earlier study by Johnson et al.,[22] it was reported that **2** was a highly selective 5-HT-releasing agent with no neurotoxic liability. This observation led us to hypothesize that serotonin and catecholamine selectivity could be modulated by the position of the oxygen atom in relation to the alkylamine side chain and the orientation of the oxygen

Table III. IC_{50} for Monoamine Uptake Inhibition[a]

compd	IC_{50} (nM)		
	[^{3}H]5-HT	[^{3}H]DA	[^{3}H]NE
4	322 ± 27[b]	1997 ± 225	980 ± 78
5	130 ± 13	7089 ± 956[c]	3238 ± 150[c]
6	82 ± 6	1847 ± 213	849 ± 82
7	121 ± 22	6436 ± 440[c]	3371 ± 180[c]
1a	369 ± 62[b]	1356 ± 225	629 ± 50

[a] The ability of the test compounds to inhibit accumulation of monoamines was examined in crude synaptosomes. The test compounds were examined with 9 or 10 concentrations, each run in triplicate. The data from three or four experiments were combined and the IC_{50} values ± SEM (nM) were calculated by curve fitting followed by appropriate statistics (see Experimental Section). [b] $P <$ 0.004 vs 5–7. [c] $P < 0.0001$ vs 4, 6, 1a.

lone pair electrons. For example, in 2 the *O*-methyl is forced into an *anti* conformation relative to the 4-methyl group due to steric interactions between these two substituents. This causes the lone pair electrons of the ether oxygen atom to be directed toward the 4-methyl group in a *syn* orientation. This orientation may be highly unfavorable for bonding interactions with the catecholamine carrier protein, and thus leads to low affinity for the DA and NE uptake sites. Conversely, the 5-HT carrier does not appear to have such requirements for the *m*-methoxy group, and the result is the observed high selectivity for the 5-HT uptake carrier relative to catecholamine uptake sites.[22] This hypothesis led us to predict that compounds 4 and 5 would show differential selectivity for the uptake sites, with 4 being more selective for catecholamine sites and 5 being more selective for the 5-HT carrier.

A comparison of the IC_{50} values for 4 and 5 (Table III) shows that this is indeed the case. These results, taken with those of compound 2,[22] clearly demonstrate that monoamine-releasing activity is facilitated by a proper orientation of the lone-pair electrons of the ring oxygen substituents. To achieve high-affinity interactions with the catecholamine carriers, it appears necessary to have the lone-pair electrons of the oxygen *meta* to the side chain directed away from the *para* position (in an *anti* orientation), as in 4. Activity at catecholamine sites is abolished, however, if the orientation is *syn*, as illustrated by the pharmacological profile of 2. Conversely, interactions with the 5-HT carrier protein appear to be favored by the presence of an oxygen atom *para* to the side chain, as in 5, although this is not an absolute requirement. Hence, the 5-HT site can tolerate either an *anti* or *syn* orientation of the *meta*-oxygen electron pairs with respect to the 4-position.

However, these arguments only apply when an oxygen atom is present at the 3- or 4-position of the aromatic ring; the nonoxygenated analog 6 showed activity quite similar to both 1a and 4 in the catecholamine assays and was found to inhibit 5-HT accumulation at low concentration (Table III). Indeed, 6 was the most potent compound in the series for inhibiting [^{3}H]-5-HT uptake. Since 6 is so potent at all of the monoamine transport sites examined, one conclusion is that ring oxygen atoms are not required for tight binding to these proteins. However, alternative mechanisms to account for these observations cannot be ruled out. Compound 7, by comparison, shows a large reduction of *in vitro* activity at the catecholamine uptake sites, but not the 5-HT site. This observation indicates a decreased degree of tolerance for steric bulk by the catecholamine transporter. The lack of full substitution in the *in vivo* behavior assays parallels Shulgin's finding that analogous homologation of 1b (MDMA) to (ethylenedioxy)methamphetamine (EDMA) resulted in a concomitant loss of clinical activity.[29]

