# SYNTHESIS OF SOME CONFORMATIONALLY RESTRICTED ANALOGS OF SEROTONIN

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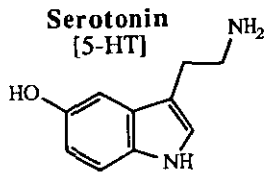
**Abstract** - 3-(2-Aminocycloalkyl)-5-methoxyindoles (**3**) have been synthesized via a three step procedure starting with 5-methoxyindole. These molecules represent conformationally restricted analogs of serotonin.

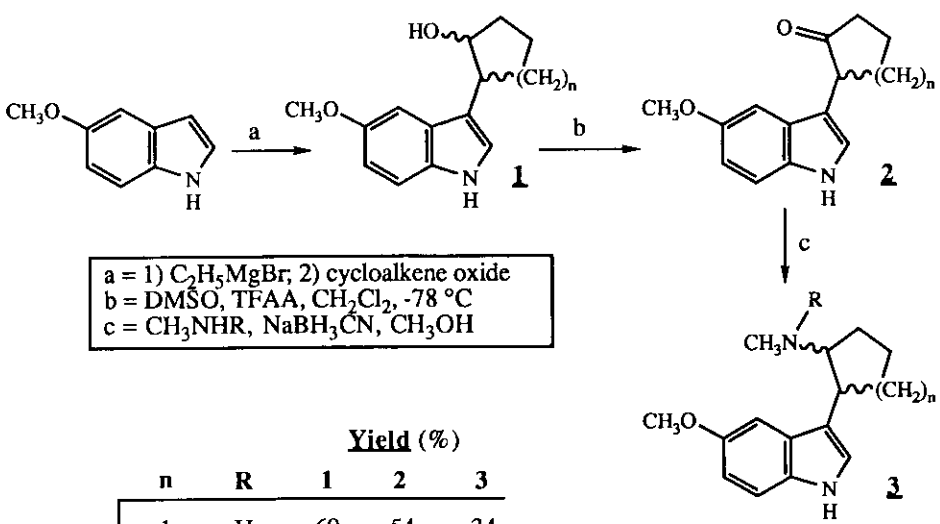
The synthesis of conformationally restricted analogs of biologically relevant molecules represents an important approach towards understanding the molecular recognition requirements of the receptor or enzyme which binds those molecules. This is especially applicable when the ligand under study binds to a number of similar receptors. By synthesizing direct analogs of the ligand in structurally rigid frameworks, and studying these compounds *in vitro*, subtle differences in the requirements for ligand binding between the different receptors can be understood. This avenue of research may eventually lead to important new pharmaceuticals with unparalleled selectivity and, consequently, fewer side-effects. Additionally, selective ligands for specific receptors/enzymes have been modified to incorporate either a radio- or photoaffinity label, and these compounds become important tools in the localization and isolation of receptors/enzymes.[1]

The serotonin [5-hydroxytryptamine (5-HT)] family of central nervous system (CNS) receptors has been divided into three groups of receptors designated as 5-$HT_1$, 5-$HT_2$, and 5-$HT_3$ receptors.[2] The 5-$HT_1$ group of serotonin receptors has been further subdivided into four receptor subtypes: 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1C}$, and 5-$HT_{1D}$. Only two of these receptors have truly specific agonists: 8-OH-DPAT [(8-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin][3] for the 5-$HT_{1A}$ receptor and CP-93129 [3-(1,2,5,6-tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one][4] for the 5-$HT_{1B}$ receptor. Since serotonin appears to play a role in depression, anxiety, feeding behavior, sleep, and



sexual function,[5] a clear understanding of the molecular recognition requirements of the individual serotonergic receptors would be desirable. This may be accomplished through the synthesis of conformationally restricted analogs of serotonin. This paper details the synthesis of a series of serotonin analogs with the 3-ethylamino sidechain conformationally restricted.

