Derivatives of 1-(1,3-Benzodioxol-5-yl)-2-butanamine: Representatives of a Novel Therapeutic Class

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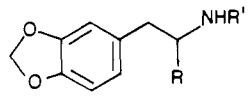
The α-ethyl phenethylamine derivative 1-(1,3-benzodioxol-5-yl)-2-butanamine was prepared. An asymmetric synthesis was used to prepare the enantiomers of this compound and the related α-methyl homologue (MDA). The racemates and enantiomers of both compounds were evaluated in the two-lever drug discrimination assay in rats trained to discriminate saline from 0.08 mg/kg of LSD tartrate. Stimulus generalization occurred with the racemate and the *R*-(−) enantiomer of the α-methyl homologue and the *S*-(+) enantiomer of the α-ethyl primary amine. No generalization occurred with the other enantiomers or with the *N*-methyl derivatives of either series. Human psychopharmacology studies revealed that the *N*-methyl derivative of the title compound was nonhallucinogenic and that it had a new, novel psychoactive effect. It is suggested that this compound is the prototype of a new pharmacologic class that may have value in facilitating psychotherapy and that this class be designated as entactogens.

Our efforts over many years have been directed toward understanding the effects of chemical structure on the pharmacology and human psychopharmacology of hallucinogenic, or psychedelic, drugs.[1] We have previously reported on the chemistry and pharmacology of *N*-methyl-1-[3,4-(methylenedioxy)phenyl]-2-aminopropane (**2a**, MDMA).[2,3] Although the primary amine **1a**, MDA, has generally been classified as an hallucinogen, it clearly has atypical effects, in that it enhances empathy and has less potential to produce severe sensory disruption.[4] Indeed, MDA became a popular recreational drug and gained a street reputation as the "love drug", emphasizing this enhancing effect on empathy.[5]



1a, R = CH_3; R' = H **2a**, R = R' = CH_3
b, R = CH_2CH_3; R' = H **b**, R = CH_2CH_3; R' = CH_3

However, the N-methylation of **1a** to give **2a**, MDMA, has several dramatic effects on activity. First, the duration of action of the compound is decreased considerably. Second, the overall effects are less powerful, and the hallucinogenic quality of the compound seems to be abolished.[6] On the other hand, the ability to elicit an increased sense of empathy is retained, or even increased, when compared with MDA. Furthermore, there is evidence that the mechanism of action differs for **1a** and **2a**. The clearest indication of this is the fact that it is the *S*-(+) isomer of **2a** that is more active, while it is the *R*-(−) isomer of **1a**, and other substituted amphetamines, that possesses hallucinogenic activity.[7] Recently, a great deal of media attention has been focused on **2a**, which was available on the street market as "ecstasy", or "XTC". This drug became popular as a recreational substance, probably due, in part, to its relatively mild effects and its ability to facilitate interpersonal communication. However, a number of psychiatrists have claimed that **2a** has unique properties in facilitating psychotherapy, by reducing the anxiety or fear that normally accompanies the discussion of emotionally painful events.[8] Although there is continuing controversy regarding this issue, it seemed possible that **2a** might indeed possess novel pharmacology that merited further exploration.

In order to develop further the potential therapeutic qualities manifested by **2a**, but to decrease abuse potential, we considered ways to modify its structure. We had previously suggested that **2a** might exert its action partly through a mechanism involving the release of endogenous monoamine neurotransmitters, similar to the action of amphetamine or *N*-methylamphetamine.[2,3] This was based on the parallel fact that it is the *S*-(+) isomer of amphetamine that is more effective as a neurotransmitter releasing agent. We also noted from the patent literature[9] the claim that the α-ethyl homologue, 1-phenyl-2-aminobutane, is a CNS stimulant, perhaps indicating that neurotransmitter release and/or reuptake blocking mechanisms are still operative in compounds possessing an α-ethyl function in the side chain. By contrast, the homologation to an α-ethyl in the hallucinogens such as DOM (1-[2,5-dimethoxy-4-methylphenyl]-2-aminopropane) completely abolishes hallucinogenic activity in all examples so far studied.[10] Indeed, several α-ethyl analogues have been evaluated as novel antidepressive agents,[11] although the 3,4-(methylenedioxy) substituted compound apparently was not studied.

Therefore, compounds **1b** and **2b** were proposed as homologues of **1a** and **2a** that might retain the useful therapeutic aspects displayed by the latter, but which should lack the profile more typical of the hallucinogens, or psychedelics.

This report details the synthesis and preliminary pharmacology for compounds **1b** and **2b**. We also report the preparation and evaluation of the optical isomers of these two compounds. In view of the current interest in **2a**, we also include the complete experimental details for the preparation of *R*- and *S*-**2a**, which were lacking in our

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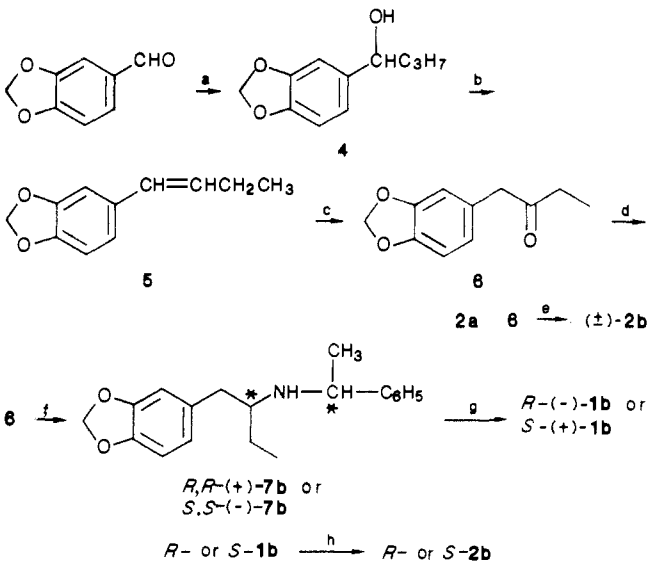
Scheme I[a]



[a] (a) C_3H_7Br, Mg, ether; (b) $KHSO_4$, heat; (c) 1. H_2O_2, HCOOH, 2. H^+, MeOH, heat; (d) NH_4OAc, $NaCNBH_3$; (e) CH_3NH_2, Al-Hg; (f) 1. (*R*)- or (*S*)-$C_6H_5CH(NH_2)CH_3$, $-H_2O$, 2. W-2 Raney Ni, 50 psig H_2; (g) 10% Pd–C, 50 psig H_2; (h) 1. $HCOOCH_3$, heat, 2. $LiAlH_4$.

earlier report.[3] The procedure for the determination of enantiomeric purity is also described for all isomers.