To summarize, our findings indicate that, generally, the catecholamine-releasing agents have more rigorous structure–activity requirements than agents which affect 5-HT release. For example, in oxygenated compounds, it appears necessary for high potency that there be an oxygen atom *meta* to the side chain with lone-pair electrons directed *anti* to the 4-position to attain a high degree of potency. An additional requirement for catecholamine activity is that there be limited steric bulk around the 3,4-positions of the aromatic ring. Within the series of compounds examined in this study, serotonin-releasing activity was reduced only in agents that possessed a *meta*-oxygen atom. This may be due to the fact that the *anti*-directed, *meta*-oxygen, lone-pair electrons, as in 1a and 4, interfere in some way with the 5-HT-release mechanism. In racemic 2, however, the orientation of the *meta*-oxygen lone pairs in *syn*, and this compound retains high activity as a selective 5-HT releasing agent.[22] Behaviorally, all compounds in our study somewhat resemble the training drugs 1c and 3, except for compound 7, whose high potency at 5-HT sites but lack of substitution for these drugs may be due to factors other than simply being able to initiate neurotransmitter release (e.g., unfavorable pharmacokinetics). To further correlate the observed behavioral responses with the *in vitro* data, it is clear that all the compounds of this class have in common their ability to simultaneously release both 5-HT and the catecholamines DA and NE, albeit to varying degrees. Certain nuances of behavioral effect, however, seem to arise from shifts in the potency ratio in affecting catecholamine and 5-HT release. Thus, agents which have a lower potency in catecholamine systems, such as 5, behaviorally resemble agents like 3, while compounds with greater effects on catecholamine systems would be expected to elicit behavioral responses more similar to those produced by 1a. Clearly, further research in this area is warranted to enable a better understanding of the behavioral effects caused by modulating the selectivity between 5-HT and catecholamine release.

Experimental Section

Melting points were determined using a Mel-Temp apparatus and are uncorrected. Reactions were conducted under a dry nitrogen atmosphere. Thin-layer chromatographic (TLC) analyses were performed on silica gel IB2-F, plastic-backed plates (2.5 × 7.5 cm, J. T. Baker), and visualization was by UV light and I_2 vapor. ^{1}H NMR spectra were recorded on a Chemagnetics A-200 or a Varian VXR-500S spectrometer. Chemical shifts are reported in δ units (ppm) relative to tetramethylsilane as an internal standard. The following designations are used to denote NMR signal patterns: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; dd, doublet of doublets; b, broad. Mass spectra, EI or CI (methane as carrier gas), were obtained on a Finnigan 2000 spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Elemental analyses were performed at Galbraith Laboratories in Knoxville, TN, and all values are within 0.4% of those calculated.

***N*-(Trifluoroacetyl)-1-(3-methoxyphenyl)-2-aminopropane (9).** To an ice-cooled solution of 2.7 g (16 mmol) of 1-(3-methoxyphenyl)-2-aminopropane (8) dissolved in 100 mL of dry CH_2Cl_2 was added 2.0 g (19.7 mmol) of triethylamine. The mixture was stirred for 10 min and 9.8 g (49 mmol) of trifluoroacetic anhydride in 50 mL of CH_2Cl_2 was introduced dropwise to the reaction vessel over a 10-min period. The reaction was allowed to warm to room temperature. After 1.5 h the solvent was removed by rotary evaporation and the oily, yellow residue

was taken up in ether. The organic phase was washed with H_2O (2 × 25 mL), 2 N HCl (25 mL), 5% $NaHCO_3$ (25 mL), and brine and then dried over $MgSO_4$ and filtered through Celite. After complete removal of solvent *in vacuo*, a quantitative yield of white solid was obtained. This was recrystallized from ethyl acetate–petroleum ether to afford 3.73 g (89%) of **9** as fluffy white crystals: mp 62–63 °C; ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 3, CH_3), 2.6 (m, 2, $ArCH_2$), 3.2 (m, 1, $ArCH_2CH$), 3.8 (s, 3, CH_3O), 6.2 (bs, 1, NH), 6.7 (m, 3, ArH), 7.3 (m, 1, ArH); MS *m/z* 262 (M + 1). Anal. ($C_{12}H_{14}F_3NO_2$) C, H, N.

