91849-00-2; **37**, 96428-33-0; **38**, 96428-34-1; **39**, 96428-35-2; **40**, 79707-47-4; **41**, 91848-84-9; **41**·HCl, 96428-36-3; **42**, 85332-97-4; **43**, 85332-64-5; **44**, 85332-96-3; **45**, 91849-03-5; **46**, 96428-37-4; **47**, 96428-38-5; **48**, 96428-39-6; **49**, 96428-40-9; **50**, 79707-49-6; **51**, 79707-47-4; **52**, 96428-41-0; **53**, 96428-42-1; **54**, 96428-43-2; **55**, 79707-18-9; **56**, 96444-48-3; **57**, 79707-13-4; **58**, 96428-44-3; **59**, 79707-35-0; **60**, 79707-36-1; **61**, 79707-37-2; **62**, 79707-41-8; **63**, 79707-40-7; **64**, 79707-42-9; **65**, 96428-45-4; **66**, 85333-39-7; **67**, 96428-46-5; **68**, 96428-47-6; **69**, 96428-48-7; **70**, 96428-49-8; **71**, 96428-50-1; **72**, 96428-51-2; **73**, 96444-49-4; **74**, 96428-52-3; **75**, 96428-53-4; **76**, 79707-61-2; **77**, 96428-85-2; **77**·HCl, 96428-54-5; **78**, 96428-55-6; **79**, 85333-37-5; **80**, 79707-34-9; **81**, 96428-86-3; **81**·1/2HCl, 96428-56-7; **82**, 96428-57-8; **83**, 96444-50-7; **84**, 96444-51-8; **85**, 96428-58-9; **86**, 96428-59-0; **87**, 96428-87-4; **87**·HCl, 96428-60-3; **88**, 96428-61-4; **89**, 96428-62-5; **90**, 79707-32-7; **91**, 79707-50-9; **92**, 96428-63-6; **93**, 96428-64-7; **94**, 79707-57-6; **95**, 96444-52-9; **96**, 96428-65-8; **97**, 96428-88-5; **97**·HCl, 96428-66-9; **98**, 96428-67-0; **99**, 96428-68-1; **100**, 96428-69-2; **101**, 96428-70-5; **102**, 96428-71-6; **103**, 79707-33-8; **104**, 96428-89-6; **104**-HBr, 96428-72-7; **105**, 96428-73-8; **106**, 96428-74-9; **107**, 96428-75-0; **108**, 96428-76-1; **109**, 96428-77-2; **110**, 96428-78-3; **111**, 96428-79-4; 4-(methylsulfonyl) benzyl bromide, 53606-06-7; 3-picolyl chloride hydrochloride, 39901-94-5; 4-picolyl chloride hydrochloride, 1822-51-1; 3-(2-phenylethenyl)pyridine, 2633-06-9; 3-(2-phenylethyl)pyridine, 6312-09-0; 4-(2-phenylethyl)pyridine, 2116-64-5; 2-(2-phenylethyl)pyridine, 2116-62-3; 2,3-diaminopyridine, 452-58-4; benzaldehyde, 100-52-7; 4-oxopentanenitrile, 927-56-0; *p*-fluorobenzyl chloride, 352-11-4; 4-(trifluoromethyl)benzyl chloride, 939-99-1; 4-cyanobenzyl chloride, 874-86-2; 4-methoxybenzyl chloride, 824-94-2; 2,4,6-trimethoxybenzyl chloride, 96428-90-9; methyl iodide, 74-88-4; sodium cyanide, 143-33-9; thienyl bromide, 872-31-1; 3-furanyl bromide, 22037-28-1; α-naphthyl bromide, 90-11-9; 2-methyl-8-phenoxyimidazo[1,2-*a*]pyridine, 96428-91-0; 8-(chloromethyl)-2,3-dimethylimidazo[1,2-*a*]pyridine, 96428-92-1; phenol, 108-95-2; thiophenol, 108-98-5; *tert*-butyl cyanoacetate, 1116-98-9; tosylmethyl isocyanide, 36635-61-7; 3-(aminomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, 96428-93-2; ethyl formate, 109-94-4; 3-[(formylamino)methyl]-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, 85333-38-6; dimethylamine hydrochloride, 506-59-2; paraformaldehyde, 30525-89-4; sodium methoxide, 124-41-4; sodium ethoxide, 141-52-6; sodium methylmercaptide, 5188-07-8; ethylenediamine *p*-toluenesulfonate, 14034-59-4.

