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Stereocontrolled Syntheses of Some Conformationally Restricted Analogs of Serotonin

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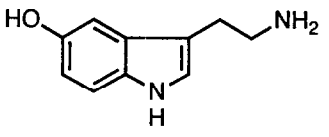
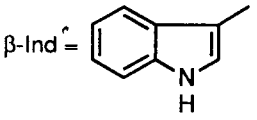
Key Words: Serotonin; restricted conformation analogs; Mitsunobu with retention; stereoselective reductive amination; dibenzylamino derivative as a source of primary amine.

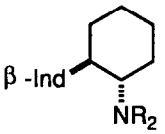
Abstract: Syntheses of serotonin analogs **2** and **3** are described including a case of retention in the Mitsunobu reaction. An unusual stereoselectivity in a reductive amination sequence is also described. Dopamine and serotonin activity of the eight analogs has been determined.

Serotonin (5-HT), **1**,[1a,b,c] and its derivatives continue to be of great interest because of their crucial role in several physiological functions,[2] e.g. anxiety, depression, behavior, feeding, sleep and sexual function. It seemed important to prepare some rigid, i.e., conformationally restricted, analogs of 5-HT (**1**), a project that also attracted the interest of Macor and Ryan.[3] We describe below the synthesis of some analogs of serotonin in which the 3-(β-aminoethyl) side chain has been incorporated into a cyclohexane ring. Both sets of diastereomers (**2** and **3**) have been prepared.

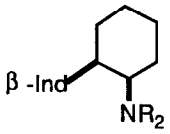


1
Serotonin (5-HT)





2 a) R=H
b) R=Me
c) R=Pr
d) R=Bz



3 a) R=H
b) R=Me
c) R=Pr
d) R=Bz

Many of the reactions proceeded in the expected manner with respect to stereochemical outcome. However, we made two notable observations: retention of configuration in a Mitsunobu conversion of an alcohol to an amine (and bromide) and stereoselectivity in reductive amination of 2-(β-indolyl)cyclohexanone.

Three procedures were employed to generate compounds **2** and **3**. The first procedure is shown in Scheme 1 and the other two are outlined in Scheme 2.

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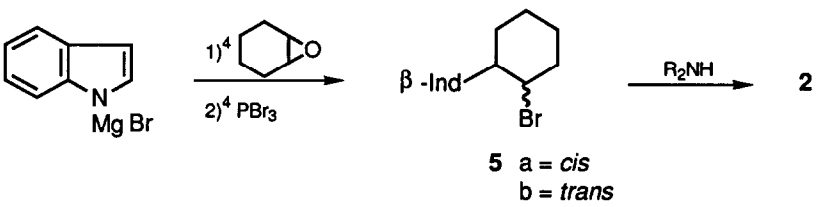
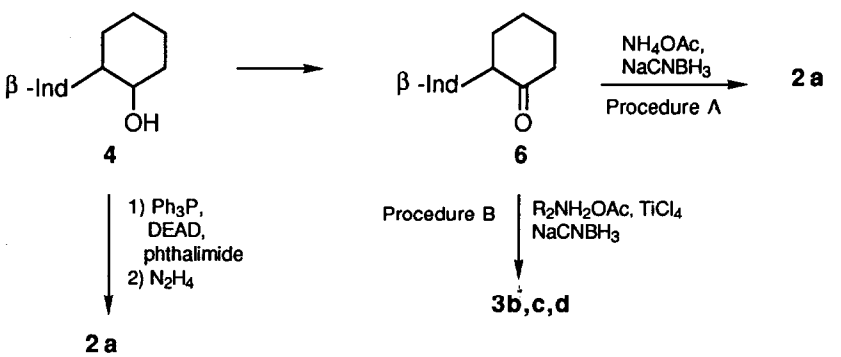
Preparation of the *trans*-series **2** was straightforward as summarized in Scheme 1. Bromide **5** had been prepared previously but without assignment of stereochemistry.[4] The phosphorus tribromide reaction might be expected to occur with inversion to yield compound **5a**. The ^1H NMR spectra of the amines prepared from **5** show them to be the *trans* compounds (Table 1) expected from S_N2 displacement of compound **5a**. However, this logical assignment proved incorrect as shown below.