***N*-(Trifluoroacetyl)-1-[3-methoxy-4-(chloroacetyl)phenyl]-2-aminopropane (10).** A solution of 3.5 g (13.4 mmol) of **9** in 75 mL of 1,2-dichloroethane was stirred and cooled to 0 °C on an ice bath. Chloroacetyl chloride (2.6 mL, 33.5 mmol) was added to the mixture at once, followed by the portionwise addition of 4.5 g (33.5 mmol) of $AlCl_3$ through a powder addition funnel. After 20 min the ice bath was removed and the flask was gently warmed to 45 °C on an oil bath. The dark yellow reaction mixture was quenched after 4 h by pouring into 100 mL of an ice-cold solution of 1 N HCl. The layers were separated, and the aqueous phase was extracted with 2 × 25 mL of CH_2Cl_2. The organic fractions were combined and washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and filtered through a thin pad of silica gel on Celite. The solvent was removed by rotary vacuum evaporation, and the product was dried under high vacuum to yield 4.09 g (90%) of a light-yellow solid. This crude product was recrystallized from ethyl acetate–hexane to give 3.5 g of white crystalline **10**: mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 CH_3), 3.0 (m, 2, $ArCH_2$), 4.0 (s, 3, CH_3O), 4.4 (m, 1, $ArCH_2CH$), 4.8 (s, 2, $COCH_2Cl$), 6.2 (bs, 1, NH), 6.8 (m, 2, ArH), 7.85 (d, 1, ArH); MS *m/z* 338 (M + 1). Anal. ($C_{14}H_{15}ClF_3NO_3$) C, H, N.

6-[2-[*N*-(Trifluoroacetyl)amino]propyl]-2,3-dihydrobenzofuran-3-one (11). A solution of 5.3 g (15.7 mmol) of **10** in 350 mL of dry CH_2Cl_2 was cooled to −78 °C in a solid CO_2–acetone bath. BBr_3 (7 mL, 62.7 mmol) was then added slowly by syringe. The reaction was allowed to proceed for 12 h as the cooling bath gradually warmed to room temperature. The mixture was again cooled to −78 °C and quenched by the addition of 100 mL of cold water. After warming to room temperature, another 100 mL of H_2O was added, and the layers were separated. The aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2, and the organic fractions were combined and washed with 50 mL water and 50 mL brine. The solvent was removed by rotary evaporation to yield a mass of off-white solid which was unstable to air. This product was therefore immediately taken up into 600 mL of CH_3OH, 7.5 g (55 mmol) of NaOAc was added, and the mixture was heated at reflux on an oil bath for 1.5 h to effect ring closure. After cooling to 0 °C, the mixture was filtered through Celite and the solvent was removed by rotary evaporation. The orange residue was taken up into 200 mL of ether and washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered through a thin pad of silica gel on Celite. After removal of the solvent *in vacuo*, an orange solid was obtained which was recrystallized from ethyl acetate–hexane to yield 2.56 g (57%) of **11** as dense orange crystals. An analytical sample was further purified using radial chromatography ("Chromatotron") on a silica rotor and elution with dichloromethane. This gave a light-yellow solid with a sharp melting point: mp 127 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (d, 3, CH_3), 3.0 (m, 2, $ArCH_2$), 4.4 (m, 1, $ArCH_2CH$), 4.6 (s, 2, $COCH_2O$), 6.2 (bs, 1, NH), 6.9 (m, 2, ArH), 7.55 (d, 1, ArH); MS *m/z* 288 (M + 1). Anal. ($C_{13}H_{12}F_3NO_3$) C, H, N.