Supplementary Material Available: Tables of fractional atomic coordinates and thermal parameters (Tables V–VII), bond lengths and angles (Table VIII), torsion angles (Table IX), and least-squares planes (Table X) and unit cell dimensions for **27** (8 pages). Ordering information is given on any current masthead page.

Psychotomimetic *N*-Methyl-*N*-isopropyltryptamines. Effects of Variation of Aromatic Oxygen Substituents

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Eight *N*-methyl-*N*-isopropyltryptamines (MIPTs) possessing various aromatic oxygen substituents were prepared, characterized, and evaluated for hallucinogenic activity in man. In at least two instances (the Ar H and the Ar 5-OCH_3, **1** and **4**) the unsymmetrical nitrogen substitution led to a substantial increase in potency as well as oral activity when compared to the symmetrical dimethyl homologues. Qualitatively, 4-hydroxy-*N*-methyl-*N*-isopropyltryptamine (**2**) was the most interesting in overall effect, producing a classic hallucinogenic profile. The 5-methoxy congener **4** resulted in a state characterized by heightened conceptual stimulation lacking in visual phenomena. Other members of the series exhibited diminished effects.

Over the past two decades, considerable synthetic and pharmacological effort has been expended in studies directed to the "fine-tuning" of hallucinogenic phenethylamines and tryptamines. The basic goal of this research has been to gain a better understanding of the human structure–activity relationships of these substances. This has been accomplished in some measure by producing a succession of subtle molecular changes in a parent compound such as psilocin,[1-3] *N*,*N*-dimethyltryptamine,[4-6] or mescaline.[7-9] With the phenethylamines the principle modality of variation has been the substitution pattern of the aromatic ring.[8-11] Within the tryptamine family, however, the major chemical alterations have involved changes in the amine alkyl substituents. This has been partly due to the relative ease of synthetic manipulation at this site and also because substantial biological differences can be attributed to even minor changes in these substituents. For example, DMT and 5-methoxy-DMT are active only when administered parenterally. However, lengthening and/or branching of the *N*-alkyl groups of these molecules produces orally active compounds.[4,5,7-12] Other human and animal studies with potential tryptamine hallucinogens have shown that an abrupt loss of activity occurs with *N*,*N*-di-*n*-butyl substitution,[13,14] apparently

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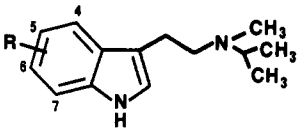
Table I. Human Quantitative Properties of Substituted MIPTs



compd	R	N^a	T^b	effective dose, mg (mg/kg)[c]	onset,[d] min	duration,[e] h
1	H	5	12	25 (0.33)	40–50	3.0–4.0
2	4-OH	4	11	10 (0.14)	20–35	6.0–7.0
3	4-OCH_3	4	10	30 (0.40)	45–60	2.0–2.5
4	5-OCH_3	5	12	5 (0.07)	9–16	3.0–3.2
5	6-OCH_3			*f*		
6	7-OCH_3			*f*		
7	5,6-$(OCH_3)_2$			*f*		
8	5,6-O–O			*f*		

[a] Number of subjects. [b] Number of trials. [c] Effective dose required for the elicitation of the complete psychotomimetic spectrum of the compound (see Experimental Section). [d] Time between ingestion and first noticeable symptoms. [e] Time after ingestion at which central effects begin to decline. In most cases residual insomnia and/or anorexia persisted for 8–15 h postdose. [f] Not effective at 50 mg.