Scheme 1



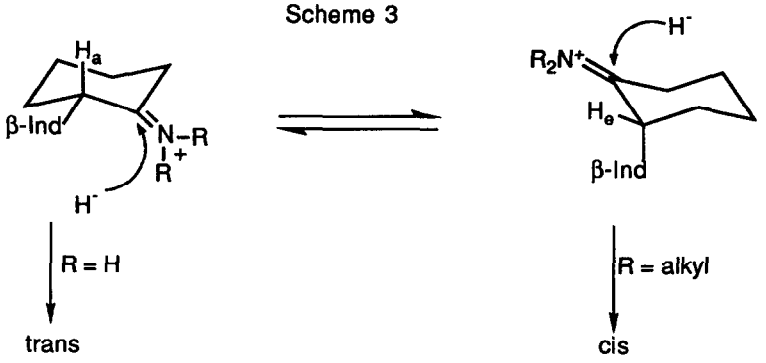
Two reductive amination procedures were applied to ketone **6** obtained by Swern oxidation[5] of alcohol **4** (Scheme 2). The usual conditions, ammonium acetate and sodium cyanoborohydride, failed to produce useful amounts of amine but, under the modified Danheiser conditions[6] (2-propanol, 3 Å molecular sieves, Procedure A, applied in two cases), predominantly *trans* amine **2a** was obtained (9:1 *trans:cis*). However, under the same conditions, dimethylammonium acetate afforded exclusively the *cis*-amine **3b**.

Scheme 2



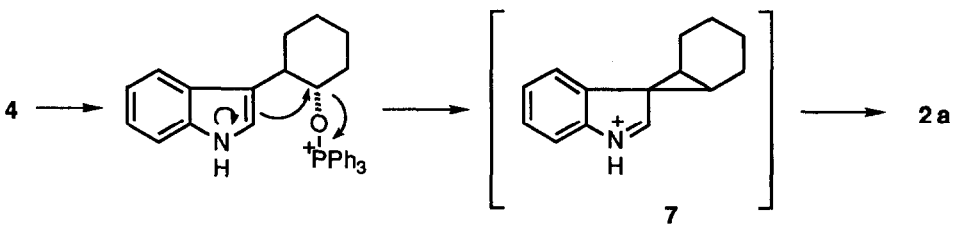
The second procedure involved conversion of the ketone to the enamine under $TiCl_4$ catalysis,[7] followed by reduction with $NaCNBH_3$ (Procedure B, applied in three cases). Again exclusively *cis* products were obtained when secondary amines were employed. We suggest that the stereochemical results we observed, i.e., *cis* products when R=Me, Pr and Bz but *trans* product when R=H, may be explained by conformational preferences of the intermediate iminium derivatives wherein the larger substituents on nitrogen force the indole group to adopt an axial position (Scheme 3).

Scheme 3



To obtain *cis* amine **3a** we attempted a Mitsunobu transformation[8] of alcohol **4**, but only *trans* amine **2a** was obtained. This unexpected retention[9] result may be explained on the basis of the intervention of the spiroindoline **7**[10] (Scheme 4). Since the conversion of alcohol **4** to bromide **5** (see Scheme 1) might well have occurred

Scheme 4



through the same intermediate, we carefully examined the NMR spectrum of a purified sample of **5**. Based upon the similarity of the coupling constants of the axially disposed methine protons (Table 1) to those of the other *trans* compounds, we conclude that **5** in Scheme 1 also has *trans* stereochemistry. Thus this conversion did not involve simple S_N2 displacement but apparently the intervention of spiroindoline **7**. Presumably the final conversion of compound **5b** to *trans* amine **2** also involves intermediate **7**.

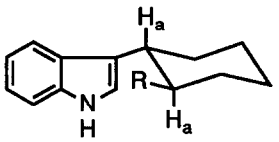
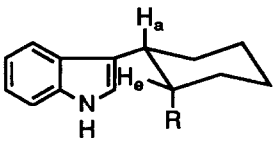
The *cis* amine **3a** was obtained ultimately by employing Goel's[11] method, making first the *cis*-dibenzylamine **3d** by reductive amination and then debenzylating using Pearlman's catalyst and ammonium formate.