6-[2-[*N*-(Trifluoroacetyl)amino]propyl]-2,3-dihydrobenzofuran (12). A solution of 2.9 g (10 mmol) of **11** in 300 mL of absolute ethanol was placed in a Parr hydrogenation flask with 1 g of 20% PdOH/C. The mixture was shaken under 52 psig of H_2 for 12 h and then filtered through Celite. The alcohol was removed by rotary vacuum evaporation to give, quantitatively, a yellow oil which spontaneously crystallized upon standing. Recrystallization from ethanol–hexane produced **12** as white crystals: mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3, CH_3), 2.7 (m, 2, $ArCH_2CH$), 3.2 (t, 2, $ArCH_2CH_2$), 4.25 (m, 1, $ArCH_2CH$), 4.5 (t, 2, $ArOCH_2$), 6.1 (bs, 1 NH), 6.6 (m, 2, ArH), 7.1 (d, 1, ArH); MS *m/z* 273 (M). Anal. ($C_{13}H_{14}F_3NO_2$) C, H, N.

6-(2-Aminopropyl)-2,3-dihydrobenzofuran Hydrochloride (4). A solution of 1.4 g (5.12 mmol) of **12** in 110 mL of 2-propanol was vigorously stirred while 10 mL of 2 N KOH was added, and the mixture was heated at reflux for 5 h. After cooling, the solvent was removed by rotary evaporation. The residue was taken up into 150 mL of 3 N NaOH and the aqueous solution was extracted with CH_2Cl_2 (4 × 50 mL). The organic fractions were combined and then extracted with 4 × 50 mL of 3 N HCl. The acidic aqueous extracts were combined and then basified with 5 N NaOH to pH 11 (external damp pH paper) while cooling on an ice bath. The free amine **4** was extracted into CH_2Cl_2 (4 × 25 mL) and the organic phase dried ($MgSO_4$), filtered through Celite, and concentrated on the rotary evaporator. The residual yellow oil was dissolved in 15 mL of anhydrous ether, and the hydrochloride salt was formed by the addition of 6 mL of 1.0 N HCl in anhydrous ethanol. After removal of the volatiles by rotary evaporation, the resulting white solid was recrystallized from ethanol–hexane to yield 0.86 g (78%) of white crystalline **4**·HCl: mp 252–254 °C; ^{1}H NMR (DMSO-d_6) δ 1.2 (d, 3, CH_3), 2.6 (dd, 1, $ArCH_2CH$), 3.1 (dd, 1, $ArCH_2CH$), 3.2 (t, 2, $ArCH_2CH_2$), 3.4 (m, 1, $ArCH_2CH$), 4.55 (t, 2, $ArOCH_2$), 6.75 (d, 2, ArH), 7.2 (d, 2, ArH), 8.2 (bs, 3, NH_3^+); MS *m/z* 178 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

5-Formyl-2,3-dihydrobenzofuran (14a).[30] Dihydrobenzofuran **13a** (3.0 g, 25 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 0 °C on an ice bath. With vigorous stirring, 9.76 g (44 mmol) of $SnCl_4$ was added all at once via syringe, followed by the dropwise introduction of 2.87 g (25 mmol) of dichloromethyl methyl ether over a 10-min period. After 20 min the ice bath was removed, and the dark mixture was quenched by the addition of 50 mL of ice–water. The aqueous layer was discarded, and the organic phase was washed with water (3 × 25 mL), 3 N HCl (3 × 25 mL), and brine (2 × 25 mL). The purple organic solution was then treated with activated carbon and filtered through a thin pad of silica gel on Celite. After removal of the solvent under vacuum, 3.34 g (90%) of **14a** was obtained as a yellow oil which was sufficiently pure to carry on the next step. A portion of the aldehyde was purified for analysis by conversion to its bisulfite addition product, followed by decomposition in saturated K_2CO_3 solution and extraction into dichloromethane: ^{1}H NMR ($CDCl_3$) δ 3.25 (t, 2, $ArCH_2$), 4.6 (t, 2, $ArOCH_2$), 6.9 (d, 1, ArH), 7.7 (m, 2, ArH), 9.8 (s, 1, ArCHO); MS *m/z* 149 (M + 1), 297 (2M + 1); IR 1686 cm^{-1}.