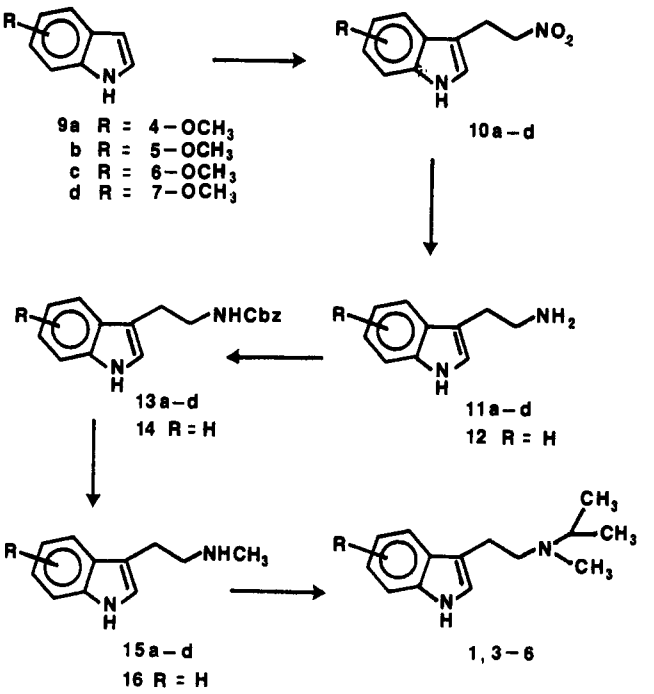
establishing a critical upper limit.

Aryl substitution of *N,N*-dialkyltryptamines can also profoundly alter both the quantitative and qualitative nature of the observed biological effects. With *N,N*-dimethyl substitution, psilocin (4-hydroxy-DMT) shows considerable hallucinogenic activity in man,[15] while its 5-hydroxy isomer (bufotenine) is devoid of such effects.[16] *O*-Methylation of bufotenine restores psychotomimetic activity,[5] but parenteral administration is required. The 6- and 7-methoxy-*N,N*-dimethyltryptamines have been reported to be less active in animal studies than the 4- and 5-methoxy isomers.[17-19]

The major metabolic pathway for dialkyltryptamines in the rat is via 6-hydroxylation. This finding led Szara and Hearst[13] to suggest that such compounds were responsible for the hallucinogenic effects of the parent tryptamines. However, 6-hydroxylation is only a minor metabolic route in man,[20] and other studies have led to a general concensus that 6-oxygenation reduces hallucinogenic potency.[21-24] A single report on 5,6,7-trimethoxy-*N,N*-dimethyltryptamine suggests that it might have "marked behavioral effects" in rats.[25]

Two reports support the concept that unsymmetrical alkyl substitution of tryptamine nitrogen might dramatically influence the central nervous system (CNS) effects of these compounds: In conditioned avoidance response studies with rats, Gessner et al.[26] found that the order of potency of a series of alkylated tryptamines was 5-methoxy-*N*-methyl-*N*-ethyl- > 5-methoxy-DMT ≥ 5-methoxy-*N,N*-diethyl-4-hydroxy-DMT > *N,N*-diethyl- = 4-methoxy-DMT = 5-acetoxy-DMT > 6-methoxy-DMT > 7-methoxy-DMT. Our preliminary data[11] indicated that 4-hydroxy-*N*-methyl-*N*-isopropyltryptamine was orally active in man and was at least as potent as psilocin. The rank order of potency observed in a series of *N,N*-dialkyl-4-hydroxytryptamines was methyl, isopropyl > methyl, ethyl > methyl, methyl > methyl, *n*-propyl > ethyl, ethyl > isopropyl, isopropyl > *n*-propyl, *n*-propyl > methyl, *tert*-butyl.[27] On the basis of these reports and on the above discussion, compounds 1–8 were prepared and evaluated for their psychotomimetic properties.

