D50, 82830-33-9; D51, 91860-66-1; D52, 82830-26-0; D53, 91860-67-2; D54, 70579-33-8; D55, 1492-81-5; D56, 3850-94-0; D57, 4022-58-6; D58, 13351-02-5; D59, 51012-14-7; D60, 70743-55-4; D61, 4038-60-2; D62, 70650-60-1; D63, 70579-36-1; D64, 70606-63-2; D65, 70579-38-3; D66, 7317-78-4; D67, 7319-46-2; D68, 58-14-0; D69, 94635-31-1; D70, 94635-30-0; D71, 94635-33-3; D72, 94635-32-2; G01, 2922-56-7; G02, 24425-52-3; G03, 24425-53-4; G04, 6803-16-3; G05, 24425-55-6; G06, 24425-56-7; G07, 24435-26-5; G08, 24435-27-6; G09, 6803-17-4; G10, 33812-35-0; G11, 33812-36-1; G12, 33812-37-2; G13, 6803-18-5; G14, 31702-37-1; G15, 33812-40-7; G16, 33812-41-8; G17, 33812-42-9; G18, 33812-44-1; G19, 33812-46-3; G20, 33812-47-4; G21, 33812-64-5; G22, 33812-48-5; G23, 33812-50-9; G24, 33812-51-0; G25, 33812-52-1; G26, 33812-53-2; G27, 33812-54-3; G28, 32728-47-5; G29, 114446-20-7; G30, 85261-24-1; G31, 114446-21-8; G32, 42583-87-9; G33, 70-18-8; G34, 528-48-3; G35, 117-39-5; G36, 480-16-0; G37, 480-40-0; G38, 15485-76-4; G39, 67604-48-2; G40, 118-71-8; G41, 84-79-7; DHFR, 9002-03-3; glyoxalase I, 9033-12-9.

Synthesis and Serotonin Receptor Affinities of a Series of Enantiomers of α-Methyltryptamines: Evidence for the Binding Conformation of Tryptamines at Serotonin 5-HT_{1B} Receptors

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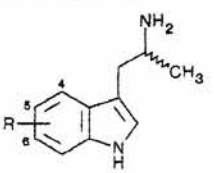
A procedure for the preparation of optically pure α-methyltryptamines (AMTs) from substituted indoles was developed. The key step in the sequence was the reductive amination of substituted indole-2-propanones with the commercially available pure enantiomers of α-methylbenzylamine, followed by the chromatographic separation of the resulting pair of diastereomeric amines by preparative centrifugal (Chromatotron) chromatography. Catalytic N-debenzylation then afforded the pure AMT enantiomers. Optical purity was established by chiral HPLC analysis of the 2-naphthoylamide derivatives. An improved procedure for the preparation of indole-2-propanones was also developed. To probe structure–activity relationships of serotonin receptors, affinities of the α-methyltryptamine enantiomers were then measured at the 5-HT_2 antagonist receptor subtype, with displacement of [^{3}H]ketanserin, and were estimated at the 5-HT_{1B} receptor, with displacement of [^{3}H]serotonin, respectively, in rat frontal cortex homogenates. Enantioselectivity at the receptor subtypes varied, depending on aromatic substituents. For a 5-hydroxy or 5-methoxy, the *S* enantiomer had higher affinity or was equipotent to the *R* enantiomer. This selectivity at [^{3}H]serotonin binding sites was reversed for 4-oxygenated α-methyltryptamines, where a 4-hydroxy or 4-methoxy did not enhance affinity over the unsubstituted compounds. These results can be explained, for the [^{3}H]serotonin displacement data, if the binding conformation is one where the ethylamine side chain is trans and lying in a plane perpendicular to the indole ring plane.

As part of our ongoing research into the mechanism of action of hallucinogens and other centrally active substances, it was of interest to prepare certain α-methyltryptamines (AMTs, **1a–f**) in an optically pure form. These compounds were designed to serve as chiral probes of serotonin (5-hydroxytryptamine) receptors. A general synthetic route was sought, such that several selected A-ring-substituted indoles might be transformed into the corresponding optically active AMTs. Another general concern was that reaction conditions be mild enough to allow the preparation of hydroxy-substituted AMTs as well, via their *O*-benzyl ethers.



1a, R = H
b, R = 4-OCH_3
c, R = 5-OCH_3
d, R = 6-OCH_3
e, R = 4-OH
f, R = 5-OH

It has been hypothesized that 4- and 5-hydroxy-substituted tryptamines might bind to serotonin receptors in two different conformational extremes, such that the amine-to-oxygen distances in the two conformers would remain approximately the same.[1] It was anticipated that if this hypothesis were valid, a reversal of receptor stereoselectivity might be observed for binding of the enantiomers of 4- versus 5-hydroxy-substituted α-methyltryptamine.

This paper describes a general method for the synthesis of substituted α-methyltryptamine enantiomers. Ability of the isomers to displace [^{3}H]ketanserin and [^{3}H]serotonin from rat brain frontal cortex homogenates was then measured, as an indication of affinity for 5-HT_2 and 5-HT_{1B} receptors, respectively.

Chemistry

It was initially envisioned that a procedure analogous to that developed previously[2] for the preparation of optically pure substituted phenylisopropylamines from 1-phenyl-2-propanones could be employed, but with 1-indol-3-yl-2-propanones as the starting material. It fact, this procedure did work in principle, but it was accompanied by several serious problems. As a consequence, the approach was modified considerably, and this method is outlined in Scheme I.

Indole-2-propanones were prepared from the corresponding indolylnitropropanes (Scheme I). The alkoxyindoles **2a–d** used as starting materials either were purchased from commercial sources or were prepared from the appropriate *o*-nitrotoluenes by using our recently reported method.[3] Preparation of indole-2-propanone and 5-methoxyindole-2-propanone from the corresponding gramines has been reported by Heath-Brown and Phil-

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(2) Nichols, D. E.; Barfknecht, C. F.; Rusterholz, D. B.; Benington, F.; Morin, R. D. *J. Med. Chem.* **1973**, *16*, 480.

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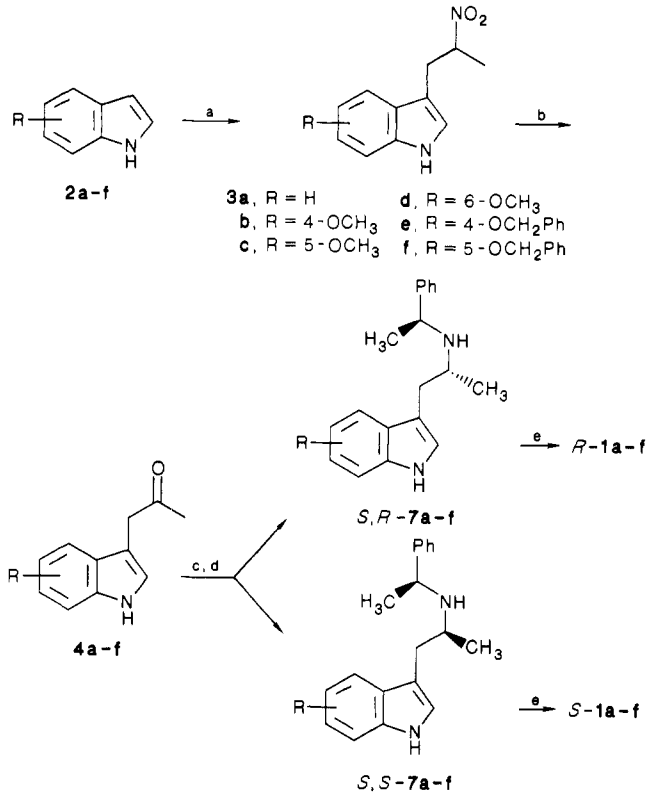
Scheme I[a]

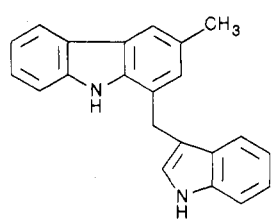


[a] (a) $CH_2CH(CH_3)NO_2$, C_6H_6, reflux; (b) $NaOCH_3$, $TiCl_3$; (c) *R*- (or *S*)α-methylbenzylamine, $NaBH_3CN$; (d) chromatographic resolution; (e) H_2, $Pd(OH)_2$–C.