The incorporation of a cycloalkyl ring into the serotonin aminoethyl sidechain would limit the rotational freedom of that sidechain, thus creating semi-rigid molecules with more easily defined areas for potential receptor/ligand interactions. The synthesis of this series of compounds is outlined below. Since indoles react with epoxides at C3,[6] reaction of the magnesium salt of 5-methoxyindole with cyclopentene oxide and cyclohexene oxide at room temperature afforded the desired 3-(*trans*-2-hydroxycycloalkyl)-5-methoxyindoles (**1**)[7] in moderate yield. This reaction was run in both anhydrous tetrahydrofuran and anhydrous ether, and while both solvents are acceptable, use of ether appears to consistently afford a higher yield of **1**. Since a significant decrease in the yield of this reaction was seen when the crude reaction mixture was not immediately chromatographed, one day purification was essential to achieve the reported yields. However, these alcohols (**1**) are stable in their crystalline solid form.




| | | | Yield (%) | | |
|---|---|---|---|---|---|
| | n | R | 1 | 2 | 3 |
| a | 1 | H | 69 | 54 | 34 |
| b | 2 | H | 64 | 55 | 44 |
| c | 1 | $CH_3$ | -- | -- | 48 |
| d | 2 | $CH_3$ | -- | -- | 51 |

Straightforward Swern oxidation[8] led to the 3-(2-oxocycloalkyl)-5-methoxyindoles (**2**) in moderate yields (approximately 50%). Reductive amination of **2** proved to be troublesome. Using standard methods (i.e. amine hydrochloride, $NaBH_3CN$), only low yields of the desired amines were isolated from the reactions. In addition to recovered starting ketone, the major by-product was the alcohol (**1**). Other reductive amination procedures (i.e. amine, $TiCl_4$, $NaBH_4$) also gave disappointing results. Finally, use of unbuffered conditions in the reductive amination (i.e. excess free base amine in absolute methanol with $NaBH_3CN$ at room temperature) afforded reasonable yields of the desired targets (**3**). It is interesting to note that use of dimethylamine led to only the *cis* diastereomer (as seen by $^1H$ nmr)[9] in the cases of **3c** and **3d**, while use of monomethylamine led to mixtures of *cis* and *trans* diastereomers in the cases of **3a** and **3b** (as seen by $^1H$ nmr).[10] With rigorous column chromatography, the diastereomers of **3a** and **3b** were separable.

Only the *trans* diastereomers (as seen by $^1H$ nmr)[7] of the alcohols (**1**) were isolated from the reaction of the indole magnesium salt on the cycloalkene oxides. This diastereoselectivity was presumably a result of $S_N2$ attack of C3 of the indole on the epoxides. Therefore, a stereochemically controlled replacement of -OH for -$NR_2$ would yield stereogenically defined, conformationally restricted analogs of serotonin. Specifically, standard Mitsunobu[11] replacement of -OH for -$NR_2$ (phthalimide) with inversion was attempted to generate the *cis* diastereomer of our desired series of compounds. Unfortunately, this approach failed, and no other diastereoselective approaches were attempted.

The conformationally restricted analogs of serotonin (**3**) did not show any appreciable affinity for serotonin (5-HT) receptors in standard serotonin *in vitro* binding assays. We are presently studying whether these results indicate that **3** possesses the wrong directionality for interaction or whether the added steric bulk of the serotonin analogs (**3**) inhibits binding. This study will include further syntheses of other conformationally restricted analogs of serotonin.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer IR-283B Infrared Spectrophotometer, and nmr spectra were obtained on either a Bruker AM-300 (300 MHz) or a Varian XL300 (300 MHz) spectrometer. Nmr data are reported in parts per million ($\delta$) and are referenced to the deuterium lock signal

from the sample solvent. Low resolution mass spectra were obtained on a Finnigan 4310 instrument; high resolution mass spectra were obtained on a AEI MS-30 instrument. Elemental analyses were performed at Central Research Division, Pfizer, Inc., Groton, CT. and at Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich Gold Label tetrahydrofuran (THF) and diisopropylamine. General procedures listed here represent typical reaction procedures for the class of compounds described. Column chromatography was performed using 32-63 μm silica gel and was executed under nitrogen pressure (flash chromatography) conditions. Room temperature (rt) refers to 20 - 25° C.