Chemistry. Initially, the preparation of **1b** was attempted by the usual condensation between piperonal and nitropropane, with a subsequent reduction of the 1-phenyl-2-nitrobutene. However, a variety of reaction conditions failed to provide this latter intermediate in yields better than about 20%; the reaction between piperonal and 1-nitropropane is very sluggish, and the formation of byproducts proceeds at an appreciable rate.

Therefore, both **1b** and **2b** were prepared by reductive amination of 1-[3,4-(methylenedioxy)phenyl]-2-butanone (**6**). This ketone was prepared starting with piperonal, as shown in Scheme I, by hydrogen peroxide oxidation of the olefin **5** and acid-catalyzed rearrangement to the desired ketone **6**. Although it was anticipated that treatment of 3,4-(methylenedioxy)phenylacetonitrile with triethylaluminum[12] would directly yield the ketone, in practice substantial cleavage of the dioxole ring occurred and this approach proved unsuccessful.

Reductive amination of the ketone **6** was accomplished by using ammonium acetate and sodium cyanoborohydride for the primary amine **1b** and methylamine and aluminum amalgam for the secondary amine **2b**. The enantiomers of **1b** and **2b** were conveniently prepared, using the method developed in our laboratory,[13] by a reductive amination of the ketone using (*R*)- or (*S*)-α-methylbenzylamine and W-2 Raney nickel. The intermediate *N*-α-phenylethylamines **7a** and **7b** were subsequently catalytically N-debenzylated, as their hydrochloride salts, using hydrogen at a pressure of 3 atm and Pd–C catalyst. This afforded the enantiomers of the primary amines **1a** and **1b**. This route has also been applied to the preparation of the enantiomers of other α-ethylphenethylamines.[11] The primary amine enantiomers were then converted to their N-formyl derivatives **8a** and **8b** and reduced with lithium aluminum hydride to afford the enantiomers of **2a** and **2b**. It was anticipated that these enantiomers had the *R*-(−) and *S*-(+) absolute configurations, by analogy to earlier studies.[13] Recently, single-crystal X-ray crystallographic studies have confirmed this (manuscript in preparation).

The enantiomeric excess for the isomers of **2a** and **2b** was established by preparing the diastereomeric derivatives of the amine by reaction with (−)-camphanic acid chloride. GLC analysis of these derivatives was used to demonstrate enantiomeric excess greater than 98% for each isomer.

Pharmacology. The enantiomers of **1a**, **2a**, **1b**, and **2b** were evaluated in the two-lever drug discrimination assay, in a colony of rats trained to discriminate saline from injections of LSD tartrate (0.08 mg/kg, ip), using methods we have described previously.[14] This was done to determine whether compounds **1b** and **2b** did, in fact, lack discriminable properties similar to LSD and to compare these effects with those produced by **1a** and **2a**. This was an important consideration, since it was felt that these compounds would have therapeutic value only if they did not disrupt normal sensory processing.

The enantiomers of **1b** and **2b**, and their racemic mixtures, were then evaluated in humans following the procedures described by Shulgin et al.[15] It was clear from previously published reports on the pharmacology of compounds **1a** and **2a**[3,4] that animal studies would probably fail to identify the type of therapeutic action that was of interest with compounds **1b** and **2b**.

Results and Discussion

The results of the drug discrimination studies in rats are presented in Table I. Testing of various doses of the training drug, LSD, produced a dose-dependent increase in LSD-lever selections (ED_{50} = 0.025 μM/kg, 95% CI = 0.012–0.050 μM/kg or 0.011 mg/kg, 95% CI = 0.005–0.021 mg/kg). All rats tested with saline selected the saline-appropriate lever.

Stimulus generalization was produced with (±)-MDA and *R*-(−)-MDA but not *S*-(+)-MDA. This is in general agreement with studies done using 1.0 mg/kg of (±)-DOM,[16] a phenethylamine hallucinogen, as well as 3.0 mg/kg of 5-OMe-DMT,[17] an indolealkylamine hallucinogen, as training drugs.

The only other compound tested that produced complete generalization was *S*-(+)-**1b**. This result was unexpected in view of our arguments regarding the α-ethyl effect on hallucinogenic potency. However, false positives can occur in drug discrimination studies with rats.[18] Indeed, Winter[19] reported testing a similar compound, BL3912A, the α-ethyl homologue of DOM, known to be nonhallucinogenic in man, and observed complete generalization in rats trained to discriminate 0.1 mg/kg of LSD from saline. Other investigators[20] seem to be in agreement with Winter's comment that "even complete substitution of a drug for LSD in the rat is not necessarily associated with the production by that drug of hallucinations in man."[19] Neither the *R*-(−) isomer of **1b** nor racemic **1b** produced stimulus generalization, with a maximum of only

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50% of the rats selecting the LSD-appropriate lever.

No generalization was observed when MDMA, **2a**, was tested. The separate enantiomers as well as the racemate all produced stimulus effects leading to a maximum of only 50% of the rats selecting the LSD-appropriate lever. Similar results were reported when **2a** was tested in rats trained to discriminate 1.0 mg/kg of (±)-DOM from saline.[16]

It seems clear, from the drug discrimination studies in rats carried out thus far, that MDMA does not resemble an hallucinogen. Glennon[21] has suggested that the N-methylation of MDA might unveil the stimulant component of the dualistic cue produced by this compound, by selectively decreasing only the "hallucinogenic" component. The stimulant properties of MDA and MDMA are evidenced by the complete substitution of these compounds for 1.0 mg/kg of (+)-amphetamine.[16] However, Overton has made the point that drug discrimination assays, "like many other assay procedures, suffer from an inability to identify genuinely new compounds, and instead identify compounds with actions similar to those of already available drugs."[22] Therefore, the classification of MDMA as a stimulant based on drug discrimination data may lack validity, especially in light of the observed effects in humans.[6,8]

Interestingly, although interpretation of partial generalization results is controversial, (±)-**2b** produced the least LSD-appropriate responding of all the compounds tested in this study, with a maximum of less than 15% ($^1/_7$) of the rats tested selecting the LSD-appropriate lever. Both *R*-(−)-**2b** and *S*-(+)-**2b** failed to substitute for 0.08 mg/kg of LSD.