5-[1-(2-Nitrophenyl)]-2,3-dihydrobenzofuran (15a). To a solution of 3.3 g (22.3 mmol) of **14a** in 10 mL of nitroethane was added 0.92 g (12 mmol) of ammonium acetate. The mixture was heated with stirring to 110 °C on an oil bath for 3.5 h. The volatiles were then removed by rotary evaporation. The crude product was triturated in 10 mL of cold CH_3OH, collected by suction filtration, and recrystallized from methanol to yield 3.06 g (67%) of **15a** as a fluffy yellow crystalline solid: mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3, CH_3), 3.3 (t, 2, $ArCH_2$), 4.7 (t, 2, $ArOCH_2$), 6.85 (d, 1, ArH), 7.35 (m, 2, ArH), 8.1 (s, 1, ArCH=C); MS *m/z* 206 (M + 1). Anal. ($C_{11}H_{11}NO_3$) C, H, N.

5-(2-Aminopropyl)-2,3-dihydrobenzofuran Hydrochloride (5). A solution of 2.3 g (11.5 mmol) of **15a** was dissolved in 75 mL of dry THF and added dropwise to a stirring suspension of 1.2 g (29 mmol) of $LiAlH_4$ in 400 mL of dry THF. After complete addition, the mixture was heated at reflux for 5 h on an oil bath. The mixture was then cooled on an ice bath, and the excess $LiAlH_4$ was decomposed by the careful addition of 10 mL of H_2O. The mixture was filtered through Celite, the filter cake was rinsed well with ether, and the solvent was removed by rotary vacuum evaporation. The oily residue was taken up into 100 mL of ether and the product was extracted with 5 × 50 mL of 3 N HCl. The aqueous extracts were combined and rendered strongly basic with the addition of 5 N NaOH, and the free base was extracted into dichloromethane (4 × 50 mL). The combined organic extract was dried ($MgSO_4$), filtered through Celite, and concentrated by rotary evaporation. The residual oil was dissolved in 20 mL of anhydrous ether and the hydrochloride salt was formed by the addition of 5 mL of 1.0 N HCl in anhydrous ethanol. After removal of the volatiles *in vacuo*, the resulting white solid was recrystallized from ethanol to yield 1.44 g (58%) of **5**·HCl as shimmering white crystals: mp 231–232 °C; ^{1}H-NMR (DMSO-d_6) δ 1.2 (d, 3, CH_3), 2.6 (dd, 1, $ArCH_2CH$), 3.05 (dd, 1, $ArCH_2CH$), 3.3 (t, 2, $ArCH_2CH_2$), 3.4 (m, 1, $ArCH_2CHNH$), 4.52

(t, 2, $ArOCH_2$), 6.75 (d, 1, ArH), 6.95 (d, 1, ArH), 7.1 (s, 1, ArH), 8.1 (bs, 2, NH_3^+); MS m/z 178 (M + 1). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

2,3-Dihydro-1H-indene-5-carboxaldehyde (14b).[31] As in the procedure above for **14a**, 10 g (84.6 mmol) of indan **13b** was treated with 15 mL (127 mmol) of $SnCl_4$ and 9.72 g (84.6 mmol) of dichloromethyl methyl ether in 100 mL of CH_2Cl_2 for 30 min to give, after workup, 12.2 g (98%) of **14b** as a yellow oil which was purified via its bisulfite adduct: ^1H NMR ($CDCl_3$) δ 2.18 (p, 2, $ArCH_2CH_2$), 3.0 (m, 4, $ArCH_2$), 7.38 (d, 1, ArH), 7.65 (dd, 1, ArH), 7.7 (d, 1, ArH), 9.95 (s, 1, ArCHO); MS m/z 147 (M + 1), 293 (2 M + 1); IR 1691 cm^{-1}.