General Synthesis of 3-(2-Hydroxycycloalkyl)-5-methoxyindoles (**1**). To a stirred solution of 5-methoxyindole (5.07 g, 34.45 mmol) in anhydrous ether (15 ml) at rt was added a solution of ethyl magnesium bromide (3.0 M, 11.5 ml, 34.5 mmol, 1 eq.) dropwise under nitrogen allowing the reaction solution to gently reflux. The resulting dark colored solution was stirred at rt under nitrogen for 45 min. Then a solution of the cycloalkene oxide (34.5 mmol, 1 eq.) in anhydrous ether (10 ml) was added dropwise (slight exotherm), and the resulting reaction mixture was stirred at rt under nitrogen overnight. A saturated solution of sodium bicarbonate (50 ml) was then added to the reaction mixture, and this aqueous mixture was extracted with ethyl acetate (2 x 50 ml). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was column chromatographed (300 g silica gel) eluting with 35-40% ethyl acetate in hexane to afford **1** as a white solid.

3-(2-Hydroxycyclopentyl)-5-methoxyindole (**1a**). Cyclopentene oxide was used in the reaction. **1a** (69%) was isolated as a white solid: mp, 124.0-126.0° C; ir (KBr) 3460, 3260, 1625, 1585, 1490, 1470, 1445, 1210 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ 8.01 (br s, 1H), 7.21 (d, J=8.8 Hz, 1H), 7.14 (d, J=2.3 Hz, 1H), 6.94 (d, J=2.4 Hz, 1H), 6.86 (dd, J=2.4 and 8.8 Hz, 1H), 4.29 (br q, J=6.6 Hz, 1H), 3.85 (s, 3H), 3.14 (br q, J=7.7 Hz, 1H), 2.25-2.04 (m, 2H), 1.96-1.65 (m, 5H); $^{13}C$ nmr ($CDCl_3$) δ 153.8, 131.9, 127.6, 121.3, 117.6, 112.1, 111.9, 101.6, 79.4, 56.0, 45.7, 33.8, 30.4, 21.7; lrms, m/z (relative intensity) 232 (24), 231 ($M^+$, 83), 186 (58), 174 (28), 161 (54), 160 (100), 130 (28); hrms calcd for $C_{14}H_{17}NO_2$ 231.1260, found 231.12163 (5.2 ppm deviation, 5 scans). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.47; H, 7.43; N, 6.00.

3-(2-Hydroxycyclohexyl)-5-methoxyindole (**1b**). Cyclohexene oxide was used in the reaction. **1b** (64%) was isolated as a white solid: mp, 119.0-122.0° C; ir ($CHCl_3$) 3565, 3470, 1625, 1585, 1480, 1450 $cm^{-1}$;

$^1$H nmr ($CDCl_3$) δ 8.22 (br s, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.13 (d, J=2.2 Hz, 1H), 6.98 (d, J=2.2 Hz, 1H), 6.85 (dd, J=2.1 and 8.9 Hz, 1H), 3.85 (s, 3H), 3.76-3.66 (m, 1H), 2.71 (ddd, J=6.5, 5.2, and 1.8 Hz, 1H), 2.18-2.11 (m, 1H), 2.00-1.30 (m, 8H); $^{13}$C nmr ($CDCl_3$) δ 153.9, 131.8, 127.6, 122.1, 117.3, 112.4, 112.0, 101.4, 75.0, 56.1, 44.3, 34.3, 32.6, 26.3, 25.1; lrms, m/z (relative intensity) 246 (39), 245 ($M^+$, 99), 186 (80), 173 (35), 160 (100), 130 (33); Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.03; H, 8.07; N, 5.43.

General Synthesis of 5-Methoxy-3-(2-oxocycloalkyl)indoles (2). Trifluoroacetic anhydride (5.72 ml, 40.4 mmol, 1.5 eq.) was added to a solution of dimethyl sulfoxide (3.8 ml, 54 mmol, 2 eq.) in methylene chloride (50 ml) at -78° C under nitrogen, and this solution was stirred at -78° C under nitrogen for 30 min. To this reaction mixture was added a solution of **1** (27.0 mmol) in anhydrous tetrahydrofuran dropwise slowly, and the resultant reaction mixture was stirred at -78° C under nitrogen for 1 h. Triethylamine (11.3 ml, 81.1 mmol, 3 eq.) was added to the reaction, and then it was allowed to warm to rt. Water (150 ml) was added, and this aqueous mixture was extracted with methylene chloride ( 2 x 100 ml). The organic extracts were combined, back extracted with brine (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was column chromatographed (250 g silica gel) eluting with 30% ethyl acetate in hexane to afford **2**.