Clinical evaluation of racemic, (+)-, and (−)-**2b** revealed certain parallels with the α-methyl homologue **2a**. Effective doses of racemic **2b** were in the range 150–210 mg. Initial effects were detectable in some individuals within 20 min after administration. Usually, however, it was 30–45 min before a clear and definite effect was observed. In contrast to the hallucinogens, this material had a subtle and gentle onset. The overall chronology of effect lasted approximately 5 h, and sleep was possible at the fifth or sixth hour.

The drug effect was characterized as a pleasant state of introspection, with interpersonal communication greatly facilitated. Subjects could readily talk about emotionally painful past events if they wished, without apparent embarrassment or inhibition. There was a pronounced sense of empathy and compassion between subjects. After reaching maximum effect between the first and second hour, there was a gradual tapering off of action until about the fifth hour. Subjects felt able to drive an automobile and function normally at least by that time. There were no apparent visual distortions or hallucinations. However, some subjects did report mild nystagmus. There was no closed-eye imagery, even in a darkened room.

All subjects had prior experience with a broad range of psychotropic drugs. There was unanimous agreement that this material did not elicit the pharmacological spectrum of action that would typically be expected after ingestion of an hallucinogen.

All subjects also had prior experience with MDMA, **2a**. MDMA did differ from **2b** in certain respects, although the two were generally similar in effect. First, the onset of action of **2b** was slower and more gentle than MDMA; there was little of the anxiety that sometimes can occur at onset of the drug effect. Second, there seemed to be less euphoria associated with **2b** than with **2a**.

In a separate experiment with four subjects, involving a double-blind, placebo-controlled (lactose) crossover study, *S*-(+)-**2b** (125 mg, po) was found to be the biologically more active enantiomer and was easily distinguished from the same dose of *R*-(−)-**2b**. This parallels the stereoselectivity of action found for **2a**.[3] These subjects were familiar with the effects of sympathomimetic agents such as amphetamine and methylphenidate and felt that the subjective effects produced by *S*-(+)-**2b** differed substantially from those produced by the former agents. In particular, typical CNS stimulants produce motor stimulation and increased levels of physical activity. By contrast, subjects who took **2b** were usually content to sit or lie quietly.

Although **1a**, MDA, has been considered to be an hallucinogen, neither its *N*-methyl derivative **2a** nor **2b** should be considered in this way. Indeed, at effective doses, **2b** did not produce significant sensory disturbances. Rather, it had a selective enhancing effect on the sense of empathy, reduced the anxiety associated with the discussion of painful emotional material, and produced a sense of well-being. More important, however, to our conclusions are these findings with respect to the mechanism of action for **2b**, as contrasted with the substituted amphetamine-type hallucinogens. First, the reversal of stereoselectivity for **2b**, where it is the *S* configuration that is more active, argues strongly against a similarity to hallucinogens such as DOM, where the *R* configuration is more active. Our previous suggestion[3] that **2a** may act by an indirect mechanism, possibly involving catecholaminergic sites, either by affecting monoamine release or by inhibiting reuptake into nerve terminals, may also apply to the action of **2b**.

Second, and perhaps even more important, is the fact that **2b** possesses an α-ethyl group. It is known that in the hallucinogenic amphetamines homologation of the α-methyl to an α-ethyl completely abolishes hallucinogenic activity.[11] For example, the α-ethyl homologue of DOM, (*R*)-(−)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminobutane (BL3912A), has no detectable hallucinogenic activity at doses more than 100-fold those that are effective for DOM.[19] Indeed, BL3912A was evaluated for antidepressant activity.[11] Therefore, the presence of the α-ethyl in **2b** should, in principle, abolish any residual component of the action that would be related to that found in the phenethylamine hallucinogens. That **2b** retains activity is a clear indication that its primary mechanism of action cannot be at the same receptor site(s) as the classical hallucinogens.

In summary, **2b** represents a novel type of psychoactive compound that is not hallucinogenic, but rather facilitates communication and introspective states. We propose to designate this compound as representative of a new therapeutic class to be called "entactogens". This is derived from the Greek roots "en" for within or inside and "gen" to produce or originate and the Latin root "tactus" for touch. Hence, the connotation of this word is that of producing a "touching within". It is important to draw a sharp contrast between the entactogens and the hallucinogens or psychedelics, since the former should have no capacity to produce profound sensory experiences or distortions or to induce the type of powerful visionary experience that is characteristic of mescaline, psilocybin, or LSD.

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Table I. Drug Discrimination Results: Generalization Studies Using 0.186 μM/kg (0.08 mg/kg) LSD as the Training Drug