Scheme I



Chemistry. The syntheses of compounds 2 and 8 were previously described.[2,6] The 4-,[28] 5-,[29] 6-,[30] and 7-meth-

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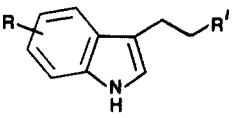
Table II. Physical Data



compd	R	R′	mp, °C	yield, %	formula	anal.[a]
1	H	—N(CH3)2	82–83	56	$C_{14}H_{20}N_2$	C, H, N
3	4-OCH_3	—N(CH3)2	80–81	27	$C_{15}H_{22}N_2O$	C, H, N
4	5-OCH_3	—N(CH3)2	162–163[b]	68	$C_{15}H_{23}N_2ClO$	C, H, N
5	6-OCH_3	—N(CH3)2	89–91	43	$C_{15}H_{22}N_2O$	C, H, N
6	7-OCH_3	—N(CH3)2	72–73	65	$C_{15}H_{22}N_2O$	C, H, N
7	5,6-OCH_3	—N(CH3)2	71–72	72	$C_{16}H_{24}N_2O_2$	C, H, N
10a	4-OCH_3	NO_2	93–94	95	$C_{11}H_{12}N_2O_3$	C, H, N
10b	5-OCH_3	NO_2	75–76	85	$C_{11}H_{12}N_2O_3$	C, H, N
10c	6-OCH_3	NO_2	102–103	27	$C_{11}H_{12}N_2O_3$	C, H, N
10d	7-OCH_3	NO_2	83–84	55	$C_{11}H_{12}N_2O_3$	C, H, N
13a	4-OCH_3	NHCbz[c]	84	60	$C_{19}H_{20}N_2O_3$	C, H, N
13b	5-OCH_3	NHCbz	oil	93	$C_{19}H_{20}N_2O_3$	C, H, N
13c	6-OCH_3	NHCbz	118–119	86	$C_{19}H_{20}N_2O_3$	C, H, N
13d	7-OCH_3	NHCbz	83	72	$C_{19}H_{20}N_2O_3$	C, H, N
14	H	NHCbz	84–86	85	$C_{18}H_{18}N_2O_2$	C, H, N

[a] ^1H NMR spectra were in agreement with assigned structures. [b] HCl salt. [c] Cbz = CO_2CH_2Ph.

oxyindoles[29] (**9a–d**) were prepared via the Leimgruber–Batcho method.[31,32] 5,6-Dimethoxyindole (**9e**) was made by the method of Huebner et al.[33] The tryptamines **1** and **3–6** were prepared as shown in Scheme I. Compound **7** was made as previously described for **8**.[6]

The methoxylated indoles were condensed with 2-nitroethyl acetate by using the general procedures described by Flaugh and colleagues[34] to provide the crystalline nitroethyl derivatives **10a–d**. Catalytic reduction then afforded the amines **11a–d**. Reaction of the amines with benzyl chloroformate followed by lithium aluminum hydride reduction provided **15a–d**. Reductive alkylation with acetone completed the sequence. Compound **1** was prepared from tryptamine **12** by using only the last three steps of Scheme I.

Results and Discussion

Certain conclusions can be drawn from the clinical findings involving the eight tryptamines shown in Table I. While DMT is active in man following parenteral administration of 50–100 mg,[5] the homologue **1** is some 4 times more potent and is active orally. Psilocin is orally active in the 10–15-mg[9] range and compound **2** is quantitatively similar. 5-Methoxy-DMT is again active parenterally in the range of 6–10 mg.[4] The 5-methoxy-*N*-methyl-*N*-isopropyl homologue **4** is somewhat more potent and maintains the oral activity of the other compounds of this study. Generally, the homologation of *N*,*N*-dimethyl to *N*-methyl-*N*-isopropyl increases the observed potency of hallucinogenic tryptamines and makes them orally active.

Holding the nitrogen substituent pattern constant as *N*-methyl-*N*-isopropyl, there is a remarkable influence seen in the quantitative potencies as a consequence of ring-substitution changes. The 5-methoxyl group (as in **4**) provides the most active tryptamine in this study. Effects are noticed with doses as low as 0.8 mg–1.5 mg (0.011–0.02 mg/kg) and the compound has an effective dose of 5 mg (0.067 mg/kg). In comparison, compounds that have a 4-hydroxyl (**2**) or no substituent at all (**1**) are somewhat reduced in potency. Moving the methoxyl to position C-6 or C-7 (**5** and **6**) greatly reduces or abolishes activity. The addition of a methoxyl to C-5 of the inactive 6-methoxy analogue (to provide the 5,6-dimethoxy compound **7**) results in no noticeable effect at the doses employed. Similar results were obtained from the 5,6-methylenedioxy isomer **8**.

