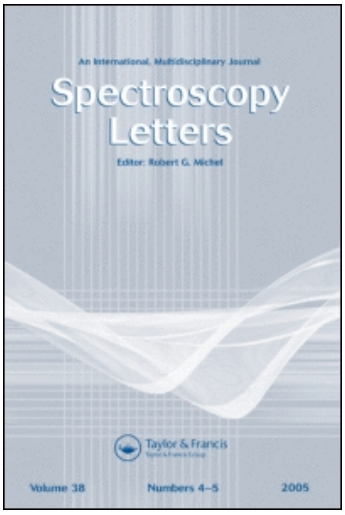

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Proton and Carbon-13 NMR Studies of Some Tryptamines, Precursors, and Derivatives: *Ab Initio* Calculations for Optimized Structures

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Proton and Carbon-13 NMR Studies of Some Tryptamines, Precursors, and Derivatives: *Ab Initio* Calculations for Optimized Structures

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Abstract: Proton and carbon-13 NMR data are presented for 5-methoxytryptamine, **1**; 6-methoxytryptamine, **2**; *N,N*-diisopropyl-5-methoxytryptamine, **3**, (5-MeO-DIPT); and *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide, **4**, at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ at ambient temperature. Compound **3**, considered a potential hallucinogen, had been placed into Schedule I of the Controlled Substances Act, effective April 4, 2003, by the U.S. Drug Enforcement Administration. Compound **4** can serve as a possible precursor to **3**. We believe that these are the first proton NMR assignments obtained at medium field (7 tesla) using selective homodecoupling and two-dimensional homonuclear chemical shift correlation spectra (using one or more of the COSY45, COSY90, and COSYLR experiments) for rigorous aryl proton assignments in this group of compounds. Significant observed differences in the proton and carbon-13 NMR spectra should allow facile distinction of the 5-methoxy series, **1** and **3**, from the 6-methoxy series, **2**. Energy minimizations to obtain optimized structures for each compound were performed at the Hartree–Fock level with the 6-31G* basis set, and the resulting geometries are discussed. The presented geometry calculations appear to be the most accurate reported to date for **1** based on the basis set employed, and the first HF/6-31G* structures for compounds **2**, **3**, or **4**. Appreciable geometry differences in **3** and **4** for the pendant sidechain containing the $N[CH(CH_3)_2]_2$ moiety are noteworthy. Proximity of the carbonyl oxygens in **4** to

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H2 and H4 is suggested as a possible contributing factor in the deshielding of these protons in the NMR spectrum.

Keywords: Controlled substances, hallucinogens, Hartree–Fock/6-31G*, 5-methoxytryptamine, 6-methoxytryptamine, *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide, *N,N*-diisopropyl-5-methoxytryptamine

INTRODUCTION

N,N-Diisopropyl-5-methoxytryptamine, **3**, known as 5-MeO-DIPT [or 5-MeO $T(iPr)_2$], had been placed in Schedule I of the Controlled Substances Act, effective April 4, 2003, by the U.S. Drug Enforcement Administration; 5-MeO-DIPT is considered a potential hallucinogen with an estimated human hallucinogenic dose of 6–10 mg.[1–3] In order to facilitate the identification of samples of this material and to help distinguish it from related isomers, analogues and possible precursors, we wanted to present proton and carbon-13 NMR data for **3** with comparative data for 5-methoxytryptamine (5-MeO-T), **1**; 6-methoxytryptamine (6-MeO-T), **2**; and for *N,N*-diisopropyl-5-methoxyindole-3-glyoxyl amide [5-MeO amide or glyox (iPr_2)], **4**. Compound **4** can be a synthetic precursor to **3**, and compounds **1** and **2** were of interest to observe spectral effects of different methoxy substitution positions. Structures are shown in Fig. 1 with atom numbering. Although NMR data for **1** have appeared, early proton spectra obtained at 60 MHz had insufficient dispersion for easy characterization of the aryl proton signals, which were described as a 4H multiplet.[4] Later reports with medium field strength spectrometers (e.g., ca. 200–400 MHz proton frequencies), did not appear to apply selective homodecoupling or two-dimensional (2D) homonuclear chemical shift correlation techniques that might have allowed rigorous aryl proton assignments, and published reports evidently did not give these assignments.[5–8] We were not able to locate any published NMR reports for compounds **2**, **3**, or **4**. Our present results appear to be the first for this group of compounds for proton and carbon-13 NMR data, with rigorous aryl proton assignments. These spectral studies were complemented by computational studies of the four compounds with *ab initio* geometry optimizations at the Hartree–Fock level using the 6-31G* basis set. B. Pullman and co-workers had used the semiempirical PCILO method for a study of 5-Meo-T and related compounds[9] and further computational studies have been applied recently.[10] In the latter work, the actual *ab initio* geometry optimizations used the simpler and less accurate 3-21G* basis set compared to the 6-31G* basis set employed by us. No other computational studies for the compounds **2**, **3**, or **4** appear to have been reported (but see the end of the "Results and Discussion" section, below). The resulting geometric parameters from our present HF/6-31G* calculations on all four compounds are discussed.