5-Methoxy-3-(2-oxocyclopentyl)indole (2a). Trituration of the chromatographic residue in ether/hexane afforded **2a** (54%) as a pale yellow amorphous powder; mp, 115-123° C; ir (KBr) 1730, 1690, 1625, 1585, 1485, 1460, 1440, 1215; $^1$H nmr (DMSO-$d_6$) δ 10.8 (br s, 1H), 7.24 (d, J=8.8 Hz, 1H), 7.11 (d, J=2.4 Hz, 1H), 6.95 (d, J=2.4 Hz, 1H), 6.74 (dd, J=2.4 and 8.7 Hz, 1H), 3.75 (s, 3H), 3.61-3.55 (m, 1H), 2.44-2.32 (m, 3H), 2.14-1.87 (m, 3H). $^{13}$C nmr (DMSO-$d_6$) δ 218.0, 153.0, 131.5, 127.2, 123.3, 112.0, 111.9, 111.0, 101.1, 55.4, 46.4, 37.6, 30.8, 20.7; lrms, m/z (relative intensity) 230 (26), 229 ($M^+$, 79), 173 (100), 158 (52), 130 (49). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.04; H, 6.51; N, 6.00.

5-Methoxy-3-(2-oxocyclohexyl)indole (2b). **2b** was isolated as an oil (55%); ir ($CHCl_3$) 1708, 1625, 1586, 1480, 1450 cm$^{-1}$; $^1$H nmr ($CDCl_3$) δ 8.06 (br s, 1H), 7.20 (d, J=8.6 Hz, 1H), 7.04 (d, J=2.3 Hz, 1H), 6.87 (d, J=2.3 Hz, 1H), 6.83 (dd, J=2.3 and 8.6 Hz, 1H), 3.89-3.83 (m, 1H), 3.83 (s, 3H), 2.61-2.41 (m, 2H), 2.39-2.30 (m, 1H), 2.16-1.96 (m, 3H), 1.94-1.82 (m, 2H); lrms, m/z (relative intensity) 244 (26), 243 ($M^+$, 89), 215 (44), 214 (38), 186 (100), 173 (29), 160 (41); hrms calcd for $C_{15}H_{17}NO_2$

243.1260, found 243.1280 (8.4 ppm deviation, 5 scans). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.66; H, 7.33; N, 5.62.

General Synthesis of 3-(2-Aminocycloalkyl)-5-methoxyindoles (3). A mixture of **2** (2.08 mmol) and condensed amine (approx. 1 ml) in absolute methanol (5 ml) was stirred at 0° C under nitrogen for 15 min. Sodium cyanoborohydride (0.13 g, 2.07 mmol, 1 eq.) was then added as a solid all at once, and the resulting mixture was stirred at 0° C under nitrogen for 1 h, at which time additional sodium cyanoborohydride (0.18 g, 2.86 mmol, 1.4 eq., 2.4 eq. total) was added, and reaction mixture was stirred at rt under nitrogen overnight. The resultant reaction mixture was evaporated under reduced pressure, suspended in a saturated solution of sodium bicarbonate (10 ml), and this aqueous mixture was extracted with ethyl acetate (3 x 10 ml). These extracts were combined, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residue was column chromatographed (45 g silica gel) eluting first with methanol and then with 1% triethylamine in methanol. The product from this chromatography was further purified, if needed, by trituration or recrystallization.