Pharmacological Results.

Dopamine precursor (DOPA) and serotonin precursor (5-HTP) effects:

Using a standard protocol of biochemical assay in this study, DA agonists and antagonists produce characteristic changes in brain levels of the DA precursor, DOPA. For instance, pretreatment with the agonist apomorphine reduced DOPA while pretreatment with the antagonist haloperidol increased DOPA (data not shown). Similarly, pretreatment with the serotonin agonist 8-OH-DPAT reduced 5-HTP (data not shown); interestingly, serotonin antagonists do not effect brain levels of 5-HTP.

Table 1 Characteristic[a] NMR Spectral Data of Compounds **2**, **3**, **4** and **8**.

 trans			 cis		
Compound	^{1}H chemical shift (ppm), *J*. (Hz)		Compound	^{1}H chemical shift (ppm), *J*. (Hz)	
	H, α to R Interactions 2 a-a, 1a-e	H, α to Indole Interactions 2 a-a, 1 a-e		H, α to R Interactions 2 a-e, 1 e-e	H, α to Indole Interactions 1 a-a, 2 a-e
4 (R = OH)	3.78, (td, *J* = 10.1, 4.3, 1 H)	2.75, (m, 1 H)	...	...	...
5b (R = Br)	4.36, (td, *J* = 11.1, 4.1, 1 H)	3.14, (td, *J* = 10.1, 4.1, 1 H)	...	...	...
2a	2.98, (td, *J* = 10.5, 3.9, 1 H)	2.56, (m, 1 H)	**3a**	3.46, (q, *J* = 3.2, 1 H)	3.16, (dt, *J* = 12.1, 3.1, 1 H)
2b	3.17, (m, 1 H)[b]	2.97, (td, *J* = 11.3, 3.8, 1 H)[b]	**3b**	3.81, (q, *J* = 3.8, 1 H)	2.46, (dt, *J* = 11.8, 3.8, 1 H)
2c	2.98, (td, J = 10.9, 3.5, 1 H)[b]	2.94, (m, 1 H)[b]	**3c**	3.72, (q, *J* = 4.1, 1 H)	2.85, (dt, *J* = 11.8, 4.0, 1 H)
2d	3.06, (td, *J* = 11.3, 3.5, 1 H)	2.90, (td, *J* = 11.0, 3.1, 1 H)	**3d**	3.82, (q, *J* = 3.9, 1 H)	2.95, (m, 1 H)

[a] NMR analysis of the compounds in Table 1.

In the trans isomers the hydrogen on the cyclohexane carbon adjacent to the indole and the hydrogen on the carbon bearing the substituent R are both axial, as evidenced by the large coupling between the two (e.g. $J > 10$ Hz).

In the cis isomers in all cases the hydrogen on the carbon adjacent to the indole is axial, whereas the proton adjacent to the carbon bearing the substituent R is equatorial. This is supported by the small coupling between these two protons (e.g. $J < 4.2$ Hz).

Comparison of the hydrogens on the carbon bearing the substituent R in the trans and cis series reveals that the chemical shift of this hydrogen in the cis series (equatorial) is always at a higher field than the trans (axial) series. This is in accord with literature observations in the case of many cyclohexane derivatives.

[b] Determined on Bruker 500 MHz spectrometer in $CDCl_3$ solution.

The activities of the rigid analogues of serotonin in this assay are shown in Table 2. Activity was found only in the case of the *cis* isomers. Among *cis* isomers, dopamine and serotonin agonist activity was found in the dimethyl analogue (**3b**) i.e. in the case of compound **3b** DOPA decreased (-37.8%) indicating dopamine agonist activity and 5-HTP decreased (-20.9%) indicating serotonin agonist activity. Increasing the alkyl chain length to propyl and benzyl (**3c** and **3d**, respectively) resulted in the complete loss of both activities. Elimination of the alkyl chain led to the primary amine (**3a**) and resulted in the loss of serotonin agonist activity, but the dopamine agonist activity was retained (DOPA decreased by 22.8% from control).