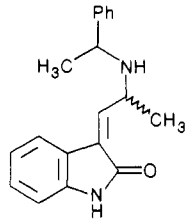
pott,[4] in which indolylnitropropanes were reduced to the indole-2-propanones with use of iron dust in hydrochloric acid. It was felt that the strongly acidic conditions of this reduction would be inappropriate for the synthesis of (benzyloxy)indole-2-propanones necessary for the preparation of hydroxy-AMTs. A more efficient synthesis of the indolylnitropropanes as well as a milder reduction method was sought.

The report by Ranganathan et al.[5] that nitroethene readily reacts with indole at the 3-position had earlier led us to investigate the analogous reaction between indoles and 2-nitropropene.[3] In this way the three-carbon side chain could be attached in a single step. Although the reaction is somewhat more sluggish than when nitroethene is used, the desired indolylnitropropanes **3a–f** were obtained in satisfactory yield and good purity. Additionally, the formation of diadducts reported by Ranganathan did not occur to any significant extent with 2-nitropropene. Treatment of the nitro compounds with sodium methoxide in methanol followed by titanium(III) chloride in an aqueous ammonium acetate buffer (pH 6–7)[6] readily afforded the required indole-2-propanones **4a–f**.

Attempts to condense the indolepropanones with the enantiomers of α-methylbenzylamine proved problematic. With use of the same conditions reported[2] for the condensation of phenylpropanones, indolepropanone underwent a base-catalyzed dimerization to yield the carbazole derivative **5** as the major product. When the reaction was run at high dilution, reaction times became unacceptably long, with numerous byproducts evident by TLC analysis. The use of acetic or toluenesulfonic acid catalysis did not appreciably increase reaction rate and led to formation of numerous byproducts, detected by TLC. Use of molecular sieves[7] accelerated the condensation significantly, but only in quantities that retained substantial amounts of product.



5



6

A more serious problem in this approach was the formation of side products tentatively identified as oxindoles **6**. Although these appear to arise as a result of reaction of the electron-rich enamine with molecular oxygen, attempts to degas the molecular sieves and flushing the reaction vessel with nitrogen proved ineffective in completely eliminating their formation. Chromatographic mobility of the desired *N*-α-phenethyl diastereomers, obtained in the next step, and these oxindoles was nearly identical and separation on a preparative scale was not feasible.

During the course of this work it was observed that partial separation of the minor diastereomeric amine from the major diastereomer often occurred during column chromatographic purification of the reduction mixtures. Although resolution was inadequate for preparative applications, with centrifugal thin-layer ("Chromatotron")[8] chromatography the separation of the diastereomeric amines could be quickly and easily accomplished on a useful scale. Therefore, the successful method employed a reductive amination with optically pure α-methylbenzylamine using sodium cyanoborohydride,[9] followed by separation of the resulting diastereomeric pair. Some stereoselectivity in the reduction was observed, such that the *R,R* or *S,S* diastereomer was obtained in an isolated ratio of about 2:1 to that of the *R,S* or *S,R* diastereomer, respectively. This procedure proved to be a clean, efficient, and general method for the preparation of the required *N*-α-phenethyl-AMTs in optically pure form.

The final AMT enantiomers were obtained by catalytic N-debenzylation with Pearlman's catalyst[10] at 50 psig of hydrogen. The enantiomers of α-methyltryptamine obtained by this method possessed specific rotations identical with those of materials prepared by Repke et al.[11] from the isomers of tryptophan.

Hydrogenolysis of the 5-benzyloxy diastereomers effected both N- and O-debenzylation, as expected. The resulting enantiomers of α-methylserotonin (*R*- and *S*-**1f**) were isolated and characterized as the free bases, as salts were found to be hygroscopic. However, deprotection of the 4-benzyloxy diastereomers (**7e**) led to an unexpected and previously undocumented side reaction. TLC analysis of the reaction at various times indicated that O-debenzylation occurred very rapidly; reaction was complete in 15 min at 1 atm of hydrogen pressure in the presence of 20% palladium hydroxide. N-Debenzylation then proceeded at a much slower rate, to produce the desired **1e**.

(5) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrota, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185.
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(8) Harrison and Harrison Research, Palo Alto, California.
(9) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
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(11) Repke, D. B.; Ferguson, J. *J. Heterocycl. Chem.* **1976**, *13*, 775.

However, at this point reduction of the benzenoid ring also begins to occur, to produce a 6,7-dihydroindolone. The rate of this reduction was found to be close to that for the N-debenzylation. By the time N-debenzylation was complete, the major material present in the reaction mixture was the undesired dihydroindolone.

Attempts to inhibit the overreduction by varying solvent, catalyst, and hydrogen pressure were successful only in slowing the rate of N-debenzylation. In order to optimize formation of the desired compound, the hydrogenolysis was run at 1 atm of hydrogen pressure for 1 h. At that point, the reaction mixture contained O-debenzylated material, the desired 4-hydroxy-α-methyltryptamine, and the dihydroindolone in approximately equal proportions. These three components were easily separated with the chromatotron. The O-debenzylated material was subjected to further hydrogenolysis and chromatographic separation. The combined product fractions amounted to a modest, but acceptable, 50% yield as reported in Table III. It should be noted that this did not occur with any other compound, including the 5-benzyloxy-substituted intermediates, but was peculiar to the 4-benzyloxy substitution.

Enantiomer purities of compounds **1a–d** were established by HPLC analysis of the 2-naphthoylamide derivatives using a chiral (Pirkle)[12] stationary phase. A similar separation of the analogous 2-naphthoylamphetamines has also been reported.[13] With use of conditions of optimal resolution determined for the racemic amides, none of the minor enantiomer could be detected in the optically active derivatives. It was therefore concluded that the optical purity of the final AMTs was primarily determined by the optical purity of the α-methylbenzylamine used in the reductive amination (greater than 98%).