5-[1-(2-Nitropropenyl)]-2,3-dihydro-1H-indene (15b). As in the procedure for **15a**, 4.0 g (15.9 mmol) of **14b** was heated at reflux with 30 mL of nitroethane and 1.22 g (15.9 mmol) of ammonium acetate for 4 h to yield 2.43 g (76%) of **15b** as a yellow oil which could be crystallized with difficulty from methanol afer radial chromatography (CH_2Cl_2 as eluant): mp 33–34 °C; ^1H NMR ($CDCl_3$) δ 2.15 (p 2, $ArCH_2CH_2$), 2.45 (s, 3, CH_3), 2.98 (t, 4, $ArCH_2$), 7.22 (d, 1, ArH), 7.32 (d, 2, ArH), 8.16 (s, 1, ArCH=C); MS m/z 204 (M + 1). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

5-(2-Aminopropyl)-2,3-dihydro-1H-indene Hydrochloride (6). In a method similar to that for the formation of **5**, 2.9 g (14.3 mmol) of **15b** in 100 mL of dry THF was added dropwise to a stirred suspension of 1.5 g (35.6 mmol) of $LiAlH_4$ in 150 mL of THF and the reaction was stirred for 5 h at room temperature. After the usual workup, **6** was precipitated as its hydrochloride salt and recrystallized to give 2.18 g (72%) of the product as shimmering, white flakes: mp 218–219 °C; ^1H NMR ($CDCl_3$) δ 1.39 (d, 3, CH_3), 2.05 (p, 2, $ArCH_2CH_2$), 2.8 (dd, 1, $ArCH_2CH$), 2.85 (t, 4, $ArCH_2CH_2$), 3.21 (dd, 1, $ArCH_2CH$), 3.57 (m, 1, $ArCH_2CH$), 6.98 (d, 1, ArH), 7.1 (s, 1, ArH), 7.17 (d, 1, ArH), 8.42 (bs, 3, NH_3^+); MS m/z 176 (M + 1), 351 (2 M + 1). Anal. ($C_{12}H_{18}ClN$) C, H, N.

5,6,7,8-Tetrahydronaphthalene-2-carboxaldehyde (14c).[31] As described above for compound **14a**, 10.0 g (75.6 mmol) of 1,2,3,4-tetrahydronaphthalene (**13c**) was treated with 13.3 mL (113 mmol) of $SnCl_4$ and 8.7 g (75.6 mmol) of dichloromethyl-methyl ether in 90 mL of $CHCl_3$ for 1 h. Workup afforded 12 g (98%) of **14c** as a yellow oil. The aldehyde was purified and could be stored as its bisulfite adduct: ^1H NMR ($CDCl_3$) δ 1.8 (m, 4, $ArCH_2CH_2$, 2.82 (m, 4, $ArCH_2$), 7.2 (d, 1, ArH), 7.3 (dd, 1, ArH), 7.6 (d, 1, ArH), 9.92 (s, 1, ArCHO); MS m/z 161 (M + 1), 321 (2 M + 1); IR 1696 cm^{-1}.

2-[1-(2-Nitropropenyl)]-5,6,7,8-tetrahydronaphthalene (15c). Using the method for **15a**, but with 1.1 g (6.92 mmol) of **14c**, 15 mL of nitroethane, and 0.54 g (6.92 mmol) of ammonium acetate and heating at reflux for 3 h, gave, after workup, 1.33 g (88%) of a crude yellow solid. One crop of **15c** as yellow crystals was obtained by recrystallization from methanol, and the remaining crude product was purified by radial chromatography (CH_2Cl_2 as eluant): mp 46–47 °C; ^1H NMR ($CDCl_3$) δ 1.82 (m, 4, $ArCH_2CH_2$), 2.45 (s, 3, CH_3), 2.8 (m, 4, $ArCH_2$), 7.1–7.2 (m, 3, ArH), 8.05 (s, 1, ArCH=C); MS m/z 218 (M + 1). Anal. ($C_{13}H_{15}NO_2$) C, H, N.