Experimental Section

General. All reactions were carried out in a nitrogen atmosphere. Melting points were taken in a Thomas Hoover apparatus, and are uncorrected. All of the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Product purities were routinely checked by TLC. Preparative layer chromatography (PLC) was done with silica gel 60 HF_{254} (E. Merck). Drying of organic layer was done with sodium sulfate. Flash chromatography was done using silica gel (60-200 Mesh) under nitrogen. DMSO and CH_2Cl_2 were dried and distilled over CaH_2, and THF was dried over benzophenone ketyl. Other commercial reagents and solvents were used without further purification.

200 MHz ^1H NMR spectra were recorded on a Magnachem instrument, 300 MHz ^1H NMR and 75.6 MHz ^{13}C NMR spectra were obtained on a GN 300 spectrometer and 500 MHz spectra were run on a Bruker instrument in $CDCl_3$ solution. Peak positions are indicated in ppm downfield from internal TMS in δ units. IR spectra were recorded on a Perkin-Elmer 1420 Ratio Recording IR spectrophotometer. Mass spectra were obtained on a MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers. Elemental analyses were performed by The Upjohn Company.

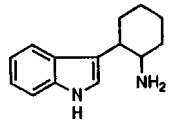
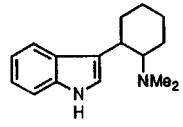
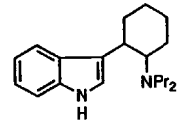
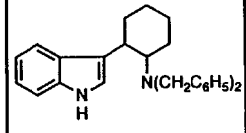
***trans*-3-(2-Hydroxycyclohexyl)indole (4).**

To a well-stirred solution of indole (10 g, 85.4 mmol) in Et_2O (30 ml) under nitrogen was added dropwise a solution of methyl magnesium bromide (3.0 M, 29 ml, 87 mmol) at room temperature. The rate of addition was adjusted to maintain a gentle reflux. After completion of the addition, the resulting solution was stirred another 45 min at room temperature. A solution of cyclohexene oxide (8.5 g, 87 mmol) in Et_2O (20 ml) was then added dropwise, and the suspension was left stirring overnight (12 h). The reaction was quenched slowly by the dropwise addition of a saturated solution of $NaHCO_3$ (100 ml), filtered and the white precipitate was washed repeatedly with EtOAc (4x50 ml). The combined organic layer was dried and evaporated under reduced pressure to leave a yellowish white solid. This was crystallized from EtOAc/hexane to give **4** (12g, 65%): mp 160-62 °C (lit.[4] mp 157 °C); ^1H NMR (300 MHz) δ 1.31-2.31 (m, 9 H), 2.75 (m, 1 H), 3.78 (td, J = 10.1 Hz, 4.3 Hz, 1 H), 7.09 (d, J = 2.4 Hz, 1 H), 7.10-7.25 (m, 2 H), 7.39 (d, J = 8.1 Hz, 1 H),7.74 (d, J = 7.9 Hz, 1 H), 8.14 (br s, 1 H).

***trans*-3-(2-Bromocyclohexyl)indole (5b).**

To a stirred suspension of indolylcyclohexanol (**4**) (4 g, 18.5 mmol) in CH_2Cl_2 (130 ml) was added dropwise a solution of phosphorus tribromide (1.79 ml, 18.9 mmol) in CH_2Cl_2 (20 ml). The resulting clear solution was then allowed to stir for 5 h while the bath temperature slowly raised to 20 °C. The reaction mixture was then poured into 100 g of crushed ice, and the separated aquous layer was extracted with CH_2Cl_2 (2x25 ml). The combined organic extract was washed with aqueous Na_2CO_3 (5%, 50 ml), brine (50 ml) and dried.

Table 2. Structure activity relationships of rigid analogues of serotonin in the catechol indole assay.