Several qualitative differences can be noted when discussing these tryptamines. 4-Hydroxy-MIPT was the most interesting in terms of overall effect. Twenty minutes after ingestion a feeling of euphoria and a rapid heightening of all senses ensued, reaching a plateau in 40 min. Verbal communication was difficult and was accompanied by illusory alteration in the size of and distance to objects. The visual sphere was marked by multiple images of the same object which displayed intense colored halos. Sounds were intensified and the separation of sounds was often acute. These perceptual illusions were integrated with conceptual alterations. Flights of ideation occurred with fundamental philosophical overtones. Physiologically, a mild vertigo was felt which was not associated with nausea. Effects began to decline at 6 h with residual anorexia and insomnia lasting up to 12 h.

MIPT and 5-methoxy-MIPT, while similar to each other, differ from 4-hydroxy-MIPT. An extremely rapid onset of symptoms characterizes 5-methoxy-MIPT, including a general heightening of awareness accompanied

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by amphetamine-like central stimulation (as defined by Randrup and Munkvad[35] and Weiss and Laties[36]). As with MIPT, this material does not produce the intense visual phenomena associated with 4-hydroxy-MIPT.

Perhaps the most interesting compound is 4-methoxy-MIPT (3) because of its greatly diminished activity with respect to 4-hydroxy-MIPT (2). With the former, disturbances in the visual field, including color enhancement and object distortion, were very mild. Effects build gradually and then decline over a 2-h period with no noticeable plateau. Minor stimulation was not accompanied by anxiety. Uyeno[37,38] has demonstrated the decreased activity of 4-methoxy-DMT with respect to psilocybin in studies of the size-discrimination performance of monkeys and the swimming ability of rodents.

The results of this study establish narrow criteria for oxygenated tryptamine hallucinogens: (1) Unsymmetrical *N*-methyl-*N*-isopropyl substitution leads to greater (oral) activity when compared to symmetrical *N*-alkyl substitution. (2) A 5-methoxy group results in increased CNS-stimulant (amphetamine-like) effects at the expense of visual phenomena. (3) A 4-hydroxy group enhances general hallucinogenic profile while etherification of this group reduces activity. (4) Methoxy groups at C-6 or C-7 abolish the activity shown by ring-unsubstituted dialkyltryptamines. (5) Dioxygenation at C-5 and C-6 abolishes hallucinogenic activity when compared to the ring-unsubstituted analogue.

Experimental Section

Proton magnetic resonance spectra were recorded with either a Bruker WH 90 300-MHz NMR or a Varian EM 390 90-MHz NMR and are reported in ppm (δ) downfield from an internal standard of tetramethylsilane. All spectra were recorded in $CDCl_3$ unless otherwise noted. Elemental analyses were performed by the Analytical Laboratory of Syntex Corp. Melting points are uncorrected. Physical constants of known compounds matched literature values. Reactions were monitored by TLC on glass plates coated with 250-μm layers of silica gel GF. Details of the syntheses outlined in Scheme I are illustrated for compound **6**.

The authors are solely responsible for the contents of this manuscript.

β-Pyrrolidino-2-nitro-3-methoxystyrene. A solution of 5 g (30 mmol) of 2-nitro-3-methoxytoluene, 4.25 mL (32 mmol) of *N,N*-dimethylformamide dimethyl acetal, and 2.5 mL (30 mmol) of pyrrolidine in 50 mL of DMF was stirred and heated at 130 °C under a nitrogen atmosphere for 3 h. The solvent was removed under reduced pressure and 50 mL of *i*-PrOH was added to the residue. The resulting orange crystals were collected and dried in vacuo to leave 3.98 g, mp 114–115 °C (54%). Anal. ($C_{13}H_{16}N_2O_3$) C, H, N. ^{1}H NMR δ 1.91 (m, 4 H), 3.22 (m, 4 H), 3.82 (s, 3 H), 6.52 (d, 1 H, J = 10 Hz), 6.93 (d, 1 H, J = 10 Hz), 7.16 (m, 3 H).