Pharmacology and Structure–Activity Results and Discussion

Saturation experiments yielded specific, saturable binding for both [^{3}H]-5-HT and [^{3}H]ketanserin in a concentration-dependent manner. Scatchard least-squares analysis yielded K_d values of 2.03 ± 0.04 and 2.22 ± 0.26 nM (mean ± SEM) for [^{3}H]-5-HT and [^{3}H]ketanserin, respectively. B_{max} values were 200 fmol/mg protein for 5-HT$_1$ sites and 340 fmol/mg protein for 5-HT$_2$. These values are in reasonable agreement with those reported in other studies for 5-HT$_1$ and 5-HT$_2$ sites.[14,15]

Serotonin 5-HT$_1$ receptors have been further subdivided into 5-HT$_{1A}$, 5-HT$_{1B}$, and 5-HT$_{1C}$ subtypes.[16] Although in rat cortex serotonin labels all three subtypes with approximately equal densities,[17] in rat *frontal* cortex, the tissue used in this study, serotonin labels primarily (70–90%) the 5-HT$_{1B}$ subtype.[18] In agreement with that report, in the present study it was found that only 22% of the [^{3}H]-5-HT bound to rat frontal cortex homogenate was displaced by 1000 nM 8-OH-DPAT, a selective 5-HT$_{1A}$ ligand. Conversely, addition of 1000 nM TFMPP, a selective 5-HT$_{1B}$ ligand, displaced 78% of the specifically bound [^{3}H]serotonin. Thus, in the context of the present work, the affinity data for displacement of [^{3}H]serotonin have been taken to represent affinity for the 5-HT$_{1B}$ receptor subtype. However, we must caution that these conclusions are only tentative. Without a more detailed analysis, utilizing radioligands specific for the 5-HT$_1$ receptor subtypes, and requiring quantities of displacing ligands larger than were available for the present study, one cannot be certain that these structure–activity relationships truly represent those of the 5-HT$_{1B}$ subtype.

Table I. Radioligand Binding Data for α-Methyltryptamine Enantiomers[a]

compound	R	ligand: [^{3}H]serotonin pK_i (±SEM)	ligand: [^{3}H]ketanserin pK_i (±SEM)
serotonin		8.46 (0.12)	6.01 (0.12)
5-methoxytryptamine		8.19 (0.04)	5.99 (0.43)
R-**1a**	H	5.86 (0.21)	5.37 (0.21)
S-**1a**	H	5.82 (0.04)	5.29 (0.08)
R-**1b**	4-OCH$_3$	6.11 (0.30)*[b]	5.84 (0.11)
S-**1b**	4-OCH$_3$	5.57 (0.07)	6.02 (0.04)
R-**1c**	5-OCH$_3$	6.42 (0.06)	5.89 (0.004)
S-**1c**	5-OCH$_3$	6.38 (0.04)	6.15 (0.09)
R-**1d**	6-OCH$_3$	5.67 (0.21)*	K_i > 10 μM
S-**1d**	6-OCH$_3$	5.14 (0.19)	K_i > 10 μM
R-**1e**	4-OH	5.81 (0.02)*	5.46 (0.10)
S-**1e**	4-OH	5.39 (0.19)	5.21 (0.04)
R-**1f**	5-OH	6.92 (0.10)**[c]	5.50 (0.22)**
S-**1f**	5-OH	7.34 (0.23)	6.01 (0.01)

[a] All values represent the mean of two or three determinations. [b] (*) The pK_i for the *R* isomer is significantly greater than the pK_i for the *S* isomer. Student's *t* test $p < 0.05$. [c] (**) The pK_i for the *S* isomer is significantly greater than the pK_i for the *R* isomer. Student's *t* test $p < 0.05$.

The pK_i values for the isomers of the 4-, 5-, and 6-substituted α-methyltryptamines (AMT) as well as *R*- and *S*-AMT, 5-hydroxytryptamine (5-HT), and 5-methoxytryptamine are reported in Table I. At both sites, the order of affinity is 5-substituted > 4-substituted > unsubstituted > 6-substituted. It has been noted earlier[1,19] that 6-substitution generally abolishes or greatly attenuates affinity for serotonin receptors. Statistical analysis indicated a significant stereoselectivity, with higher affinity for the *S* isomer of 5-hydroxy-α-methyltryptamine over the *R* isomer at both 5-HT$_{1B}$ and 5-HT$_2$ sites. By contrast, the enantiomers of both 4-hydroxy-α-methyltryptamine and 4-methoxy-α-methyltryptamine demonstrated stereoselectivity, with higher affinity for the *R* isomer at 5-HT$_{1B}$ sites, but not at 5-HT$_2$ sites. Similarly, (*R*)-6-methoxy-α-methyltryptamine had a higher affinity for 5-HT$_{1B}$ sites than its *S* isomer, while the affinities for both isomers were greater than 10 μM at the 5-HT$_2$ site.

A major question to be answered from these studies was whether the affinity data provided any evidence for the binding of different conformers of the α-methyltryptamines, depending on whether they were oxygenated at the 4- or 5-position.[1] A comparison of unsubstituted *R*-**1a** and 4-methoxy *R*-**1b** or 4-hydroxy *R*-**1e** indicates that the 4-oxygen has no significant effect on affinity at the serotonin receptor subtypes examined. Thus, there seems no need to invoke arguments that different conformations may bind, in order to maintain a critical N to O distance, and no support for the hypothesis of different binding conformations is gained from these studies.

However, there are a number of interesting findings in the data. In considering these structure–activity relationships, it seems most appropriate to consider the data for [^{3}H]serotonin displacement. It is at this site that the

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(18) Pazos, A.; Palacios, M. *Brain Res.* **1985**, *346*, 205.
(19) Glennon, R. A.; Schubert, E.; Jacyno, J. M.; Rosecrans, J. A. *J. Med. Chem.* **1980**, *23*, 1222.

α-methyltryptamines have the closest structural resemblance to the competing ligand, and inferences should be most clear. This intuitive approach is reinforced by observing that all the α-methyltryptamines have higher affinity for the 5-HT_{1B} site than for the 5-HT_2 site.

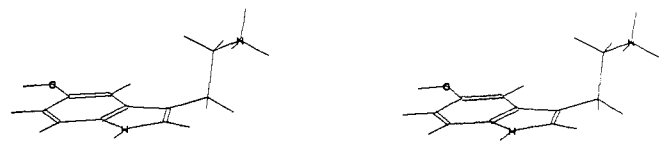
The 5-HT_{1B} site is much more sensitive to the presence of substitution in the side chain, as affinity drops with α-alkylation. This is illustrated by a comparison of the affinity of serotonin with its α-methyl derivative *S*-**1f** at the two sites. At 5-HT_{1B} receptors the α-methyl compound has a 10-fold lower affinity, while at the 5-HT_2 site there is no difference in affinity.

It is also evident that O-methylation has a different effect at the two sites. In 5-oxygenated tryptamines, at the [^{3}H]serotonin binding site, O-methylation only slightly decreases affinity, as seen in the comparison of serotonin with 5-methoxytryptamine. These results are in excellent agreement with those published by Richardson et al.,[20] who obtained virtually identical affinities with those reported here. However, O-methylation in the 5-oxygenated α-methyltryptamines has a significant effect on 5-HT_{1B} binding, with a 10-fold decrease in affinity for the *S* enantiomer (compare 5-hydroxy *S*-**1f** and 5-methoxy *S*-**1c**), and an elimination of stereoselectivity for 5-methoxy *R*- and *S*-**1c**. Although one could speculate that perhaps a free hydroxy proton is necessary for receptor binding, the affinity of serotonin and 5-methoxytryptamine at both sites is similar.