compd	dose μM/kg	dose mg/kg	N^a	D^b	result[c]	ED_{50}[d]
LSD	0.006	0.0025	8	0	0/8	0.025 μM/kg
	0.012	0.005	8	0	4/8	(0.0124–0.0498)
	0.023	0.01	8	0	4/8	
	0.047	0.02	8	0	5/8	0.011 mg/kg
	0.093	0.04	8	0	6/8	(0.005–0.0214)
	0.186	0.08	8	0	8/8	
saline	0	0	8	0	0/8	
(+/−)-**1a**	1.5	0.32	11	3	0/8	4.52 μM/kg
	3	0.63	8	0	2/8	(3.11–6.57)
	6	1.29	10	2	5/8	0.97 mg/kg
	8	1.72	23	15	7/8	(0.67–1.42)
R-(−)-**1a**	0.75	0.16	8	0	1/8	2.94 μM/kg
	1.5	0.32	9	1	2/8	(1.67–5.17)
	3	0.63	9	1	2/8	0.63 mg/kg
	6	1.29	10	2	7/8	(0.36–1.11)
S-(+)-**1a**	0.75	0.16	8	0	1/8	
	1.5	0.32	8	0	2/8	
	3	0.63	10	2	2/8	
	6	1.29	18	10	3/8	
	7.5	1.62	31	25	2/6	
	8	1.73	5	5	0/0[e]	
(+/−)-**2a**	1.5	0.34	10	2	2/8	
	3	0.69	10	2	0/8	
	6	1.38	8	0	2/8	
	8	1.84	21	13	3/8	
	9	2.19	5	4	0/1[e]	
R-(−)-**2a**	0.75	0.17	8	0	1/8	
	1.5	0.34	8	0	3/8	
	3	0.69	9	0	2/9	
	6	1.38	9	1	2/8	
	7.5	1.72	14	6	4/8	
	9	2.07	18	10	3/8	
	10.5	2.41	19	11	3/8	
	12	2.76	14	5	3/9	
	15	3.44	15	7	4/8	
	18	4.14	20	16	2/4[e]	
S-(+)-**2a**	0.75	0.17	9	1	2/8	
	1.5	0.34	8	0	2/8	
	3	0.69	9	1	4/8	
	6	1.38	14	6	4/8	
	7.5	1.72	30	22	4/8	
	8	1.83	5	5	0/0[e]	
(+/−)-**1b**	1.5	0.34	8	0	0/8	
	3	0.69	10	2	0/8	
	6	1.38	11	3	3/8	
	8	1.84	19	15	2/4[e]	
R-(−)-**1b**	0.75	0.17	8	0	2/8	
	1.5	0.34	9	1	2/8	
	3	0.69	10	2	0/8	
	6	1.38	11	3	1/8	
	7.5	1.72	16	7	2/9	
	9	2.07	17	7	3/10	
	10.5	2.41	11	3	3/8	
	12	2.76	13	5	4/8	
	15	3.45	15	7	3/8	
	18	4.14	13	5	2/8	
	24	5.52	17	15	1/2[e]	
S-(+)-**1b**	0.75	0.17	8	0	1/8	6.00 μM/kg
	1.5	0.34	8	0	1/8	(1.99–18.09)
	3	0.69	8	0	1/8	
	6	1.38	10	2	3/8	1.38 mg/kg
	7.5	1.72	13	5	2/8	(0.46–4.16)
	9	2.07	18	10	3/8	
	10.5	2.41	13	5	8/8	
(+/−)-**2b**	1.5	0.37	12	4	0/8	
	3	0.73	10	2	0/8	
	6	1.46	16	8	1/8	
	8	1.95	17	10	1/7	
	9	2.07	5	5	0/0[e]	
R-(−)-**2b**	0.75	0.17	8	0	3/8	
	1.5	0.37	8	0	1/8	
	3	0.73	8	0	1/8	
	6	1.46	9	1	1/8	
	7.5	1.83	10	2	1/8	
	9	2.19	14	6	2/8	

Table I (Continued)

compd	dose μM/kg	dose mg/kg	N^a	D^b	result[c]	ED_{50}[d]
	10.5	2.56	16	8	2/8	
	12	2.92	14	6	3/8	
	15	3.65	7	6	0/1[e]	
S-(+)-**2b**	0.75	0.17	8	0	0/8	
	1.5	0.37	9	1	1/8	
	3	0.73	8	0	2/8	
	6	1.46	8	0	0/8	
	7.5	1.83	15	7	2/8	
	9	2.19	26	16	4/10	
	10.5	2.56	11	7	2/4	
	12	2.92	6	6	0/0[e]	

[a] N = total number of rats tested. [b] D = number of disruptions (50 presses not completed in 5 min). [c] Number of rats selecting the LSD lever/number of rats responding. [d] Listed in μM/kg and mg/kg with 95% CI in parentheses. [e] Highest dose tested due to number of disruptions.

Entactogens, thus, are not simply variants of the hallucinogenic class of compounds, but demand a unique position as a new and novel category of psychoactive agent. Based on these results, it is our opinion that the entactogens may be valuable agents in facilitating psychotherapy.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian FT-80 spectrometer. Chemical shifts are reported in δ values (parts per million) relative to an internal reference of Me_4Si in $CDCl_3$. Abbreviations used in NMR analysis include the following: bs, broad singlet, d, doublet, dd, doublet of doublets, hex, hextet, m, multiplet, p, pentet, q, quartet, s, singlet, t, triplet, and AMBA, α-methylbenzylamine. Only one NMR analysis is reported for each pair of enantiomers, as the spectra of optical antipodes were virtually identical. Mass spectral analysis was performed on a Finegan 2000 spectrometer. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. Microanalysis was performed at the Purdue Microanalysis Laboratory, and all values were within 0.4% of the calculated composition.

Chemistry. 1-(1,3-Benzodioxol-5-yl)butan-1-ol (4). To 14 g (0.56 mol) of Mg turnings in 50 mL of dry ether was added, dropwise, 52 g (0.42 mol) of 1-bromopropane over 20 min. After complete addition, the reaction was stirred for 10 min and then a solution of 50 g (0.33 mol) of piperonal in 200 mL of dry ether was added dropwise over 30 min. The reaction was heated at reflux for 8 h and then was cooled and quenched by dropwise addition of 75 mL of cold, saturated ammonium chloride solution, while being stirred vigorously and cooled externally with an ice bath. The mixture was then vacuum filtered, and the filtrate was washed with 200 mL (3×) of cold 1.5 N HCl solution. The ether layer was then dried ($MgSO_4$), filtered, and concentrated by rotary vacuum evaporation to yield 62.2 g (96.3%) of crude alcohol. A small sample was purified by vacuum distillation for analysis: bp 98 °C (0.07 mmHg); ^1H NMR ($CDCl_3$) δ 6.75–6.84 (m, 3, Ar H), 5.92 (s, 2, OCH_2O), 4.48–4.64 (m, 1, CH), 2.39 (bs, 1, OH, D_2O exch), 1.59–1.75 (m, 2, β-CH_2), 1.12–1.39 (m, 2, α-CH_2), 0.90 (t, 3, CH_3). Anal. ($C_{11}H_{14}O_3$) C, H.

1-(1,3-Benzodioxol-5-yl)butene (5). A catalytic amount (ca. 50 mg) of $KHSO_4$ was added to 20 g (0.1 mol) of alcohol 4 in the flask of a vacuum distillation apparatus. The flask was gradually heated in an oil bath, under 0.05 mmHg vacuum, and the olefin was distilled at 82 °C to yield 16.5 g (91%) of colorless oil: ^1H NMR ($CDCl_3$) δ 6.88–6.72 (m, 3, ArH), 6.22 (s, 1, =CH), 6.14–6.07 (m, 1, =CH), 5.91 (s, 2, OCH_2O), 2.27–2.11 (m, 2, CH_2), 1.06 (t, 3, CH_3). Anal. ($C_{11}H_{12}O_2$) C, H.