7-Methoxyindole (9d). A mixture of 10 g (40 mmol) of β-pyrrolidino-2-nitro-3-methoxystyrene and 25 g of Raney nickel in 40 mL of MeOH and 40 mL of THF was stirred at 60 °C and a solution of 4 mL of hydrazine hydrate in 30 mL of THF was added over 60 min. The reaction mixture was cooled to room temperature and filtered (Celite), and the filtrate was concentrated under reduced pressure. The residue was chromatographed over a column of silica gel with 10% Et_2O/hexane. Product fractions were combined and concentrated to a clear oil, 2.94 g (50%). Anal. (C_9H_9NO) C, H, N. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3 H), 6.57 (m, 2 H), 7.11 (m, 3 H), 8.33 (br s, 1 H, ex with D_2O).

3-(2-Nitroethyl)-7-methoxyindole (10d). A stirred mixture of 5.0 g (34 mmol) of 7-methoxyindole, 5.2 g (39 mmol) of 2-nitroethyl acetate,[34] and 100 mg (0.6 mmol) of *tert*-butylcatechol in 50 mL of xylene was refluxed under a nitrogen atmosphere for 3 h. The solvent was removed under reduced pressure and the dark residue was chromatographed over a column of silica gel with 30% Et_2O/hexane. Product fractions were combined and concentrated under reduced pressure to leave a crystalline residue, 3.74 g (50%), mp 83–84 °C. Anal. ($C_{11}H_{12}N_2O_2$) C, H, N. ^{1}H NMR ($CDCl_3$) δ 3.46 (t, 2 H), 3.91 (s, 3 H), 4.61 (t, 2 H, J = 4.5 Hz), 6.63 (dd, 1 H, J = 5 Hz, J = 11 Hz), 6.94 (d, 1 H, J = 1 Hz), 7.00 (t, 1 H, J = 5 Hz), 7.12 (dd, 1 H, J = 5, 1 Hz), 8.24 (br s, 1 H, ex with D_2O).

7-Methoxytryptamine (11d). Five grams (23 mmol) of compound **10d** and 1 g of 10% Pd/C in 50 mL of EtOH were shaken under 50 psi of H_2 (Parr apparatus) for 12 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The solid weighed 4.2 g (95%), mp 134 °C. Anal. ($C_{11}H_{14}N_2O$) C, H, N. ^{1}H NMR ($CDCl_3$) δ 1.37 (br s, 2 H, ex with D_2O), 2.94 (m, 4 H), 3.90 (s, 3 H), 6.58 (d, 1 H), 7.20 (t, 3 H), 8.75 (br s, 1 H, ex with D_2O).

***N*-(Benzyloxycarbonyl)-7-methoxytryptamine (13d).** To a stirred mixture of 4.0 g (21 mmol) of 7-methoxytryptamine and 5.52 g (40 mmol) of K_2CO_3 in 50 mL of toluene and 50 mL of H_2O was added dropwise a solution of 3.0 mL (21 mmol) of benzyl chloroformate in 20 mL of toluene. The reaction was stirred at room temperature for 15 h and then diluted with 200 mL of ethyl acetate. The organic layer was separated and dried ($MgSO_4$). The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from Et_2O/hexane, 4.9 g (72%), mp 83 °C. Anal. ($C_{19}H_{20}N_2O_3$) C, H, N. ^{1}H NMR ($CDCl_3$) δ 2.95 (t, 2 H, J = 4.5 Hz), 3.52 (dd, 2 H, J = 4.5 Hz), 3.94 (s, 3 H), 4.82 (br s, 1 H, ex with D_2O), 5.12 (s, 2 H), 6.65 (dd, 1 H), 7.13 (m, 3 H), 7.36 (s, 5 H), 8.24 (br s, 1 H, ex with D_2O).