In the 4-oxygenated series, O-methylation actually enhances binding. However, the affinity of the 4-oxygenated AMTs is not significantly greater than that of the ring-unsubstituted tryptamines (e.g. compare *R*-**1e** and *R*-**1a**). This finding agrees with the data published by Engel et al.,[21] who reported similar affinities for 4-hydroxytryptamine and tryptamine at 5-HT_1 receptors. Thus, the 4-oxygen may play no role at all in binding to the 5-HT_{1B} receptor. Rather, it may serve only to interfere with active binding conformations of the side chain, causing a decrease in affinity (compare unsubstituted *S*-**1a** with 4-methoxy *S*-**1b**). On the other hand, a 4-hydroxy group could also decrease affinity by an intramolecular interaction with the amino group. We have previously shown[22] that the 4-hydroxy group of the hallucinogenic tryptamine psilocin causes a decrease in the amino pK_a and an increase in hydrophobicity. It seems likely that a 4-hydroxy could have a similar effect in the present series, and that this might result in a decreased in affinity for the 5-HT_{1B} receptor. If the hydroxy serves as an intramolecular hydrogen bond donor, this effect could not occur in the 4-methoxy series, and interestingly, the 4-hydroxy (*R*-**1e**) does have decreased affinity relative to the 4-methoxy (*R*-**1b**).

While the concept of different active binding conformations, depending on the location of the oxygen substituent, does not seem warranted on the basis of these data, stereoselectivity at the 5-HT_{1B} site was observed with several pairs of enantiomers. Furthermore, this selectivity was reversed in the 4- and 5-hydroxy series, with the *S*-5-hydroxy (**1f**) having higher affinity than the *R* enantiomer, but *R*-4-hydroxy (**1e**) having higher affinity than its *S* enantiomer.

This observed stereoselectivity can be most easily explained by postulating a binding conformation for serotonin where the side chain is trans and lies above, and approximately in a plane perpendicular to, the aromatic ring plane, as shown below. This corresponds to the "trans" low-energy conformation calculated by Kumbar and Sivi Sankar[23] and to the trans rotamer of serotonin observed in solution by ^{1}H NMR.[24] In such a conformation, the α-alkyl will have no significant interaction with a 5-substituent. On the other hand, a 4-substituent (hydroxy or methoxy) will provide a serious nonbonded interaction, where the *S* enantiomer will be most disfavored, due to interaction of the α-methyl with the 4-substituent. For example, the affinities of unsubstituted *R*-**1a** and 4-methoxy *R*-**1b** or 4-hydroxy *R*-**1e** are not significantly different, while those of 4-methoxy *S*-**1b** or 4-hydroxy *S*-**1e** are decreased relative to unsubstituted *S*-**1a**.



On the basis of our previous molecular mechanics calculations,[1] it also seems improbable that the α-methyltryptamines can adopt an LSD-like conformation, as proposed by Glennon et al.[25] This is principally due to the nonbonded steric interaction between the side-chain hydrogens, or α-methyl in the AMTs, and the substituent at the 4-position.

Experimental Section

Melting points were determined in open glass capillaries with a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 spectrometer and chemical shifts are reported in parts per million relative to TMS as the internal standard. The multiplicities are noted as s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, hp = heptet, m = multiplet, and br s = broad singlet. IR spectra were recorded on a Beckman IR-33 instrument. Mass spectra were recorded on a Finnegan 2000 spectrometer and exact masses were determined on a Kratos MS50 mass spectrometer. Thin-layer chromatography (TLC) was performed on 0.25-mm silica (SIL G/UV254) precoated plastic plates, and the samples were visualized with UV light and (for indoles) Ehrlich's reagent (*p*-(dimethylamino)benzaldehyde in ethanol and concentrated HCl) applied with a spray bottle and allowed to develop at room temperature.

2-Nitropropene was prepared by a modification of the method of Ranganathan et al.[5] Phthalic anhydride (29.6 g, 200 mmol) and 10.5 g (100 mmol) of 2-nitro-1-propanol were combined in a round-bottom flask equipped with a Vigreux column and distilling head. The reactants were heated until a homogeneous solution was formed, and then the pale-green product was gently distilled (41 °C at 76 mmHg). The water that codistilled was carefully removed with a disposable pipet to leave 8.18 g of damp 2-nitropropene (94% yield). This material was dried over $CaCl_2$ and stored at 0 °C as a benzene solution (1.0 g/10 mL) over $CaCl_2$: ^{1}H NMR ($CDCl_3$) δ 6.50 (s, 1 H, CH), 5.80 (br s, 1 H, CH), 2.30 (s, 3 H, CH_3).

General Procedure for the Preparation of Indolylnitropropanes 3a–f.[3] To a stirred 0.5 M benzene solution of the selected indole was added 2 equiv of 2-nitropropene as a 10% benzene solution. The reaction mixture was heated at reflux under a nitrogen atmosphere until TLC analysis (chloroform/silica) indicated that all starting material was consumed (24–48 h). The dark reaction mixture was cooled to room temperature and quickly

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passed through a short silica gel column, which was washed with 1:1 toluene/hexane until product recovery was complete. Solvent removal under reduced pressure afforded material that was sufficiently pure to be carried on to the next step.

1-(4-Methoxyindol-3-yl)-2-nitropropane (3b). This material was obtained in 84% crude yield as a brown oil. TLC (silica/$CHCl_3$) showed a minor impurity (detected with Ehrlich's spray reagent, green); crystallization from toluene/petroleum ether afforded an analytically pure sample mp 90–92 °C; ^1H NMR ($CDCl_3$) δ 7.98 (br s, 1 H, NH), 7.23–6.43 (m, 4 H, Ar H), 5.05 (sx, 1 H, CH), 3.91 (s, 3 H, OCH_3), 3.66–3.09 (m, 2 H, CH_2), 1.55 (d, 3 H, CH_3); MS (EI), m/z (relative intensity) 234 (100), 188 (81), 187 (60), 160 (64). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

1-(5-Methoxyindol-3-yl)-2-nitropropane (3c). This compound was obtained in 89% yield as a dark amber solid. A pure sample was obtained by recrystallization from EtOAc/hexane: mp 93–94 °C (lit.[4] mp 93–94 °C); ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1 H, NH), 7.30–6.90 (m, 4 H, Ar H), 4.86 (sx, 1 H, CH), 3.86 (s, 3 H, OCH_3), 3.61–3.07 (m, 2 H, CH_2), 1.56 (d, 3 H, CH_3); MS (EI), m/z (relative intensity) 234 (100), 188 (66), 187 (59), 160 (69).

1-(6-Methoxyindol-3-yl)-2-nitropropane (3d). Compound **3d** was obtained in 67% yield as a brown oil. Crystallization from EtOAc/hexane provided a pure sample: mp 80–81 °C (lit.[4] mp 80–82 °C); ^1H NMR ($CDCl_3$) δ 7.93 (br s, 1 H, NH), 7.48–6.73 (m, 4 H, Ar H), 4.86 (sx, 1 H, CH), 3.83 (s, 3 H, OCH_3), 3.60–2.98 (m, 2 H, CH_2), 1.56 (d, 3 H, CH_3).