1-(1,3-Benzodioxol-5-yl)butan-2-one (6). Hydrogen peroxide (30%, 27 mL) was added dropwise to 120 mL of 88% formic acid in a 500-mL round-bottom flask fitted with a thermometer. To this was added, over 15 min, with stirring, a solution of 25.5 g (0.145 mol) of the olefin **5** dissolved in 90 mL of acetone. The reaction was cooled externally with an ice bath to maintain the temperature below 40 °C. After addition, the mixture was stirred at ambient temperature for 10 h. The reaction was then concentrated by rotary vacuum evaporation, keeping the heating bath below 40 °C. The residue was then dissolved in 150 mL of toluene and was washed with 150 mL (2×) of H_2O and 150 mL (2×) of 5% $NaHCO_3$. The washed toluene solution was then concentrated by rotary evaporation. The residue was dissolved in 45 mL of MeOH, and then 250 mL of 15% H_2SO_4 was added. This mixture was heated at reflux for 2 h and was then cooled and extracted with 150 mL (2×) of ether. The ether extract was washed with 200 mL (2×) of H_2O, 225 mL (2×) of 5% NaOH, and 200 mL (2×) of saturated NaCl solution. This ether solution was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to afford the crude ketone, which was vacuum distilled to yield 16.55 g (41.5%) of **6** as a colorless oil: bp 98 °C (0.11 mmHg); ^1H NMR ($CDCl_3$) δ 6.76–6.68 (m, 3, ArH), 5.93 (s, 2, OCH_2O), 3.58 (s, 2, CH_2), 2.46 (q, 2, CH_2), 1.02 (t, 3, CH_3). Anal. ($C_{11}H_{12}O_3$) C, H.

(±)-1-(1,3-Benzodioxol-5-yl)-2-butanamine Hydrochloride (1b·HCl). A solution of 4.6 g (23.9 mmol) of ketone **6**, 20.0 g (250 mmol) of ammonium acetate, and 1.57 g (25 mmol) of $NaBH_3CN$ was stirred in 50 mL of MeOH at room temperature, under a nitrogen atmosphere, for 24 h. The solvent was removed in vacuo, 50 mL of CH_2Cl_2 added, and the mixture extracted with 3 N HCl (3 × 75 mL). The combined aqueous extract was basified with excess NaOH, the liberated free base extracted into CH_2Cl_2 (3 × 75 mL), and the combined organic extract dried (Na_2SO_4). The extract was filtered, the solvent removed in vacuo, and the residual oil dissolved in 50 mL of absolute EtOH. The ethanolic solution was acidified with concentrated HCl, diluted with Et_2O, and cooled to yield 4.29 g (78.2%) of white crystalline **1b**·HCl mp 159–161 °C; ^1H NMR (Me_2SO-d_6) δ 8.06 (bs, 3, NH_3, D_2O exch), 6.76 (m, 3, ArH), 5.97 (s, 2, OCH_2O), 3.19 (p, 1, α-CH), 2.83 (dd, 2, β-CH_2), 0.95 (t, 3, α-CH_3, J = 7.2 Hz). Anal. ($C_{11}H_{16}NO_2Cl$) C, H, N.

(±)-*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine Hydrochloride (2b·HCl). Commercial aluminum foil (5.07 g, 0.188 mol) was cut into 1-in. squares and placed into a 500-mL Erlenmeyer flask. A solution of 0.127 g (4.6 mmol) of $HgCl_2$ in 177 mL of H_2O was added, and the mixture was swirled occasionally for 30 min to amalgamate the aluminum. The solution was decanted, and the amalgamated foil was washed with 200 mL (4×) of H_2O. To the amalgam was then added, in sequence, 7.6 g (0.133 mol) of methylammonium chloride in 7.6 mL of H_2O, 22.8 mL of *i*-PrOH, 18.3 mL of 25% NaOH solution, 6.72 g of ketone **6**, and then 44.4 mL of *i*-PrOH. The mixture was swirled occasionally for 2 h, with external ice bath cooling as necessary to keep the temperature below 50 °C. The heterogeneous reaction mixture was then filtered through Celite, and the filter cake was washed thoroughly with MeOH. The combined filtrates were concentrated by rotary evaporation. The residue was dissolved in 100 mL of ether, and the amine was extracted into 50 mL (2×) of 3 N HCl. The acid solution was back-washed with 100 mL (3×) of CH_2Cl_2. The acidic layer was then basified with excess 25% NaOH, and the liberated base was extracted into 50 mL (3×) of CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude base was then purified by distillation (bp 88 °C, 0.08 mmHg), dissolved in *i*-PrOH, acidified with an equivalent of concentrated HCl, and cooled. The product was obtained as colorless crystals: 6.07 g (71%); mp 156 °C; ^1H NMR ($CDCl_3$) δ 9.25 (bs, 1, NH, D_2O exch), 6.73 (s, 3, ArH), 5.94 (s, 2, OCH_2O), 3.18 (1, m, CH), 2.82 (2, m, CH_2), 2.64 (s, 3, NCH_3), 1.77 (m, 2, CH_2), 1.08 (t, 3, CH_3, J = 7.35 Hz). Anal. ($C_{12}H_{18}N$-

O_2Cl) C, H, N.

(*R*,*R*)-(+)-*N*-1-Phenethyl-1-(1,3-benzodioxol-5-yl)-2-propanamine Hydrochloride (*R*,*R*-7a·HCl). A mixture of 20.0 g (112 mmol) of 3,4-(methylenedioxy)phenylacetone and 14.28 g (118 mmol) of (*R*)-(+)-α-phenethylamine was heated to reflux in 100 mL of benzene under a nitrogen atmosphere for 7 h, with continuous H_2O removal using a Dean-Stark trap. The benzene was removed in vacuo, and the residual oil was taken up into 50 mL of absolute ethanol and shaken for 24 h over 5 g of W-2 Raney nickel at 50 psig H_2. The catalyst was removed by filtration through Celite, and the filtrate was acidified with concentrated HCl. After solvent removal, the crude salt was recrystallized from acetone to yield 28.05 g (78.3%) of white crystalline *R,R*-7a·HCl: mp 170–172 °C; $[\alpha]_D$ +36.78° (*c* 2, H_2O); ^1H NMR ($CDCl_3$) δ 9.98 (bs, 2, NH_2, D_2O exch), 7.43 (m, 5, AMBA ArH), 6.69 (d, 1, ArH), 6.49 (dd, 2, ArH), 5.90 (s, 2, OCH_2O), 4.38 (q, 1, AMBA H, *J* = 6.9 Hz), 3.32 (m, 1, β-CH), 2.91 (m, 1, α-CH), 2.80 (m, 1, β-CH), 1.94 (d, 3, AMBA CH_3, *J* = 6.9 Hz), 1.40 (d, 3, α-CH_3, *J* = 5.8 Hz). Anal. ($C_{18}H_{22}NO_2Cl$) C, H, N.