Structure								
Stereoisomerism	Cis	Trans	Cis	Trans	Cis	Trans	Cis	Trans
Compound	3a	2a	3b	2b	3c	2c	3d	2d
DOPA % Change From Control	-22.8*	5.3	-37.8*	6.8	-15.8	-10.0	-10.1	-7.4
5-HTP % Change From Control	-2.7	16.6	-20.9*	-2.0	-5.1	-5.9	-5.3	-1.1
Dopamine Activity	Agonist	N.S.	Agonist	N.S.	N.S.	N.S.	N.S.	N.S.
5-HT Activity	N.S.	N.S.	Agonist	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = Not Significant
*$p<0.05$

This crude product, which was reported previously[4], was directly used for the next step. However, one batch of bromide was purified through flash chromatography over silica gel using 5% EtOAc/hexane to obtain a pure sample of **5** as an oil (4.5 g, 88%) for analysis. ^{1}H NMR (300MHz) δ 1.25-2.15 (m, 7 H), 2.50 (m, 1 H), 3.14 (td, J = 10.1, 4.1 Hz, 1 H), 4.36 (td, J = 11.1, 4.1 Hz, 1 H), 6.83 (d, J = 2.4 Hz, 1 H), 7.05-7.23 (m, 3 H), 7.64 (d, J = 7.1 Hz, 1 H), 7.71 (br s, 1 H); ^{13}C NMR δ 25.81, 27.39, 35.21, 38.94, 44.98, 58.77, 111.31, 119.02, 119.09, 119.61, 120.96, 121.67, 126.36, 135.98; HRMS (EI) Calcd. for $C_{14}H_{16}BrN$: 277.0467. Found: 277.0470.

General procedure for the synthesis of *trans* amines from bromide 5b.

The bromide **5b** (1.0g, 3.6mmol) was combined in a pre-cooled autoclave with condensed ammonia or secondary amines (5-10 ml). The sealed autoclave was then heated (80-145 °C) for 15 h. The reaction mixture was cooled, the excess ammonia or the amine was evaporated when possible, and the residue was dissolved in $CHCl_3$ (30-50 ml). The $CHCl_3$ solution was washed once with water and extracted with 10% HCl (50 ml). The acid extract was basified with solid Na_2CO_3 and extracted with CH_2Cl_2 (3x25 ml). The CH_2Cl_2 extract was dried and concentrated in vacuo. The crude products were further purified by recrystallization or chromatography.

***trans*-3-(2-Aminocyclohexyl)indole (2a).**

The crude product after crystallization from benzene afforded **2a** (39%) as a white solid: mp 175-76 °C; ^{1}H NMR (300 MHz) δ 1.20-2.10 (m, 10 H), 2.56 (m, 1 H), 2.98 (td, J = 10.5, 3.9 Hz, 1 H), 7.06 (d, J = 2.3 Hz, 1 H), 7.08-7.22 (m, 2 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.73 (d, J = 7.6 Hz, 1 H), 8.09 (m, 1H); MS(EI) m/z at 214 (M^+); Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.54; H, 8.43; N, 12.96.

***trans*-3-(2-Dimethylaminocyclohexyl)indole (2b).**

The product was purified by crystallization from Et_2O/MeOH to give **2b** (64%) as a white solid: mp 147-49 °C; ^{1}H NMR (500 MHz) δ 1.29-1.49 (m, 3 H), 1.65-1.81 (m, 2 H), 1.91-2.05 (m, 2 H), 2.28 (m containing one s at 2.29, 7 H), 2.97 (td, J = 11.3 Hz, 1 H), 3.17 (m, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 7.06-7.14 (m, 2 H), 7.27 (dd, J = 8.0, 0.9 Hz, 1 H), 7.62 (dd, J = 7.9, 1.0 Hz, 1 H), 8.31 (br s, 1 H); MS(EI) m/z at 242 (M^+); Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.19; H, 9.19; N,11.19.

***trans*-3-(2-Dipropylaminocyclohexyl)indole (2c).**

The crude product was flash chromatographed using 10% EtOAc in hexane to give **2c** (40%) as an oil: ^{1}H NMR (500MHz) δ 0.6 (t, 6 h), 1.1-1.18 (m, 2 H), 1.2-1.45 (m, 6 H), 1.62-1.7 (m, 1 H), 1.75-1.8 (m, 1 H), 1.9-1.98 (m, 1 H), 2.0-2.1 (m, 2 H), 2.25-2.4 (m, 4 H), 2.90-3.0 (m, 2 H), 7.0-7.7 (m, 5 H), 7.9 (s, 1H, NH); ^{13}C NMR δ 11.58, 22.32, 26.53, 26.57, 26.95, 35.86, 39.40, 52.18, 63.55, 110.92, 118.47, 119.49, 120.79, 121.08, 121.14, 127.35, 136.24; HRMS (FAB) Calcd for $C_{20}H_{30}N_2$: 299.2487. Found: 299.2484. Anal. Calcd for $C_{20}H_{31}N_2Cl$. $1.1H_2O$: C, 67.72; H, 9.43; N, 7.90. Found: C, 67.35; H, 8.96; N, 7.79