1-[5-(Benzyloxy)indol-3-yl]-2-nitropropane (3e). This material was obtained in 96% yield as a tan solid. An analytical sample was crystallized from EtOAc/hexane: mp 80–83 °C; ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1 H, NH), 7.33 (m, 5 H, Ph), 7.29–6.85 (m, 4 H, Ar), 5.10 (s, 2 H, OCH_2), 4.82 (sx, 1 H, CH), 3.57–2.93 (m, 2 H, CH_2), 1.52 (d, 3 H, CH_3); MS (EI), m/z (relative intensity) 310 (3), 219 (3), 85 (58), 83 (100); exact mass calcd for $C_{18}H_{18}N_2O$ 310.1317, found 310.1327.

General Procedure for the Preparation of Indolylpropanones 4a–f. A 0.25 M methanolic solution of the desired indolyl nitropropane was treated with 2 equiv of sodium methoxide (commercial powder) and stirred under nitrogen for 30 min at room temperature to allow nitronate salt formation. A 0.25 M solution of 5.0 equiv of titanous chloride, as the commercially available 20% aqueous solution, in 4 M aqueous ammonium acetate, was then added all at once and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 12 h. The solution was then extracted with multiple portions of diethyl ether, which were combined and washed with 5% aqueous sodium bicarbonate. The ethereal solution was dried (Na_2SO_4) and filtered. Solvent removal under reduced pressure afforded the crude indolepropanones, which were then further purified by column chromatography (dichloromethane/silica gel).

1-Indol-3-yl-2-propanone (4a). This was obtained from 1-indol-3-yl-2-nitropropane[5] in 81% yield as an amber oil, which solidified upon standing. Recrystallization from toluene afforded a pure sample: mp 118–119 °C (lit.[4] mp 117–118 °C); ^1H NMR ($CDCl_3$) δ 8.35 (br s, 1 H, NH), 7.74–7.00 (m, 5 H, Ar), 3.86 (s, 2 H, CH_2), 2.18 (s, 3 H, CH_3); IR 1705 cm^{-1} (C=O stretch).

1-(4-Methoxyindol-3-yl)-2-propanone (4b). Compound **4b** was obtained from **3b** in 70% yield as a light yellow oil. Crystallization from toluene provided an analytical sample: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 8.12 (br s, 1 H, NH), 7.19–6.41 (m, 4 H, Ar H), 3.93 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 2.16 (s, 3 H, CH_3); IR 1705 cm^{-1} (C=O stretch). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1-(5-Methoxyindol-3-yl)-2-propanone (4c). This compound was obtained from **3c** in 76% yield as an amber solid. A pure sample was recrystallized from toluene: mp 109–110 °C (lit.[4] mp 109–110 °C); ^1H NMR ($CDCl_3$) δ 8.13 (br s, 1 H, NH), 7.29–6.78 (m, 4 H, Ar H), 3.84 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2), 2.16 (s, 3 H, CH_3); IR 1710 cm^{-1} (C=O stretch).

1-(6-Methoxyindol-3-yl)-2-propanone (4d). This was obtained from **3d** in 78% crude yield; an analytical sample was obtained by recrystallization from absolute ethanol: mp 138–140 °C; ^1H NMR ($CDCl_3$) δ 8.03 (br s, 1 H, NH), 7.46–6.73 (m, 4 H, Ar H), 3.83 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2), 2.15 (s, 3 H, CH_3); IR 1705 cm^{-1} (C=O stretch). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

1-[4-(Benzyloxy)indol-3-yl]-2-propanone (4e). Compound **4e** was obtained from the corresponding nitropropane,[3] in 42% yield, after purification by column chromatography over silica gel and elution with dichloromethane. The product solidified as a crystalline amber solid: mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 8.13 (br s, 1 H, NH), 7.38 (br s, 5 H, Ph), 7.47–6.47 (m, 4 H, Ar H), 5.09 (s, 2 H, OCH_2), 3.90 (s, 2 H, CH_2), 1.92 (s, 3 H, CH_3); MS (EI), m/z (relative intensity) 279 (13), 236 (16), 188 (30), 83 (100). Anal. ($C_{18}H_{17}NO_2$) C, H, N.

1-[5-(Benzyloxy)indol-3-yl]-2-propanone (4f). This was obtained from **3f** in 60% crude yield as a dark amber oil. Recrystallization from toluene provided an analytical sample: mp 78–81 °C; ^1H NMR ($CDCl_3$) δ 8.05 (br s, 1 H, NH), 7.40 (d, 5 H, Ph), 7.39–6.86 (m, 4 H, Ar H), 5.09 (s, 2 H, OCH_2), 3.75 (s, 2 H, CH_2), 2.13 (s, 3 H, CH_3); MS (EI), m/z (relative intensity) 279 (21), 236 (30), 188 (30), 83 (100); exact mass calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1245.

Preparation of Carbazole Dimer 5. A solution of 1.0 g (5.77 mmol) of **4a** and 0.7 g (5.77 mmol) of (*R*)-α-methylbenzylamine in 30 mL of benzene was heated at reflux with continuous removal of water for 6 days. The crude mixture was concentrated in vacuo and purified by column chromatography (silica gel/chloroform) to afford 0.71 g of an amber solid. Recrystallization from chloroform/hexane gave the following: mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 8.08–6.75 (m, 13, Ar H), 4.37 (s, 2, CH_2), 2.54 (s, 3, CH_3); exact mass calcd for $C_{22}H_{18}N_2$ 310.1470, found 310.1463.

General Procedure for the Preparation of *N*-α-Phenethyl-α-methyltryptamines 7a–f. A 0.25 M solution of (*R*)- or (*S*)-α-methylbenzylamine (>98% optically pure; Aldrich) in methanol was adjusted to a pH of 5–6 by the dropwise addition of glacial acetic acid. To this was added 1 equiv of the appropriate indolepropanone **4a–f**, followed by 1 molar equiv of sodium cyanoborohydride. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane saturated with aqueous ammonium hydroxide and passed through a short silica gel column. The column was washed with several portions of dichloromethane/ammonium hydroxide, and the combined eluates were concentrated in vacuo to provide the diastereomeric amine mixtures.

The diastereomers were separated in approximately 1-g portions on a 4-mm silica gel Chromatotron rotor, with dichloromethane as the eluting solvent under an ammonia/nitrogen atmosphere, produced by bubbling N_2 gas through concentrated NH_4OH, and drying (Drierite) before purging the Chromatotron chamber. In all cases studied, a clear separation of the two components could be visualized under UV light by the time collection began. Pooling fractions and solvent removal under reduced pressure afforded the pure diastereomerically related amines, which were then recrystallized from diethyl ether. Yields, melting points, R_f values, and specific rotations are summarized in Table II. NMR data and exact mass determinations for the *S,S* and *S,R* compounds are given below.

(*S,S*)-*N*-α-Phenethyl-1-indol-3-yl-2-aminopropane (*S,S*-7a): ^1H NMR ($CDCl_3$) δ 8.00 (br s, 1 H, NH), 7.30 (s, 5 H, Ph), 7.46–6.92 (m, 5 H, Ar H), 3.99 (q, 1 H, NCHPh), 3.07–2.60 (m, 3 H, CH_2CH), 1.51 (s, 1 H, NH), 1.29 (d, 3 H, $PhCCH_3$), 0.96 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{19}H_{22}N_2$ 278.1783, found 278.1778.