3-(2-Methylaminocyclopentyl)-5-methoxyindole (3a). Chromatography afforded **3a** (34%) as a 3:2 (*cis*:*trans*) mixture of diastereomeric oils. The less polar isomer from the chromatography appeared by $^1H$ nmr[10] to be the *cis* isomer: $^1H$ nmr ($CDCl_3$) δ 8.42 (br s, 1H), 7.23 (d, J=8.4 Hz, 1H), 7.06 (d, J=2.2 Hz, 1H), 7.01 (br d, J=2.3 Hz, 1H), 6.85 (dd, J=2.2 and 9.0 Hz, 1H), 3.85 (s, 3H), 3.39-3.30 (br m, 1H), 3.26-3.20 (br m, 1H), 2.20 (s, 3H), 2.10-1.66 (m, 6H); lrms, m/z (relative intensity) 245 (32), 244 ($M^+$, 87), 213 (23), 187 (74), 174 (41), 161 (98), 83 (74), 70 (100); hrms calcd for $C_{15}H_{20}N_2O$ 244.1577, found 244.1576 (1.9 ppm deviation, 5 scans). The more polar diastereomer from the chromatography appeared by $^1H$ nmr[10] to be the *trans* diastereomer: $^1H$ nmr ($CDCl_3$) δ 8.10 (br s, 1H), 7.22 (d, J=8.4 Hz, 1H), 7.10 (d, J=2.3 Hz, 1H), 6.98 (d, J=2.4 Hz, 1H), 6.83 (dd, J=2.2 and 8.4 Hz, 1H), 3.84 (s, 3H), 3.12-2.96 (approx dq, 2H), 2.35 (s, 3H), 2.16-2.00 (m, 2H), 1.98-1.66 (m, 4H); lrms, m/z (relative intensity) 245 (21), 244 ($M^+$, 80), 213 (17), 187 (71), 174 (28), 161 (93), 83 (71), 70 (100).

3-(2-Methylaminocyclohexyl)-5-methoxyindole (3b). Chromatography afforded **3b** (44%) as a mixture of 2:3 (*cis*:*trans*) diastereomeric oils. The less polar diastereomer from the chromatography appeared by $^1H$ nmr[10] to be the *cis* isomer: $^1H$ nmr ($CDCl_3$) 8.20 (br s, 1H), 7.46 (d, J=2.2 Hz, 1H), 7.22 (d, J=8.5 HZ, 1H), 7.06 (d, J=2.7 Hz, 1H), 6.84 (dd, J=2.4 and 8.6 Hz, 1H), 3.83 (s, 3H), 3.04 (br t, J=4.0 Hz, 1H), 2.41-2.33 (m, 1H), 2.20 (s, 3H), 2.04-1.92 (m, 1H), 1.84-1.20 (m, 7H); lrms, m/z (relative intensity) 259 (7), 258 ($M^+$, 32), 201 (25), 174 (22), 161 (74), 83 (14), 70 (100). The more polar diastereomer from the

chromatography appeared by $^1$H nmr[10] to be the *trans* isomer: $^1$H nmr ($CDCl_3$) δ 8.26 (br s, 1H), 7.22 (d, J=8.2 Hz, 1H), 7.13 (d, J=2.2 Hz, 1H), 6.99 (d, J=2.2 Hz, 1H), 6.83 (dd, J=2.8 and 9.0 Hz, 1H), 3.83 (s, 3H), 2.72-2.54 (m, 2H), 2.24 (s, 3H), 1.96-1.64 (m, 5H), 1.48-1.32 (m, 2H), 1.24-1.10 (m, 1H); lrms, m/z (relative intensity) 259 (25), 258 ($M^+$, 67), 227 (32), 201 (55), 173 (36), 161 (85), 84 (61), 70 (100); hrms calcd for $C_{16}H_{22}N_2O$ 258.1734, found 258.1733 (4.3 ppm deviation, 5 scans).

3-(2-Dimethylaminocyclopentyl)-5-methoxyindole (**3c**). Chromatography afforded **3c** (48%) as a white powder: mp, 154.0-157.0° C; ir (KBr) 1625, 1585, 1495, 1470, 1440, 1210 $cm^{-1}$; $^1$H nmr ($CDCl_3$) δ 8.35 (br s, 1H), 7.19 (d, J=2.2 Hz, 1H), 7.18 (d, J=8.5 Hz, 1H), 7.02 (d, J=2.3 Hz, 1H), 6.80 (dd, J=2.2 and 8.5 Hz, 1H), 3.85 (s, 3H), 3.53 (t, J=6.7 Hz, 1H), 2.60-2.52 (m, 1H), 2.18 (s, 6H), 2.06-1.92 (m, 2H), 1.84-1.60 (m, 4H); $^{13}$C nmr ($CDCl_3$) δ 153.7, 131.0, 128.4, 123.5, 115.6, 111.6, 111.3, 101.0, 72.6, 56.0, 45.5, 38.3, 32.7, 29.6, 21.6; lrms, m/z (relative intensity) 259 (22), 258 ($M^+$, 56), 214 (31), 161 (57), 97 (41), 84 (100); hrms calcd for $C_{16}H_{22}N_2O$ 258.1734, found 258.1727 (6.1 ppm deviation, 5 scans). Anal. Calcd for $C_{16}H_{22}N_2O \cdot 0.25\ H_2O$: C, 73.11; H, 8.62; N, 10.66. Found: C, 73.17; H, 8.59; N, 10.63.