***trans*-3-(2-Dibenzylaminocyclohexyl)indole (2d).**

The residue after usual work up was distilled in vacuo (160 °C/1mmHg) to remove most of the dibenzylamine, and the remaining oil was chromatographed over silica gel using 10% EtOAc/hexane to give **2d** an oil (51%): ^{1}H NMR (300 MHz) δ 1.19-2.01 (m, 7 H), 2.19 (m, 1 H), 2.90 (td, J = 11.0, 3.1 Hz, 1 H), 3.06 (td, J = 11.3, 3.5 Hz, 1 H), 3.39 (d, J = 13.6 Hz, 2 H), 3.67 (d, J = 13.6 Hz, 2 H), 6.64 (d, J = 2.3 Hz, 1 H), 6.85-6.98 (m, 5 H), 7.03-7.19 (m, 7 H), 7.35-7.42 (m, 2 H), 7.85 (br s, 1H); HRMS (EI) Calcd for

$C_{28}H_{30}N_2$: 394.2409. Found: 394.2396. Anal. Calcd for $C_{28}H_{31}N_2Cl.0.5\ H_2O$: C, 76.43; H, 7.33; N, 6.37. Found: C, 76.20; H, 7.80; N, 6.05.

3-(2-Oxocyclohexyl)indole (6).

A CH_2Cl_2 solution of oxalyl chloride (2M, 11 ml, 22 mmol) was diluted with CH_2Cl_2 (25 ml) and cooled to -78 °C. To the above solution, a CH_2Cl_2 (10 ml) solution of DMSO (3.4 ml, 48 mmol) was added dropwise with stirring. The solution was stirred for another 30 min at -78 °C under nitrogen. A solution of alcohol **4** (2.15 g, 10 mmol) in the minimum amount of CH_2Cl_2-DMSO was then dropwise added to the reaction mixture, and left stirring for 1h at -78 °C. Triethylamine (7 ml, 50 mmol) was added and the reaction mixture was slowly warmed to room temperature. The reaction mixture was diluted with water (100 ml), and the aqueous layer extracted with CH_2Cl_2 (2x50 ml). The combined organic layer was washed with brine (100 ml), dried and evaporated under reduced pressure to provide **6** as a colorless oil which solidified on standing (1.7 g, 80%): mp 122-23 °C (lit.[5a] mp 127 °C); ^{1}H NMR δ 1.80-2.65 (m, 9 H), 3.89 (q, J = 6 Hz, 1 H), 6.89 (d, J = 2 Hz, 1 H), 7.02-7.24 (m,3 H), 7.43 (d, J = 6 Hz, 1 H), 8.16 (s, 1 H); ^{13}C NMR (75.6 MHz) δ 26.0, 28.0, 35.0, 42.0, 58.5, 111.8, 113.0, 115.8, 119.0, 121.8, 122.1, 127.2, 136.5, 211.3; IR 1718, 1640 cm^{-1}; MS (EI) m/z at 213 (M^+). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.63; H, 7.01; N, 6.46.