(*S,R*)-*N*-α-Phenethyl-1-indol-3-yl-2-aminopropane (*S,R*-7a): ^1H NMR ($CDCl_3$) δ 8.00 (br s, 1 H, NH), 7.44–6.74 (m, 10 H, Ar H), 3.88 (q, 1 H, NCHPh), 2.76 (br s, 3 H, CH_2CH), 1.63 (br s, 1 H, NH), 1.26 (d, 3 H, $PhCCH_3$), 1.08 (d, 3 H, $NCCH_3$), exact mass calcd for $C_{19}H_{22}N_2$ 278.1783, found 278.1783.

(*S,S*)-*N*-α-Phenethyl-1-(4-methoxyindol-3-yl)-2-aminopropane (*S,S*-7b): ^1H NMR ($CDCl_3$) δ 8.01 (br s, 1 H, NH), 7.28 (s, 5 H, Ph), 6.43–5.27 (m, 4 H, Ar H), 3.87 (q, 1 H, NCHPh), 3.81 (s, 3 H, OCH_3), 3.16–2.75 (m, 3 H, CH_2CH), 1.60 (br s, 1 H, NH), 1.25 (d, 3 H, $PhCCH_3$), 0.95 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1888.

(*S,R*)-*N*-α-Phenethyl-1-(4-methoxyindol-3-yl)-2-aminopropane (*S,R*-7b): ^1H NMR ($CDCl_3$) δ 8.02 (br s, 1 H, NH), 7.11–6.35 (m, 9 H, Ar H), 3.87 (q, 1 H, NCHPh), 3.63 (s, 3 H, OCH_3), 2.83 (br s, 3 H, CH_2CH), 1.73 (br s, 1 H, NH), 1.27 (d, 3 H, $PhCCH_3$), 1.03 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1885.

(*S,S*)-*N*-α-Phenethyl-1-(5-methoxyindol-3-yl)-2-aminopropane (*S,S*-7c): ^1H NMR ($CDCl_3$) δ 7.92 (br s, 1 H, NH), 7.31

Table II. Physical Data for Diastereomeric Amines **7a–f**

compd	yield,[a] %	mp, °C	R_f[b]	sp rotation,[c] deg
R,R-**7a**	43	99–100	0.40	+10.1
S,S-**7a**	54	99–101	0.40	−11.3
R,S-**7a**	19	133–136	0.27	+84.5
S,R-**7a**	36	132–135	0.27	−82.8
R,R-**7b**	43	140–142	0.45	−38.8
S,S-**7b**	47	140–141	0.45	+39.4
R,S-**7b**	19	116–118[d]	0.28	+154
S,R-**7b**	19	135–136[e]	0.28	−156
R,R-**7c**	36	90–94	0.39	+1.11
S,S-**7c**	50	92–96	0.39	−0.336
R,S-**7c**	19	115–117[e]	0.28	+118.
S,R-**7c**	24	103–104[d]	0.28	−122.
R,R-**7d**	55	92–97	0.44	+17.8
S,S-**7d**	53	94–98	0.44	−17.0
R,S-**7d**	37	106–108	0.31	+58.3
S,R-**7d**	37	105–107	0.31	−58.4
R,R-**7e**	44	167–168	0.49	−64.8
S,S-**7e**	64	166–167	0.49	+68.3
R,S-**7e**	28	204–206	0.24	+136.[f]
S,R-**7e**	35	205–206	0.24	−143.[f]
R,R-**7f**	37	112–113	0.49	+11.3
S,S-**7f**	64	109–111	0.49	−10.3
R,S-**7f**	18	136–138	0.38	+86.7
S,R-**7f**	33	138–139	0.38	−85.0

[a] From indolepropanones 4a–f. [b] Silica gel/dichloromethane/ammonia atmosphere. [c] *c* 0.5, methanol, sodium D source, 27 °C. [d] Needles [e] Plates. [f] *c* 0.25.

(s, 5 H, Ph), 7.37–6.79 (m, 4 H, Ar H), 4.01 (q, 1 H, NCHPh), 3.76 (s, 3 H, OCH_3), 3.04–2.85 (m, 2 H, CH_2CN), 2.70–2.56 (m, 1 H, CCHN), 1.61 (br s, 1 H, NH), 1.30 (d, 3 H, $PhCCH_3$), 0.96 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1888.

(*S,R*)-*N*-α-Phenethyl-1-(5-methoxyindol-3-yl)-2-aminopropane (*S,R*-7c): ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1 H, NH), 7.30–6.75 (m, 9 H, Ar H), 3.87 (q, 1 H, NCHPh), 3.72 (s, 3 H, OCH_3), 2.84–2.68 (m, 3 H, CH_2CH), 1.68 (br s, 1 H, NH), 1.25 (d, 3 H, $PhCCH_3$), 1.08 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1881.

(*S,S*)-*N*-α-Phenethyl-1-(6-methoxyindol-3-yl)-2-aminopropane (*S,S*-7d): ^1H NMR ($CDCl_3$) δ 7.86 (br s, 1 H, NH), 7.30 (s, 5 H, Ph), 7.33–6.64 (m, 4 H, Ar H), 3.97 (q, 1 H, NCHPh), 3.82 (s, 3 H, OCH_3), 3.07–2.57 (m, 3 H, CH_2CH), 1.72 (br s, 1 H, NH), 1.28 (d, 3 H, $PhCCH_3$), 0.95 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1885.

(*S,R*)-*N*-α-Phenethyl-1-(6-methoxyindol-3-yl)-2-aminopropane (*S,R*-7d): ^1H NMR ($CDCl_3$) δ 7.91 (br s, 1 H, NH), 7.28–6.62 (m, 9 H, Ar H), 3.86 (q, 1 H, NCHPh), 3.84 (s, 3 H, OCH_3), 2.73 (br s, 3 H, CH_2CH), 1.26 (d, 3 H, $PhCCH_3$), 1.07 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{20}H_{24}N_2O$ 308.1888, found 308.1888.

(*S,S*)-*N*-α-Phenethyl-1-[4-(benzyloxy)indol-3-yl]-2-aminopropane (*S,S*-7e): ^1H NMR ($CDCl_3$) δ 7.97 (br s, 1 H, NH), 7.47–6.49 (m, 14 H, Ar H), 5.11 (s, 2 H, OCH_2Ph), 3.61 (q, 1 H, PhCHN), 2.92 (br s, 3 H, CH_2CH), 1.47 (br s, 1 H, NH), 1.08 (d, 3 H, $PhCCH_3$), 0.79 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{26}H_{28}N_2O$ 384.2201, found 384.2201.

(*S,R*)-*N*-α-Phenethyl-1-[4-(benzyloxy)indol-3-yl]-2-aminopropane (*S,R*-7e): ^1H NMR ($CDCl_3$) δ 8.00 (br s, 1 H, NH), 7.43–6.40 (m, 14 H, Ar H), 4.83 (q, 2 H, OCH_2Ph), 3.76 (q, 1 H, PhCHN), 2.89–2.54 (br s, 3 H, CH_2CH), 1.64 (s, 1 H, NH), 1.17 (d, 3 H, $PhCCH_3$), 0.78 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{26}H_{28}N_2O$ 384.2201, found 384.2199.