(*S*,*S*)-(−)-*N*-1-Phenethyl-1-(1,3-benzodioxol-5-yl)-2-propanamine Hydrochloride (*S*,*S*-7a·HCl). An exact replication of the above procedure using (*S*)-(−)-α-phenethylamine gave 25.40 g (70.9%) of white crystalline *S,S*-7a·HCl: mp 171–173 °C; $[\alpha]_D$ −35.67° (*c* 2, H_2O); CIMS (free base), *m/e* 284 (M + 1). Anal. ($C_{18}H_{18}NO_2Cl$) C, H, N.

(*R*)-(−)-1-(1,3-Benzodioxol-5-yl)-2-propanamine Hydrochloride (*R*-1a·HCl). A solution of 28.05 g (87.7 mmol) of *R,R*-7a, dissolved in 130 mL of MeOH, was added to a slurry of 500 mg 10% Pd–C in 10 mL of H_2O in a 500-mL Parr bottle. This mixture was shaken at 50 psig H_2 for 48 h. The catalyst was removed by filtration through Celite; the solvent was removed in vacuo, and the crude salt was recrystallized from EtOH/Et_2O to yield 17.76 g (93.9%) of white crystalline *R*-1a·HCl: mp 200–202 °C; $[\alpha]_D$ −25.70° (*c* 2, H_2O); CIMS (free base), *m/e* 180 (M + 1); ^1H NMR (Me_2SO-d_6) δ 8.21 (bs, 3, NH_3, D_2O exch), 6.78 (m, 3, ArH), 5.97 (s, 2, OCH_2O), 3.28 (m, 1, α-CH), 2.96 (dd, 1, β-CH), 2.63 (dd, 1, β-CH), 1.16 (d, 3, α-CH_3, *J* = 6.3 Hz). Anal. ($C_{10}H_{14}NO_2Cl$) C, H, N.

(*S*)-(+)-1-(1,3-Benzodioxol-5-yl)-2-propanamine Hydrochloride (*S*-1a·HCl). An exact replication of the above procedure using 25.40 g (79.4 mmol) of *S,S*-7a gave 15.89 g (92.8%) of white crystalline *S*-1a·HCl: mp 200–202 °C; $[\alpha]_D$ +26.52° (*c* 2, H_2O). Anal. ($C_{10}H_{14}NO_2Cl$) C, H, N.

(*R*)-(+)-*N*-Formyl-1-(1,3-benzodioxol-5-yl)-2-propanamine (*R*-8a). A solution of 8.63 g (40 mmol) of *R*-1a dissolved in H_2O was neutralized to the free base with excess NaOH. The free base was extracted into ether; the ether solution was dried (Na_2SO_4) and filtered, and the ether was removed by rotary evaporation to give the free base as a pale-yellow oil. The oil was taken up in 100 mL of methyl formate, placed into a 250-mL high-pressure "Parr bomb", and heated on a steam bath overnight. The bomb was cooled, the reaction mixture reduced in volume in vacuo, and the product spontaneously crystallized to give 7.72 g (92.7%) of white crystalline *R*-8a: mp 100–102 °C; $[\alpha]_D$ +12.34° (*c* 1, EtOH); EIMS, *m/e* 207 (M); *m/e* 208 (M + 1); ^1H NMR ($CDCl_3$) δ 8.09 (bs, 1, CHO), 6.67 (m, 3, ArH), 5.93 (s, 2, OCH_2O), 5.34 (bs, 1, NH), 4.29 (hex, 1, α-CH), 2.70 (dd, 2, β-CH_2), 1.15 (d, 3, α-CH_3, *J* = 6.6 Hz). Anal. ($C_{11}H_{13}NO_3$) C, H, N.

(*S*)-(−)-*N*-Formyl-1-(1,3-benzodioxol-5-yl)-2-propanamine (*S*-8a). An exact replication of the above procedure using *S*-1a gave 7.56 g (92.3%) of white crystalline *S*-8a: mp 100–101 °C; $[\alpha]_D$ −12.22° (c 1, EtOH); EIMS, *m/e* 207 (M); CIMS, *m/e* 208 (M + 1). Anal. ($C_{11}H_{13}NO_3$) C, H, N.

(*R*)-(−)-*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-propanamine Hydrochloride (*R*-2a·HCl). A solution of 7.72 g (37.3 mmol) of *R*-8a dissolved in 50 mL of dry Et_2O was added dropwise to a stirring suspension of 5.67 g (149.2 mmol) LAH in 100 mL of dry Et_2O. After complete addition, the mixture was allowed to reflux for 4 h on a steam bath. The excess LAH was then decomposed with H_2O, and the mixture was filtered through Celite. The ethereal filtrate was extracted with 3 N HCl (3 × 50 mL). The combined aqueous extract was basified with excess NaOH; the free base was extracted into CH_2Cl_2 (3 × 50 mL), and the combined organic extract was dried (Na_2SO_4). The extract was filtered, the solvent removed in vacuo, and the residual oil dissolved in 100 mL of absolute ethanol. The ethanolic solution was acidified with concentrated HCl, diluted with Et_2O, and cooled to yield 7.94 g (92.7%) of white crystalline *R*-2a·HCl: mp 192–193 °C; $[\alpha]_D$ −17.54° (*c* 1, H_2O); CIMS (free base), *m/e* 194 (M + 1); ^1H NMR ($CDCl_3$) δ 9.15 (bs, 2, NH_2, D_2O exch), 6.70 (s, 3, ArH), 5.93 (s, 2, OCH_2O), 3.39 (m, 1, β-CH), 3.24 (m, 1, α-CH), 2.82 (m, 1, β-CH), 2.70 (s, 3, NCH_3), 1.34 (d, 3, α-CH_3, *J* = 6.5 Hz). Anal. ($C_{11}H_{16}NO_2Cl$) C, H, N.

(*S*)-(+)-*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-propanamine Hydrochloride (*S*-2a·HCl). An exact replication of the above procedure using 7.65 g (36.9 mmol) of *S*-8a gave 7.70 g (90.8%) of white crystalline *S*-2a·HCl mp 192–193 °C; $[\alpha]_D$ +17.43° (*c* 1, H_2O). Anal. ($C_{11}H_{16}NO_2Cl$) C, H, N.