***N*-Methyl-*N*-isopropyl-7-methoxytryptamine (6).** To a stirred suspension of 760 mg (20 mmol) of lithium aluminum hydride in 50 mL of THF was added dropwise a solution of 2.5 g (7.72 mmol) of compound **13d** in 30 mL of THF. The reaction was refluxed for 30 min and cooled to 40 °C, and 50% aqueous THF was added dropwise. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in 50 mL of EtOH, 1.0 mL of acetone (13.6 mmol), and 500 mg of 10% Pd/C added and the reaction was shaken under 50 psi of H_2 for 15 h. The catalyst was removed by filtration (Celite), the filtrate was concentrated in vacuo, and the residue was recrystallized from Et_2O/hexane to give 1.71 g (90%), mp 65 °C. Anal. ($C_{15}H_{22}N_2O$) C, H, N. ^{1}H NMR δ 1.04 (s, 3 H), 1.06 (s, 3 H), 2.36 (s, 3 H), 2.72 (m, 2 H), 2.92 (m, 3 H), 3.95 (s, 3 H), 6.63 (d, 1 H), 6.98 (d, 1 H), 7.03 (t, 1 H), 7.22 (d, 1 H), 8.29 (br s, 1 H, ex with D_2O).

5,6-Dimethoxy-*N*-methyl-*N*-isopropylindole-3-glyoxylamide (17). A suspension of 885 mg (5.0 mmol) of 5,6-dimethoxyindole[33] in 50 mL of Et_2O was stirred and cooled to 0 °C and a solution of 0.87 mL (10.0 mmol) of oxalyl chloride in 5 mL of Et_2O was added dropwise over 20 min. After the addition, the reaction mixture was stirred at 0 °C for 20 min and then filtered. The red powdery filter cake was washed with 15 mL of Et_2O and then dried in vacuo. The solid was stirred in 50 mL of dry THF at 0 °C under nitrogen and a solution of 30% *N*-isopropylmethylamine[39] in Et_2O was added dropwise to pH >9. The solvent was removed under reduced pressure and the residue was partitioned between 100 mL of $CHCl_3$ and 100 mL of H_2O. The organic phase was decolorized with activated charcoal, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOAc/hexane to give 615 mg (40%), mp 204–206 °C. Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

***N*-Methyl-*N*-isopropyl-5,6-dimethoxytryptamine (7).** To a stirred suspension of 0.55 g (14 mmol) of lithium aluminum hydride in 25 mL of THF was added dropwise a solution of 529 mg (1.74 mmol) of compound **17** in 75 mL of THF. The reaction was refluxed for 30 min and cooled to ~40 °C, and then 0.55 mL of H_2O, 1.65 mL of 10% aqueous NaOH, and 0.55 mL of H_2O were added sequentially. The mixture was filtered, the filter cake was washed with three 10-mL portions of THF, and the combined

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filtrate and washings were concentrated under reduced pressure. The oily residue was crystallized from hexane to give 340 mg (71%), mp 71-73 °C. Anal. ($C_{16}H_{24}N_2O_2$) C, H, N. ^{1}H NMR δ 1.05 (s, 3 H), 1.07 (s, 3 H), 2.35 (s, 3 H), 2.73 (m, 2 H), 2.91 (m, 3 H), 4.86 (s, 3 H), 4.92 (s, 3 H), 6.76 (s, 1 H), 6.80 (s, 1 H), 6.93 (s, 1 H), 7.90 (br s, 1 H, ex with D_2O).

The following protocol was approved by the Research Committee. Five subjects took part in the screening of these materials. They ranged in age from 26-62 and all had physical examinations within the 6-month period prior to this study. All were found to be in excellent health. The subjects had prior study experience with a variety of psychopharmaceuticals.

The studies were carried out in a controlled, comfortable environment. Doses of the test compounds were chosen on the basis of the known effects of closely related materials, e.g., 5-methoxy-α-methyltryptamine, 0.03 mg/kg (effective dose in man) and psilocin, 0.13 mg/kg (effective dose in man).[40,41] All experiments were conducted in the "double conscious" technique of Alles;[42] i.e., the subjects were aware of which drug they were taking and at what dosage level. Discussion followed each session and comments of the partipicants were recorded. All substances were administered po. Test sessions were conducted at 7-10-day intervals that assured the absence of tolerance or cross-tolerance. A rough dose-response curve for each compound was established by increasing incremental doses until a threshold level was reached. Dose regimen began at 0.003 mg/kg and increased by increments of 0.005 mg/kg. Thereafter dosage was increased by 0.03 mg/kg (2.25 mg/75 kg subject) per session at the subject's discretion. The effective dose was established when all subjects agreed that higher doses did not add significantly to the character of the experience. Table I represents trials conducted at the effective dose for each substance. (An effective response for **5-8** could not be obtained with the doses employed.)