(*S,S*)-*N*-α-Phenethyl-1-[5-(benzyloxy)indol-3-yl]-2-aminopropane (*S,S*-7f): ^1H NMR ($CDCl_3$) δ 8.11 (br s, 1 H, NH), 7.47–6.81 (m, 14 H, Ar H), 4.94 (s, 2 H, OCH_2Ph), 3.98 (q, 1 H, PhCHN), 2.93–2.41 (m, 3 H, CH_2CH), 1.62 (br s, 1, NH), 1.27 (d, 3 H, $PhCCH_3$), 0.93 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{26}H_{28}N_2O$ 384.2201, found 384.2203.

(*S,R*)-*N*-α-Phenethyl-1-[5-(benzyloxy)indol-3-yl]-2-aminopropane (*S,R*-7f): ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1 H, NH), 7.41–6.86 (m, 14 H, Ar H), 4.92 (s, 2 H, OCH_2Ph), 3.88 (q, 1 H, PhCHN), 2.73 (br s, 3 H, CH_2CH), 1.65 (br s, 1 H, NH), 1.26 (d, 3 H, $PhCCH_3$), 1.08 (d, 3 H, $NCCH_3$); exact mass calcd for $C_{26}H_{28}N_2O$ 384.2201, found 384.2195.

Table III. Physical Data for α-Methyltryptamines **1a–f**

compd	yield, %	mp, °C	sp rotation,[a] deg
R-**1a**	94	127–128	−35.3[b]
S-**1a**	87	129–130	+34.3[b]
R-**1b**	80	159–160	−56.9
S-**1b**	74	159–160	+56.6
R-**1c**	68	112–113	−34.1[c]
S-**1c**	84	111–112	+34.3[c]
R-**1d**	72	110–112	−26.7
S-**1d**	74	110–111	+27.6
R-**1e**	49	*d*	−33.3
S-**1e**	53	*d*	+33.1
R-**1f**	79	*d*	−37.7
S-**1f**	82	*d*	+35.5

[a] *c* 0.5, methanol, sodium D soource, 27 °C. [b] Literature[11]: −32.1, +34.9. [c] Literature[29]: −38.3, +33.9. [d] Amorphous solids; decompose upon heating.

General Procedure for the Preparation of α-Methyltryptamines 1a–f. To a methanolic solution of **7a–f** was added an equal weight of 20% palladium hydroxide on carbon (Pearlman's catalyst[10]). The reaction mixture was shaken under 50 psig of H_2 for 24 h. The mixture was then filtered through a pad of Celite and washed with MeOH, and the filtrate was concentrated in vacuo to afford the desired α-methyltryptamines **1a–f**, which were then recrystallized from diethyl ether. Yields, melting points, and specific rotations are provided in Table III. NMR and exact mass data for the *S* compounds are given below.

(*S*)-1-Indol-3-yl-2-aminopropane (*S*-1a): ^1H NMR ($CDCl_3$) δ 8.13 (br s, 1 H, NH), 7.67–6.99 (m, 5 H, Ar H), 3.43–2.34 (m, 3 H, $CHCH_2$), 1.46 (br s, 2 H, NH_2), 1.17 (d, 3 H, CH_3).

(*S*)-1-(4-Methoxyindol-3-yl)-2-aminopropane (*S*-1b): ^1H NMR ($CDCl_3$) δ 8.36 (br s, 1 H, NH), 7.24–6.41 (m, 4 H, Ar H), 3.90 (s, 3 H, OCH_3), 3.33–2.35 (m, 3 H, CH_2CH), 1.47 (br s, 2 H, NH_2), 1.14 (d, 3 H, CH_3); exact mass calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1216.

(*S*)-1-(5-Methoxyindol-3-yl)-2-aminopropane (*S*-1c): ^1H NMR ($CDCl_3$) δ 8.08 (br s, 1 H, NH), 7.26–6.82 (m, 4 H, Ar H), 3.85 (s, 3 H, OCH_3), 3.36–3.20 (sx, 1 H, NCH), 2.90–2.56 (m, 2 H, CH_2), 1.52 (br s, 2 H, NH_2), 1.16 (d, 3 H, CH_3); exact mass calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1262.

(*S*)-1-(6-Methoxyindol-3-yl)-2-aminopropane (*S*-1d): ^1H NMR ($CDCl_3$) δ 8.01 (br s, 1 H, NH), 7.52–6.71 (m, 4 H, Ar H), 3.84 (s, 3 H, OCH_3), 3.40–2.43 (m, 3 H, CH_2CH), 1.45 (br s, 2 H, NH_2), 1.45 (br s, 2 H, NH_2), 1.16 (d, 3 H, CH_3); exact mass calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1252.

(*S*)-1-(4-Hydroxyindol-3-yl)-2-aminopropane (*S*-1e): ^1H NMR (acetone-d_6) δ 7.93 (s, 1 H, NH), 6.91–6.29 (m, 4 H, Ar H), 3.46–2.66 (m, 6 H, CH_2CHNH_2 + OH), 1.16 (d, 3 H, CH_3); exact mass calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1107.

(*S*)-1-(5-Hydroxyindol-3-yl)-2-aminopropane (*S*-1f): ^1H NMR (acetone-d_6) δ 7.91 (s, 1 H, NH), 7.21–6.60 (m, 4 H, Ar H), 3.77 (sx, 1 H, CH), 3.16 (br s, 3 H, NH_2 + OH), 2.76 (d, 2 H, CH_2), 1.11 (d, 3 H, CH_3); exact mass calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1106.

HPLC Analysis of Optical Purity. Samples of each optically active AMT and the corresponding racemates were derivatized with 2-naphthoyl chloride in carbon tetrachloride/pyridine to form the naphthoylamides that were used for HPLC analysis. Compounds were analyzed on a "Pirkle" chiral stationary phase (25 cm × 4.6 mm i.d. covalently bound (*R*)-*N*-(3,5-dinitrobenzoyl)-phenylglycine column).[12] Conditions for the separation of the enantiomeric amides were determined for the racemic compounds and were found to be optimal when 7% ethanol in hexane at a flow rate of 2 mL/min was used. The presence of the minor enantiomer could not be detected (254 nm) in any of the optically active derivatives.

Pharmacology Methods. Radioligand Binding Studies. The tissue for the receptor-binding studies was prepared according to the procedure of Middlemiss and Fozard.[26] The frontal cortex

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region from 20 to 30 male Sprague-Dawley rats (200-250 g) was rapidly removed over ice. Tissue was homogenized in 4 volumes of 0.32 M sucrose in a Brinkman Polytron (setting 6 for 20 s). The homogenate was centrifuged (36500*g* for 10 min), and the pellet was rehomogenized in the same volume of buffer. Aliquots of 4.5 mL were removed and stored at -70 °C for up to 3 weeks.