(*R*,*R*)-(+)-*N*-1-Phenethyl-1-(1,3-benzodioxol-5-yl)-2-butanamine Hydrochloride (*R*,*R*-7b·HCl). A solution of 10.0 g (52 mmol) of 1-(3,4-(methylenedioxy)phenyl)-2-butanone (**6**) and 6.6 g (54 mmol) of (*R*)-(+)-α-phenethylamine was heated to reflux in 50 mL of benzene and treated exactly as in the synthesis of *R,R*-7a, to yield 12.36 g (71.2%) of white crystalline *R,R*-7b·HCl: mp 218–220 °C; $[\alpha]_D$ +38.09° (*c* 2, H_2O); CIMS (free base), *m/e* 298 (M + 1); ^1H NMR ($CDCl_3$) δ 9.53 (bs, 2, NH_2, D_2O exch), 7.44 (m, 5, AMBA ArH), 6.74 (s, 2, ArH), 6.62 (s, 1, ArH), 5.95 (s, 2, OCH_2O), 4.07 (q, 1, AMBA H, *J* = 6.7 Hz), 3.32 (p, 1, α-CH), 2.91 (dd, 2, β-CH_2), 1.92 (d, 3, AMBA CH_3, *J* = 6.7 Hz), 1.82 (m, 2, α-CH_2), 0.95 (t, 3, α-CH_3, *J* = 7.4 Hz). Anal. ($C_{19}H_{24}NO_2Cl$) C, H, N.

(*S*,*S*)-(−)-*N*-1-Phenethyl-1-(1,3-benzodioxol-5-yl)-2-butanamine Hydrochloride (*S*,*S*-7b·HCl). An exact replication of the above procedure using (*S*)-(−)-α-phenethylamine gave 12.03 g (69.3%) of white crystalline *S,S*-7b·HCl: mp 218–222 °C; $[\alpha]_D$ −37.86° (c 2, H_2O). Anal. ($C_{19}H_{24}NO_2Cl$) C, H, N.

(*R*)-(−)-1-(1,3-Benzodioxol-5-yl)-2-butanamine Hydrochloride (*R*-1b·HCl). A 12.36-g (37 mmol) sample of *R,R*-7b was treated exactly as described for the synthesis of *R*-1a to yield 8.03 g (94.5%) of white crystalline *R*-1b·HCl: mp 178–180 °C; $[\alpha]_D$ −34.34° (*c* 2, H_2O); CIMS (free base), *m/e* 194 (M + 1); ^1H NMR (Me_2SO-d_6) δ 8.16 (bs, 3, NH_3, D_2O exch), 6.77 (m, 3, ArH), 5.98 (s, 2, OCH_2O), 3.18 (p, 1, α-CH), 2.82 (dd, 2, β-CH_2), 1.51 (m, 2, α-CH_2), 0.92 (t, 3, α-CH_3, *J* = 7.3 Hz). Anal. ($C_{11}H_{16}NO_2Cl$) C, H, N.

(*S*)-(+)-1-(1,3-Benzodioxol-5-yl)-2-butanamine Hydrochloride (*S*-1b·HCl). A similar procedure using 12.03 g (36 mmol) of *S,S*-7b gave 7.60 g (91.9%) of white crystalline *S*-1b·HCl: mp 178–180 °C; $[\alpha]_D$ +34.67° (c 2, H_2O). Anal. ($C_{11}H_{16}NO_2Cl$) C, H, N.

(*R*)-(+)-*N*-Formyl-1-(1,3-benzodioxol-5-yl)2-butanamine (*R*-8b). A sample of 4.59 g (20 mmol) of *R*-1b was treated exactly as in the procedure for the synthesis of *R*-8a to give 3.96 g (89.7%) of white crystalline *R*-8b: mp 65–66 °C; $[\alpha]_D$ +7.60° (*c* 1, EtOH); EIMS, *m/e* 221 (M); CIMS, *m/e* 222 (M + 1); ^1H NMR ($CDCl_3$) δ 8.15 (bs, 1, CHO), 6.69 (m, 3, ArH), 5.92 (s, 2, OCH_2O), 5.39 (bs, 1, NH), 4.16 (p, 1, α-CH), 2.71 (d, 2, β-CH_2), 1.48 (m, 2, α-CH_2), 0.92 (t, 3, α-CH_3, *J* = 7.2 Hz). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

(*S*)-(−)-*N*-Formyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (*S*-8b). An exact replication of the above procedure using *S*-1b gave 3.99 g (90.2%) of white crystalline *S*-8b: mp 64–65 °C; $[\alpha]_D$ −7.28° (*c* 1, EtOH); EIMS, *m/e* 221 (M); *m/e* CIMS, 222 (M + 1). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

(*R*)-(−)-*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine Hydrochloride (*R*-2b·HCl). In a replication of the procedure used for *R*-2a, 3.96 g (17.9 mmol) of *R*-8b and 2.74 g (72 mmol) of LAH gave 3.42 g (78.2%) of white crystalline *R*-2b·HCl: mp 192–193 °C; $[\alpha]_D$ −26.40° (c 1, H_2O); CIMS (free base), *m/e* 208 (M + 1); ^1H NMR ($CDCl_3$) δ 9.30 (bs, 2, NH_2, D_2O exch), 6.73 (s, 3, ArH), 5.94 (s, 2, OCH_2O), 3.25 (m, 1, β-CH), 3.13 (m, 1, α-CH), 2.91 (m, 1, β-CH), 2.64 (s, 3, NCH_3), 1.77 (m, 2, α-CH_2), 1.08 (t, 3, α-CH_3, *J* = 7.3 Hz). Anal. ($C_{12}H_{18}NO_2Cl$) C, H, N.

(*S*)-(+)-*N*-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine Hydrochloride (*S*-2b·HCl). A 3.99-g (18 mmol) sample of *S*-8b was used in a similar procedure to give 3.35 g (76.3%) of white crystalline *S*-2b·HCl: mp 192–193 °C; $[\alpha]_D$ +25.89° (*c* 1, H_2O). Anal. ($C_{12}H_{18}NO_2Cl$) C, H, N.