***cis*-3-(2-Dimethylaminocyclohexyl)indole (3b): Procedure A.**

The ketone **6** (100 mg, 0.47 mmol), sodium cyanoborohydride (30 mg, 0.47 mmol), Me_2NH_2OAc (494 mg, 4.7 mmol), powdered 3-Å molecular sieves (150 mg), and 4 mL of 2-propanol were placed in a 10-mL round bottom flask under nitrogen. The resulting suspension was stirred for 72 h at room temp . The reaction mixture was then filtered washing with methanol (20 mL). The filtrate was concentrated to get an oil which was dissolved in 20 mL of CH_2Cl_2 . The CH_2Cl_2 solution was washed with 15% aqueous NaOH . The aqueous phase was extracted once with CH_2Cl_2 (10 mL), and the combined organic phase was washed with water (10 mL) followed by brine (10 mL) and dried. Removal of solvent afforded **3b** (62%) which was crystallized from methanol: mp 207-8 °C; ^{1}H NMR (300 MHz, Varian) δ 1.45-2.05 (m, 8 H), 2.18 (s, 6 H), 2.46 (dt, J = 11.8, 3.8 Hz, 1 H), 3.81 (q, J = 3.8 Hz, 1 H), 6.98-7.11 (m, 2 H), 7.32 (s, 1 H), 7.34 (d, J = 7.3 Hz, 1 H), 7.55 (d, J = 7.5 Hz, 1 H); MS (EI) m/z at 242 (M^+). Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.42; H, 9.34; N, 11.35.

***trans*-3-(2-Aminocyclohexyl)indole (2a): Procedure A.**

The ketone **6** (380 mg, 1.78 mmol), sodium cyanoborohydride (112 mg, 1.78 mmol), NH_4OAc (1.38 g, 18 mmol), powdered 3-Å molecular sieves, and 2-propanol (10 mL) was charged in a 25 mL round bottom flask. The resulting suspension was left stirring for 72 h under nitrogen. Usual work up as above afforded the amine **2a** as a white solid (340 mg, 89%).

Analysis of the ^{1}H NMR spectrum showed it to be predominantly the *trans* compound **2a** containing <10% of the *cis* isomer **3a**.

General Procedure for the reductive amination of ketone 5 with hindered amines using $TiCl_4$: Procedure B.

A solution of the ketone **6** (1 mmol) and the secondary amines (3 mmol) in CH_2Cl_2 (10 ml) was cooled to 0 °C. To the above, a solution (~0.1 M) of $TiCl_4$ (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise via a syringe. The dark color reaction mixture was slowly brought to room temperature and left stirring under nitrogen for 3 h. This was then treated with a solution of $NaCNBH_3$ (4 mmol) in 2-propanol (10 ml), and the

light brown solution was stirred for another 12 h. The reaction mixture was then quenched with the addition of water (1 ml), and the precipitate so formed was filtered and washed with EtOH. The filtrate was concentrated in vacuo to leave a viscous material. This crude product was dissolved in CH_2Cl_2 (30 ml) and washed with brine, dried and concentrated.

***cis*-3-(2-Dimethylaminocyclohexyl)indole (3b).**

Evaporation of solvent left a solid (96%) which was identical (mp; ^{1}H NMR)with **3b** obtained from Procedure A.

***cis*-3-(2-Dipropylaminocyclohexyl)indole (3c).**

Evaporation of the solvent and the excess amine left a solid mass. This was crystallised from hexane/Et_2O to give white crystals of **3c** (92%): mp103-5 °C; ^{1}H NMR (300 MHz) δ0.68 (t, J = 7.3 Hz, 6 H), 1.22-1.45 (m, 6 H), 1.62-2.02 (m, 6 H), 2.22-2.43 (m, 4 H), 2.85 (dt, J = 11.8, 4.0 Hz, 1 H), 3.72 (q, J = 4.1 Hz, 1 H), 7.06-7.18 (m, 2 H), 7.29 (d, J = 2.3 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.66 (d, J = 7.8 Hz, 1 H), 8.29 (br s, 1 H); ^{13}C NMR (75.6 MHz) d 11.81, 20.27, 21.57, 26.22, 26.60, 32.18, 33.72, 52.11, 62.50, 110.77, 116.50, 118.66, 119.13, 121.37, 123.08, 128.29, 135.43. Anal. Calcd for $C_{20}H_{30}N_2$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.11; H, 10.48; N, 9.21.

***cis*-3-(2-Dibenzylaminocyclohexyl)indole (3d).**

The residual oil after evaporation of solvent was flash chromatographed over silica gel using 20% EtOAc/Hexane as eluent to afford **3d** (96%) as an oil: ^{1}H NMR (300 MHz) δ 1.22-1.87 (m, 8 H), 2.95 (m, 1 H), 3.34 (d, J = 14.0, 2 H), 3.54 (d, J = 14.0 Hz, 2 H), 3.82 (q, J = 3.9 Hz, 1 H), 7.02-7.27 (m, 14 H), 7.66-7.85 (m, 2 H); HRMS (EI) Calcd for $C_{28}H_{30}N_2$: 394.2409. Found: 394.2415.