On the day of the experiment, a tissue aliquot was thawed on ice and diluted 1 to 20 with 50 mM Tris·HCl (pH 7.7). The homogenate was centrifuged two more times at 36500*g* for 10 min. Between the second and third centrifugations, the tissue homogenate was incubated at 37.5 °C for 10 min to allow degradation of residual neurotransmitter by MAO. The final pellet was resuspended in 50 mM Tris·HCl with 0.1% ascorbic acid, 5.7 mM $CaCl_2$, and 10 μM pargyline (pH 7.7) and preincubated for 10 min at 37.5 °C.

Assays were performed in triplicate with the buffer described above to which 200-400 μg of protein was added. Saturation experiments were performed with varying concentrations of [^{3}H]serotonin to label 5-HT_{1B} binding sites and [^{3}H]ketanserin to label 5-HT_2 binding sites. Nonspecific binding was defined with 10 μM serotonin and 10 μM cinanserin for 5-HT_{1B} and 5-HT_2 sites, respectively. The amount of protein added to each tube was determined by the method of Bradford.[27] The ability of the test compounds to displace 1 nM [^{3}H]-5-HT and 0.75 nM [^{3}H]-ketanserin was examined. Tubes were incubated at 37.5 °C for 15 min and then filtered with a Brandel cell harvestor, modified for receptor binding studies, through Whatman GF/C filters, followed by two 3-s washes with ice-cold buffer. The filters were counted by liquid scintillation spectrometry at 45% efficiency.

Scatchard and competition binding data for each experiment were analyzed by a nonlinear least-squares curve-fitting procedure, as embodied in the EBDA and LIGAND software, adapted for the IBM PC by McPherson.[28] The K_d, B_{max}, and K_i values reported represent the average of two or three separate experiments, with 8-10 concentrations of displacing ligand per experiment. Analysis of variance and contrast comparisons were employed to analyze the results.

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Registry No. (*R*)-**1a**, 7795-52-0; (*S*)-**1a**, 7795-51-9; (*R*)-**1b**, 113997-82-3; (*S*)-**1b**, 113997-83-4; (*R*)-**1c**, 86138-18-3; (*S*)-**1c**, 86138-19-4; (*R*)-**1d**, 114127-44-5; (*S*)-**1d**, 114127-45-6; (*R*)-**1e**, 113997-84-5; (*S*)-**1e**, 113997-85-6; (*R*)-**1f**, 95114-42-4; (*S*)-**1f**, 95114-43-5; **2a**, 120-72-9; **2b**, 4237-90-5; **2c**, 1006-94-6; **2d**, 3189-13-7; **2e**, 20289-26-3; **2f**, 1215-59-4; (±)-**3a**, 113997-48-1; (±)-**3b**, 113997-49-2; (±)-**3c**, 113997-50-5; (±)-**3d**, 113997-51-6; (±)-**3e**, 113997-52-7; (±)-**3f**, 113997-53-8; **4a**, 1201-26-9; **4b**, 113997-54-9; **4c**, 4761-29-9; **4d**, 65109-60-6; **4e**, 113997-55-0; **4f**, 113997-56-1; **5**, 113997-57-2; (*R,R*)-**7a**, 113997-58-3; (*S,S*)-**7a**, 113997-59-4; (*R,S*)-**7a**, 113997-60-7; (*S,R*)-**7a**, 113997-61-8; (*R,R*)-**7b**, 113997-62-9; (*S,S*)-**7b**, 113997-63-0; (*R,S*)-**7b**, 113997-64-1; (*S,R*)-**7b**, 113997-65-2; (*R,R*)-**7c**, 113997-66-3; (*S,S*)-**7c**, 113997-67-4; (*R,S*)-**7c**, 113997-68-5; (*S,R*)-**7c**, 113997-69-6; (*R,R*)-**7d**, 113997-70-9; (*S,S*)-**7d**, 113997-71-0; (*R,S*)-**7d**, 113997-72-1; (*S,R*)-**7d**, 113997-73-2; (*R,R*)-**7e**, 113997-74-3; (*S,S*)-**7e**, 113997-75-4; (*R,S*)-**7e**, 113997-76-5; (*S,R*)-**7e**, 113997-77-6; (*R,R*)-**7f**, 113997-78-7; (*S,S*)-**7f**, 113997-79-8; (*R,S*)-**7f**, 113997-80-1; (*S,R*)-**7f**, 113997-81-2; (±)-$CH_3CH(NO_2)$-CH_2OH, 62742-29-4; $CH_3C(NO_2)$=CH_2, 4749-28-4; (*R*)-PhCH-$(CH_3)NH_2$, 3886-69-9; (*S*)-PhCH$(CH_3)NH_2$, 2627-86-3; phthalic anhydride, 85-44-9.

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Absolute Configurations and Pharmacological Activities of the Optical Isomers of Fluoxetine, a Selective Serotonin-Uptake Inhibitor

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Fluoxetine is a potent and selective inhibitor of the neuronal serotonin-uptake carrier and is a clinically effective antidepressant. Although fluoxetine is used therapeutically as the racemate, there appears to be a small but demonstrable stereospecificity associated with its interactions with the serotonin-uptake carrier. The goals of this study were to determine the absolute configurations of the enantiomers of fluoxetine and to examine whether the actions of fluoxetine in behavioral tests were enantiospecific. (*S*)-Fluoxetine was synthesized from (*S*)-(-)-3-chloro-1-phenylpropanol by sequential reaction with sodium iodide, methylamine, sodium hydride, and 4-fluorobenzotrifluoride. (*S*)-Fluoxetine is dextrorotatory (+1.60) in methanol, but is levorotatory (-10.85) in water. Fluoxetine enantiomers were derivatized with (*R*)-1-(1-naphthyl)ethyl isocyanate, and the resulting ureas were assayed by ^{1}H NMR or HPLC to determine optical purities of the fluoxetine samples. Both enantiomers antagonized writhing in mice; following sc administration of (*R*)- and (*S*)-fluoxetine, ED_{50} values were 15.3 and 25.7 mg/kg, respectively. Moreover, both enantiomers potentiated a subthreshold analgesic dose (0.25 mg/kg) of morphine, and ED_{50} values were 3.6 and 5.7 mg/kg, respectively. Following ip administration to mice, the two stereoisomers antagonized *p*-chloroamphetamine-induced depletion of whole brain serotonin concentrations. ED_{50} values for (*S*)- and (*R*)-fluoxetine were 1.2 and 2.1 mg/kg, respectively. The two enantiomers decreased palatability-induced ingestion following ip administration to rats; (*R*)- and (*S*)-fluoxetine reduced saccharin-induced drinking with ED_{50} values of 6.1 and 4.9 mg/kg, respectively. Thus, in all biochemical and pharmacological studies to date, the eudismic ratio for the fluoxetine enantiomers is near unity.

Drugs that modulate the physiological and pathophysiological actions of serotonin are useful or potentially useful in the treatment of a variety of human diseases, including depression, anxiety, alcoholism, chronic pain, emesis, and eating disorders such as obesity and bulimia.[1] One can manipulate actions of serotonin by using drugs that interfere with its biosynthesis, stimulate its release from presynaptic storage vesicles, occupy one or more of the serotonin receptor subtypes, antagonize enzymes responsible for catabolism of serotonin, or inhibit presynaptic reuptake of serotonin. All of these avenues have been explored in attempts to develop novel therapeutic agents and pharmacological tools.[2]

Fluoxetine (LY110140; *N*-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine) was one of the first

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