2-(2-Aminopropyl)-5,6,7,8-tetrahydronaphthalene Hydrochloride (7). As in the method described for **5**, 3.0 g (13.8 mmol) of **15c** in 50 mL of dry THF was added to a stirred suspension of 1.7 g (41.4 mmol) of $LiAlH_4$ in 250 mL of THF and heated at reflux for 4 h. Workup afforded 2.04 g (65%) of **7**·HCl as shimmering white crystals: mp 216 °C; ^1H NMR ($CDCl_3$) δ 1.38 (d, 3, CH_3), 1.78 (m, 4, $ArCH_2CH_2$), 2.7 (m, 4, $ArCH_2CH_2$), 2.8 (dd, 1, $ArCH_2CH$), 3.2 (dd, 1, $ArCH_2CH$), 3.53 (m, 1, $ArCH_2CH$), 6.9 (d, 2, ArH), 7.0 (d, 1, ArH), 8.42 (br, 3, NH_3^+); MS m/z 190 (M + 1). Anal. ($C_{13}H_{20}ClN$) C, H, N.

Pharmacological Methods. Animals. Male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing 175–200 g were used. Animals were group housed (for *in vitro* experiments) or individually caged (for drug discrimination experiments) in a temperature-controlled room with a 12 h day/night lighting schedule. Animals that were used for *in vitro* experiments were supplied with food (Lab Blox, Purina) and water *ad libitum*. For drug-discrimination experiments, water was freely available in the home cages and a sufficient amount of supplemental food was made available after experimental sessions so as to maintain them at approximately 80% of free feeding weight, compared with control rats housed under the same conditions.

Drug-Discrimination Studies. Animals were divided into four groups (N = 10-15 per group) and trained to discriminate (*S*)-**1c**·HCl (1.75 mg/kg), **3**·HCl (1.71 mg/kg), (*S*)-(+)-amphetamine sulfate (1 mg/kg), or LSD tartrate (0.08 mg/kg) from saline. None of the rats had previously received drugs or behavioral training. Six standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the cage, which was also equipped with two response levers, separated by a food hopper, all positioned 2.5 cm above the floor. Solid-state logic in an adjacent room, interfaced through a Med Associates Interface to a 486-based PC, controlled reinforcement and data acquisition with a locally written program.

A fixed ratio (FR50) schedule of food reinforcement (Bioserv 45 mg dustless pellets) in a two-lever paradigm was used. Details of the drug-discrimination procedure have been described elsewhere.[7,8] Half of the rats were trained on drug-L (left), saline-R (right) and the other half on the drug-R, saline-L to avoid positional preference. Training sessions lasted 15 min and were conducted at the same time each day. Training sessions were continued until an accuracy of a least 85% (number of correct presses × 100/number of total presses) was attained for eight of ten consecutive sessions. Once criterion performance was attained, test sessions were interpersed between training sessions, either one or two times per week. At least one drug and one saline session separated each test session. Rats were required to maintain the 85% correct responding criterion on training days in order to be tested. In addition, test data (less than 5%) were discarded when the accuracy criterion of 85% was not achieved on the two training sessions following a test session. Test drugs were administered ip 30 min prior to the sessions; test sessions were run under condition of extinction, with rats removed from the operant chamber when 50 presses were emitted on one lever. If 50 presses on one lever were not completed within 5 min, the session was ended and scored as disrupted. Treatments were randomized at the beginning of the study.