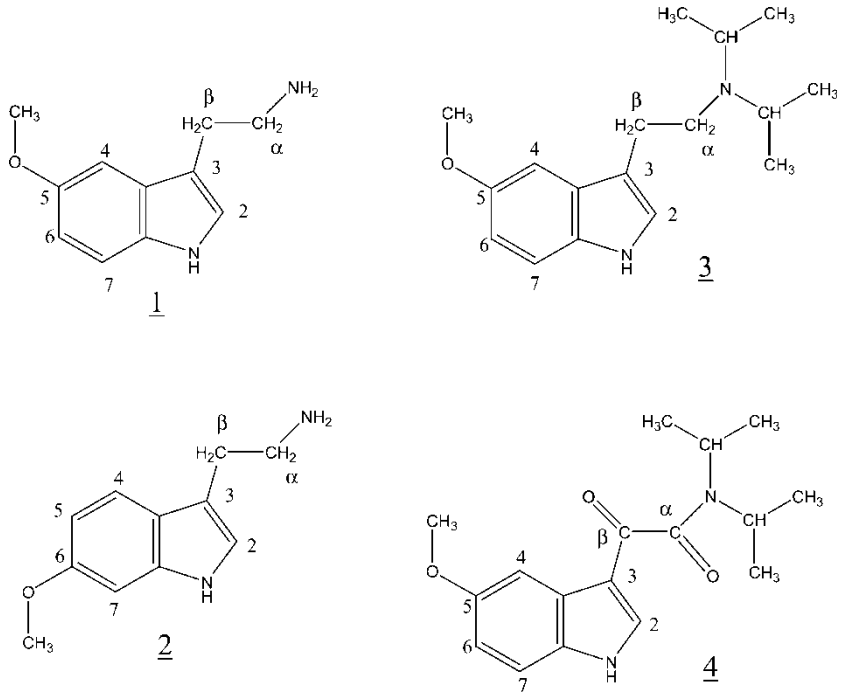

Figure 1. Compound structures and numbering.

EXPERIMENTAL

NMR spectra were acquired on a Bruker AC300F (7 tesla) spectrometer in $CDCl_3$ at ambient temperature, with the QNP "quad" nuclear probe, for observe frequencies of 300 MHz (proton) or 75 MHz (carbon-13), using the Aspect 3000 data system. Proton decoupling during one-dimensional (1D) carbon-13 spectra was achieved with WALTZ16 (BrukerSpin Corp., Billerica, MA, USA) for composite pulse decoupling. ^{1}H-^{1}H selective homo-decoupling and two-dimensional (2D) chemical shift correlation spectra (COSY45, COSY90, and the "long-range" COSYLR) were obtained using standard Bruker microprograms (BrukerSpin Corp., Billerica, MA, USA). For proton NMR, chemical shifts are reported relative to internal tetramethyl-silane (TMS) at 0.0 ppm; ^{13}C shifts are given relative to the central line of the $CDCl_3$ triplet at 77.0 ppm. NMR samples were kindly provided by the U.S. Drug Enforcement Administration (Northeast Regional Lab). Compounds **1** and **2** are commercially available from Sigma-Aldrich (Milwaukee, WI, USA). $CDCl_3$ was obtained from Aldrich (Sigma-Aldrich Co., Milwaukee, WI, USA). Materials were used as supplied. Proton NMR data are summarized in Table 1. Selected expansions of proton spectra are shown in Fig. 2. Molecular modeling calculations were performed using Spartan '04