Analysis of Enantiomeric Purity of 2a and 2b Isomers. An aqueous solution containing 0.1–1.0 mg of the amine hydrochloride salt in 1 mL of H_2O was made basic with NaOH and extracted with 2 mL of CH_2Cl_2, and the organic extract was treated with 0.5 mL of a 0.1 M solution of (−)-camphanic acid chloride

in CH_2Cl_2. Five drops of triethylamine were added, with brief vortex mixing, and the solution was evaporated to dryness with nitrogen. Then, 1 mL of toluene and 1 mL of a saturated aqueous sodium borate solution were added, and the mixture was vortexed and centrifuged. The toluene layer was separated and washed with 1 mL of 0.5 N HCl. A 1-μL aliquot of the toluene extract was injected into the gas chromatograph. GC analysis was performed with a Hewlett-Packard 5880A gas chromatograph with a split–splitless capillary inlet system, N–P detector, and a Level IV computing integrator. All injections were done in split mode with a 10:1 split ratio. The chromatography column was a 0.32 mm × 20 m fused silica capillary column cross-linked with 5% phenylmethylsilicone of 0.52 μm phase thickness. The temperature in all runs was programmed from 90 to 310 °C at 25 °C/min, after a 0.5-min initial holding period. Racemic mixtures of **2a** and **2b** were first subjected to this procedure, and their camphanylamide derivatives were injected into the GC, resulting in nearly base-line resolution of the optical isomers. The derivatized amides of *R*-**2a**, *S*-**2a**, *R*-**2b**, and *S*-**2b** had retention times of 11.60, 11.66, 11.94, and 12.03 min, which corresponded directly to the peaks seen in the racemic mixture chromatograms. In runs of the pure enantiomers only one peak was detectable by integration, indicating greater than 98–99% enantiomeric excess of the optical isomers.

Pharmacology. Animals. Male, Sprague–Dawley rats, weighing approximately 200 g at the beginning of the study, were obtained from Murphy Breeding Labs, Inc., Plainfield, IN. For the first week, all rats were group housed (8/cage) with food and water available ad lib. Following the initial acclimatization period, the rats were housed individually in a temperature-controlled room (25 °C) with an 0600–2000 lights on, 2000–0600 lights off schedule.

Immediately following scheduled discrimination sessions the animals were returned to their home cages and allowed to feed freely on rat chow (Lab Blox) for 30 min. This schedule has been reported[23] to maintain the rat at about 80% of free-feeding weight. On Sundays, no sessions were run and the animals were allowed to feed at their regularly scheduled time. Water was available continuously, except during the training and testing periods. The sample of animals participating in any given experiment was selected from the pool of trained rats available during the 5-month period taken to conduct this study.

Apparatus. Five identical standard operant chambers (Coulbourn Instruments) equipped with two response levers separated by a food pellet delivery system were employed. Food pellets (Bioserve, 45 mg dustless) were used as reinforcement. Chambers contained a white house light and masking white noise and were enclosed in ventilated, sound-attenuated cubicles. The operant chambers were controlled by solid-state logic interfaced through a Coulbourn Instruments Dynaport to an IBM-PC located in an adjacent control room. Data acquisition and control were handled by the IBM-PC using software developed in this laboratory.

Drug Administration. The training dose of *d*-LSD tartrate (NIDA) (185.5 nM/kg, 0.08 mg/kg) or appropriate test drug doses were administered in saline in a volume of 1.0 mL/kg of body weight. All test compounds except LSD were administered as hydrochloride salts, and the mg/kg and μM/kg values reflect the dose based on the weight of the salt. All injections were administered intraperitoneally 30 min before the start of discrimination sessions.

Discrimination Training. To avoid positional preference, half of the animals were trained to press LSD-L and SAL-R, while the other half were trained vice versa. Rats were trained on an FR50 schedule with 15-min maintenance sessions. The average response rate was found to be 110 ± 10 responses/min (mean ± SE) for all animals (n = 32). No significant difference in responding rate was seen between the training dose of LSD and saline ($p > 0.05$, grouped Students t test). The complete training procedure has been published in a previous article.[14]

Stimulus Generalization. Those rats that had successfully acquired 85% correct responding on the appropriate lever during the 6-week training period were included in the stimulus generalization testing procedure. Testing sessions were run on Wednesdays and Saturdays only. Training sessions were held the rest of the week with Sundays off. On test days, the animal was placed into the operant chamber 30 min after injection. Test sessions lasted until the rat emitted 50 responses on either lever or until 5 min had passed, whichever came first. If the rat did not emit 50 responses on either lever within 5 min he was scored as disrupted and was not included in the calculations. In either case no reinforcement was given. In order to receive a test drug, the animals were required to satisfy the 85% correct lever response criterion on each of the two preceding training sessions. Also, following the procedure of Colpaert et al.,[24] test data were discarded and the test condition later retested if the test session was followed by failure to meet the 85% criterion in either of the two subsequent training sessions. This procedure was employed to increase the reliability of the individual test data. It has been reported[24] that incorrect lever selections in trained rats typically occur in bursts of 1–3 sessions. This correction procedure assists in avoiding the contamination of test data that may occur during such bursts. If the animal was not included in the testing procedure on a given day, the session was used for training.

Several preliminary experiments to determine appropriate dosages for new compounds were carried out; these data were discarded. Dosages for each of the test compounds were based on these initial experiments. The drug treatments in this study, including LSD and saline, were randomized over the entire experimental period. Eight animals were tested at each dose, except in the cases where very high doses produced an excessive number of disruptions.

Data Analysis. Animals were scored as drug positive if they selected the LSD-appropriate lever (i.e., if they emitted 50 responses on the drug lever). If generalization occurred (greater than 80% of the rats selecting the LSD-appropriate lever), these quantal data were analyzed by the method of Litchfield and Wilcoxon[25] to determine an ED_{50}.

Human Psychopharmacology Studies. New compounds were evaluated following methods recently described in detail.[15] Fourteen subjects, of both sexes, ranging in age from 35 to 60, participated in the study. The number of experiments per subject was 2–4. Females were all past childbearing age. All subjects had experience with a wide variety of psychoactive materials and had participated in similar studies for up to 20 years. Subjects had a clear knowledge of the risks involved. The experimental protocol employed in this study has been approved by an appropriate human research committee made up of board-certified psychiatrists and included statements of informed consent from all subjects.

Drugs were administered as the hydrochloride salts, dissolved in water or fruit juice. The setting for the studies was informal, and the subjects were allowed to interact with one another or to remain alone, as they desired. At the conclusion of each session, written reports detailing the qualitative nature of the experience were requested. Because of the nature of the effects of these novel compounds, the usual quantitative rating scale employed for assessment of *hallucinogenic* potency was not applicable. Thus, the description of qualitative effects, and consensus opinion that these materials represent a new class of drug, is based on these written reports and subjective evaluations and comparisons based on the extensive past experience of the evaluation panel with other psychotropic substances. It was not possible to carry out double-blind crossover experiments with MDMA, since the latter had been temporarily placed in Schedule I of the Controlled Substance Act.

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