***In Vitro* [^{3}H]Neurotransmitter Uptake Studies.** Crude synaptosomes were prepared as follows: for each experiment, three rats (170–420 g) were decapitated and their brains rapidly removed over ice. The cerebellums were removed and discarded and the remaining brain tissue (ca. 4 g, wet weight) was diced, pooled, and homogenized in 5 volumes of ice-cold isotonic sucrose. Homogenization was done in a prechilled glass mortar with a motor-driven Teflon pestle at 0 °C, for two periods of 1 min each, 6 strokes/min, with a 15-s interval between periods. The tissue homogenate was centrifuged at 1090*g* for 10 min. The P_1 pellet was discarded and the supernatant was centrifuged at 1740*g* for 30 min. The P_2 pellet was resuspended with a Polytron (setting 5, 20 s; Kinematica) in 30–40 mL ice-cold, aerated (5% CO_2 in O_2) Krebs–Ringer bicarbonate (KR) buffer containing the following (mM): NaCl (124.3), KCl (2.95), $MgSO_4$ (1.30), KH_2PO_4 (1.25), $NaHO_3$ (26.0), $CaCl_2$ (2.41), *d*-glucose (10.4), pH 7.4–7.6. For catecholamine experiments, 0.06 mM sodium ascrobate was included in the buffer to inhibit oxidation of the labeled neurotransmitters.

A 200-μl aliquot of the synaptosomal suspension was added to test tubes containing 1.65 mL of ice-cold KR buffer, 50 μL of test drugs or deionized water (total and nonspecific tubes), and 50 μL of pargyline HCl solution (final concentration, 100 μM). The tubes were preincubated in an aerated (5% CO_2 in O_2; 15 psi), 37 °C, shaking water bath for 5 min. The tubes were then returned to the ice bath and chilled for 10–15 min. Tritiated neurotransmitter was added (50 μL; final concentration, 10 nM), giving a final incubation volume of 2 mL. All tubes except nonspecific tubes were returned to the aerated 37 °C shaking water bath for 5 min to initiate neurotransmitter uptake. Uptake was terminated by chilling the test tubes in an ice bath, then rapidly filtering them through glass-fiber filters (Whatman GF/C) using a 24-well cell harvester (Brandel). Filters were washed with 2 × 3 mL ice-cold KR buffer, allowed to air dry for 10 min, and then placed in plastic liquid scintillation vials. Scintillation cocktail (10 mL; Ecolite, ICN Biomedicals) was added, and the

vials were sealed, vortexed, and allowed to stand for at least 6 h. Radioactivity was measured using liquid scintillation spectroscopy (Packard 4530, 47% efficiency). Specific uptake was defined as uptake at 37 °C minus uptake at 0 °C, in the absence of drugs.

Statistical Analysis. Data from the drug-discrimination studies were scored in a quantal fashion, with the lever on which the rat first emitted 50 presses in a test session scored as the "selected" lever. The percentage of rats selecting the drug lever (%SDL) for each dose of compound was determined. The degree of substitution was determined by the maximum %SDL for all doses of the test drug. "No substitution" (NS) is defined as 59% SDL or less, and "partial" substitution is 60–79% SDL. If the drug was one which completely substituted for the training drug (at least one dose resulted in a %SDL = 80% or higher), the ED_{50} values and 95% confidence intervals (95% CI) were then determined from quantal dose–response curves according to the procedure of Litchfield and Wilcoxon.[32] If the percentage of rats disrupted (%D) was 50% or higher, the ED_{50} value was not determined, even if the %SDL of nondisrupted animals was higher than 80%.

In vitro data were transformed from dpm to percent inhibition of specific uptake and fit for a four-parameter logistic curve using the computer program EBDA,[33] from which IC_{50} values (nM) were calculated. The IC_{50} values reported are the mean ± SEM from three or four experiments run in triplicate with 9 or 10 concentrations of test drugs. Multiple comparisons were done using an ANOVA, followed by a *post hoc* Student's *t*-test.

Materials. (*S*)-(+)-Amphetamine sulfate was purchased from Smith Kline & French Laboratories (Philadelphia, PA). Pargyline hydrochloride was purchased from Sigma (St. Louis, MO). (*S*)-MBDB (**1c**) and MMAI (**3**), as their hydrochlorides, were synthesized in our laboratory.[4,22] (+)-LSD tartrate was obtained from NIDA. For drug-discrimination experiments, all drugs were dissolved in 0.9% saline and injected intraperitoneally in a volume of 1 mL/kg, 30 min before the session.

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