The hydrochloride was prepared with ethereal HCl. The resulting white solid was filtered and washed repeatedly with anhydrous Et_2O. The hydrochloride was further purified by crystallization from 2-propanol/Et_2O to get an analytically pure sample: mp 235-7 °C; Anal. Calcd for $C_{28}H_{31}N_2Cl$: C, 78.03; H, 7.25; N, 6.50; Cl, 8.23. Found: C, 77.74; H, 7.50; N, 6.38; Cl, 7.65.

Mitsunobu reaction on alcohol 4.

A 100 mL flask was charged with triphenylphosphine(1.31 g, 5 mmol), phthalimide (0.735 g, 5mmol) and THF (20 mL). To the above solution, the alcohol (1.1 g, 5 mmol) in THF (10 mL) and diethyl azodicarboxylate (0.87 g, 5 mmol) in THF (10 mL) were simultaneously added from two addition funnels with stirring over 10 min. The yellow reaction mixture was allowed to stir at room temperature for 2 days. The solvent was then removed and the solid mass was taken in MeOH (15 mL). Then N_2H_4 (0.32mL, 10 mmol) was added to it , and the mixture was refluxed for 4 h. The reaction mixture was cooled and, after addition of a solution of HCl (0.7 mL) in MeOH (2.3 mL), it was again refluxed overnight. The reaction mixture was completely acidified and extracted with CH_2Cl_2 (2x10 mL) to remove any neutral material. The acidic aqueous part was basified and reextracted with CH_2Cl_2. The organic layer was dried and evaporated to give an oil. This oil was chromatographed over silica gel using $CHCl_3$/MeOH/NH_4OH (95:4:1) to afford a solid which was crystallised from MeOH to give the trans amine **2a** (215 mg, 20%) identical (^{1}H NMR) to the sample obtained above.

***cis*-3-(2-Aminocyclohexyl)indole (3a).**

Pearlman's catalyst (10% $Pd(OH)_2$/C, 50 mg), **3d** hydrochloride (240 mg, 0.56 mmol) and HCO_2NH_4 (141 mg, 2.24 mmol) was added to MeOH (5 mL). The resulting suspension was refluxed with stirring for 2 h. The reaction mixture was allowed to cool , and filtered through Celite. The filtrate was evaporated, and the

resulting oil was basified with 1M NaOH (10 mL). The free amine was extracted with CH_2Cl_2 (3X20 mL). The CH_2Cl_2 layer was washed with brine, dried and evaporated to give **3a** free from any other impurities. This was further purified through crystallization from $CHCl_3/Et_2O$ to furnish pure sample of **3a** (110 mg, 92%): mp 150-2 °C; ^1H NMR (300 MHz) δ 0.85-1.99 (m, 10 H), 3.18 (dt, J = 12.1, 3.1 Hz, 1 H), 3.46 (q, J = 3.2 Hz, 1 H), 6.91 (d, J = 1.5 Hz, 1 H), 7.06-7.19 (m, 2 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 8.72 (br s, 1 H); ^{13}C NMR δ 19.99, 25.05, 26.27, 32.72, 39.31, 49.23, 111.12, 118.96, 121.28, 121.84, 126.73, 136.43; HRMS (EI) Calcd for $C_{14}H_{18}N_2$: 214.1470. Found: 214.1478; Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.37; H, 8.58; N, 13.05.

Pharmacological Methods.

3,4-Dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan (5-HTP) measurements:

Brain levels of DOPA and 5-HTP in rat were determined as described previously.[12] Briefly, Upjohn Sprague-Dawley rats were injected s.c. with test drug (10 mg/kg) or vehicle at time zero. Fifteen minutes later rats received an aromatic decarboxylase inhibitor (NSD 1015 at 100 mg/kg, i.p.). The rats were sacrificed 30 minutes later, and tissues were weighed and extracted in perchloric acid containing an internal standard. The extract was then injected onto an ODS column, and DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima software. Biochemical differences were compared between a control (n=6) and a test group (n=6) by unpaired t-test.

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