3-(2-Dimethylaminocyclohexyl)-5-methoxyindole (**3d**). Chromatography and trituration in ether afforded **3d** (51%) as a white solid: mp, 202.0-204.0° C; ir (KBr) 1625, 1585, 1495, 1475, 1450, 1205 $cm^{-1}$; $^1$H nmr ($CDCl_3$) δ 8.80 (br s, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.09 (d, J=2.2 Hz, 1H), 7.02 (d, J=2.3 Hz, 1H), 6.81 (dd, J=2.3 and 9.0 Hz, 1H), 3.85 (s, 3H), 3.68-3.62 (m, 1H), 2.22 (s, 6H), 2.14-2.04 (m, 1H), 1.98-1.58 (m, 5H), 1.44-1.24 (m, 3H); $^{13}$C nmr ($CDCl_3$) δ 153.7, 130.9, 128.4, 124.6, 115.0, 111.7, 111.3, 100.9, 68.0, 56.0, 43.7, 33.7, 31.6, 27.3, 25.5, 20.8; lrms, m/z (relative intensity) 273 (21), 272 (M+, 55), 228 (47), 173 (23), 161 (52), 136 (32), 111 (44), 84 (100); hrms calcd for $C_{17}H_{24}N_2O$ 272.1890, found 272.1887 (5.0 ppm deviation, 5 scans). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.56; H, 8.61; N, 10.12.

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7. In the $^1$H nmr spectrum of **1b**, the methine proton α to the -OH (located at δ 3.76-3.66) appeared as a broadened multiplet, while the methine proton α to the -N(CH$_3$)$_2$ (centered at δ 2.71) appeared as a doublet of doublet of doublets resulting from coupling constants of 6.5, 5.2, and 1.8 Hz. This pattern is typical of a $J_{ABX}$ system resulting from a *single axial-equitorial splitting* (1.8 Hz) and two axial-axial splittings (6.5 and 5.2 Hz) of the methine proton α to the -N(CH$_3$)$_2$. This indicates a *trans* geometry between the -OH and C3 of the indole ring, and was used as a pattern for *trans* geometry in these systems. Since the axial-equitorial and axial-axial coupling constants in five membered rings are similar in magnitude (approximately 5 Hz), the same analysis using the $^1$H nmr spectrum of **1a** could not be done, but the geometry of **1a** was assumed to be analogous to **1b** (i.e. *trans*).

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9. In the $^1$H nmr spectrum of **3d** the proton α to the dimethylamino group (located at δ 3.68-3.62) appeared as a broadened triplet with small $J_{ABX}$ values (i.e. less than 2 Hz) indicative of a $J_{ABX}$ system with two axial-equitorial splittings and an equitorial-equitorial splitting. This indicated that the geometry of the amine and C3 of the indole was *cis*. Since the axial-equitorial and axial-axial coupling constants in five membered rings are similar in magnitude (approximately 5 Hz), the same analysis using the $^1$H nmr spectrum of **3c** could not be done, but the geometry of **3c** was assumed to be analogous to **3d** (i.e. *cis*).

10. The presence and ratio of diastereomers could be detected via the appearance of two different resonances for the protons of the C5-OCH$_3$ and N-CH$_3$ in the $^1$H nmr spectra of **3**. An examination of the splitting patterns of the methine proton α to C3 of the indole ring and the methine proton α to the basic amine in the diastereomeric pairs and comparison of these patterns with those of **1b** and **1a** (indicative of *trans* geometry, reference 7) and **3d** and **3c** (indicative of *cis* geometry, reference 9) led to the identification of *cis* and *trans* diastereomers in **3b** and **3a**.

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