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Registry No. **1**, 96096-52-5; **2**, 77872-43-6; **3**, 96096-53-6; **4**, 96096-54-7; **4** free base, 96096-55-8; **5**, 96096-56-9; **6**, 96096-57-0; **7**, 96096-58-1; **8**, 96096-59-2; **9d**, 3189-22-8; **10a**, 96096-60-5; **10b**, 68935-49-9; **10c**, 96096-61-6; **10d**, 96096-62-7; **11d**, 2436-04-6; **13a**, 96096-64-9; **13b**, 96096-65-0; **13c**, 96096-66-1; **13d**, 96096-67-2; **14**, 38750-13-9; **17**, 96096-63-8; β-pyrrolidino-2-nitro-3-methoxystyrene, 96096-68-3; 2-nitro-3-methoxytoluene, 5345-42-6; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; hydrazine, 302-01-2; 2-nitroethyl acetate, 18942-89-7; benzyl chloroformate, 501-53-1; 5,6-dimethoxyindole, 14430-23-0; oxalyl chloride, 79-37-8; *N*-isopropylmethylamine, 4747-21-1.

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New Chiral and Isomeric Cyclopropyl Ketoxime Propanolamine Derivatives with Potent β-Adrenergic Blocking Properties

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The synthesis of *R*-(+) and *S*-(-) isomers of *O*-[3-(*tert*-butylamino)-2-hydroxypropyl] cyclopropyl methyl ketone oxime (falintolol) is described. The syn and anti isomers of falintolol were obtained in two different ways from cyclopropyl methyl ketoxime or from falintolol. For comparison purposes, the enantiomers of the dicyclopropyl ketone oxime derivatives were also prepared. Structure-activity relationships are described.

O-[3-(*tert*-Butylamino)-2-hydroxypropyl] cyclopropyl methyl ketone oxime (falintolol) is a new β-adrenergic blocking agent synthesized by our group.[1] It has been found useful in the treatment of glaucoma and is at present under clinical trial.[2,3] This molecule is characterized by the presence of an oxime function and exists as a mixture of syn and anti isomers. In view of the potent activity of falintolol and our continued interest in synthesizing the enantiomers in this series of agents,[4] the syn and anti isomers of falintolol, their corresponding enantiomers, and some related substances were prepared in order to gain further insight into the structural requirements of the β-adrenergic receptor. In this paper we present the results of that study.

Chemistry. The stereospecific synthesis of 3-(mesyloxy)-1,2-epoxypropane [(*S*)-**2** and (*R*)-**2**] was carried out as described by Baldwin et al.[5] and more recently by Leclerc et al.[4] (Scheme I). The mesylate (*S*)-**2** or (*R*)-**2** was reacted with the sodium salt of the cyclopropyl methyl ketone oxime **5** in THF, giving the enantiomeric epoxides (*S*)-**3** and (*R*)-**3**, respectively. Treating (*S*)-**3** and (*R*)-**3** with excess *t*-BuNH$_2$ gave (*S*)-**4** and (*R*)-**4**, respectively. The action of hydroxylamine on cyclopropyl methyl ketone under basic conditions[6] (AcONa or aqueous NaOH) gave a mixture of anti and syn oxime derivatives in a ratio of ca. 7:3 as analyzed by ^{1}H NMR. The major anti isomer **5** was separated in pure form by recrystallizations from petroleum ether. The anti configuration of **5** was proved by the 0.15-0.20-ppm deshielding of the methyl protons by the hydroxyl group in the NMR spectra.[7,8] The Beckmann rearrangement of *anti*-**5** carried out with the method of Graig and Naik[9] gave the cyclopropylacetamide,[10] which confirmed this anti conformation. Furthermore, melting point and ^{1}H NMR and MS spectra

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