Table 1. Proton NMR of tryptamines: chemical shifts in ppm (apparent couplings, Hz)

	Compound			
Nucleus	5-MeO T (**1**)	6-MeO T (**2**)	5-MeO DIPT (**3**)	5-MeO amide (**4**)
2	7.02 (2.20)	6.93 (2.15)	7.44 (3.19)	7.00 (2.30)
4	7.05 (2.20)	7.48 (8.61)	7.75 (2.14)	7.06 (2.45)
5		6.79 (8.64,2.26)		
6	6.86 (8.83, 2.57)		6.83 (8.86, 2.46)	6.85 (8.77, 2.43)
7	7.26 (8.46)	6.86 (2.19)	7.14 (8.86)	7.24 (8.70)
NH	7.95 br s	7.98 br s	10.38 br s	7.83 br s
MeO	3.87	3.85	3.86	3.86
CH_2	3.03 (6.44)	3.02 (6.41)		2.82 br m
CH_2	2.88 (6.62)	2.87 (6.59)		2.72
NH_2	1.33 br s	1.28 br s		
CH(a)			3.94 (6.61)	3.12 (6.55)
Me(a)			1.54 (6.81)	1.08 (6.51)
CH(b)			3.54 (6.83)	
Me(b)			1.15 (6.62)	

Compound abbreviations: 5-MeO T, 5-methoxytryptamine, **1**; 6-MeO T, 6-methoxytryptamine, **2**; 5-MeO DIPT, [or 5-MeO T$(iPr)_2$], *N,N*-diisopropyl-5-methoxytryptamine, **3**; 5-MeO amide, [or glyox $(iPr)_2$], *N,N*-diisopropyl-5-methoxyindole-3-glyoxyl amide, **4**.

ESSENTIAL (v. 2.0.0, Wavefunction, Inc.) or Spartan '04 for Windows (full version, v. 1.0.0, Wavefunction, Inc.) on Dell Pentium 4 platforms with 2.26 or 3.06 GHz processor speeds and 512 or 1024 MB memory. All software was obtained from Wavefunction, Inc. (Irvine, CA). Calculation parameters included turning symmetry "off" and convergence "on." After building each structure, **1–4**, numerous different conformations of the sidechains were separately energy-minimized using molecular mechanics (MMFF94). The lowest energy conformers were then energy-optimized with the semi-empirical AM-1 calculations prior to the final HF/6-31G*. (See "Ab Initio Computational Studies" section in the "Results and Discussion", below.)

5-Methoxytryptamine (**1**): (^{13}C-NMR): 153.96 Q; 131.58 Q; 127.93 Q; 122.78; 113.64 Q; 112.21; 111.81; 100.83; 55.96 (OMe); 42.32 (NCH_2); 29.54 (aryl CH_2).

6-Methoxytryptamine (**2**): (^{13}C-NMR): 156.54 Q; 137.17 Q; 121.96 Q; 120.70; 119.46; 113.82 Q; 109.23; 94.69; 55.69 (OMe); 42.38 (NCH_2); 29.60 (aryl CH_2).

N,N-diisopropyl-5-methoxytryptamine (**3**): (^{13}C-NMR): 153.85 Q; 131.38 Q; 128.05 Q; 122.08; 115.07 Q; 111.97; 111.72; 100.96; 55.88 (OMe); 49.01 ($2 \times \underline{N}\underline{C}H$); 46.50 ($NCH_2$); 28.23 (aryl CH_2); 20.81 ($4 \times \underline{C}\underline{H}_3$).

N,N-diisopropyl-5-methoxyoxalyltryptamine (**4**): (^{13}C-NMR): 186.27 Q (aryl C═O); 168.31 Q (NC═O); 156.61 Q; 134.75; 131.57 Q; 126.04 Q;

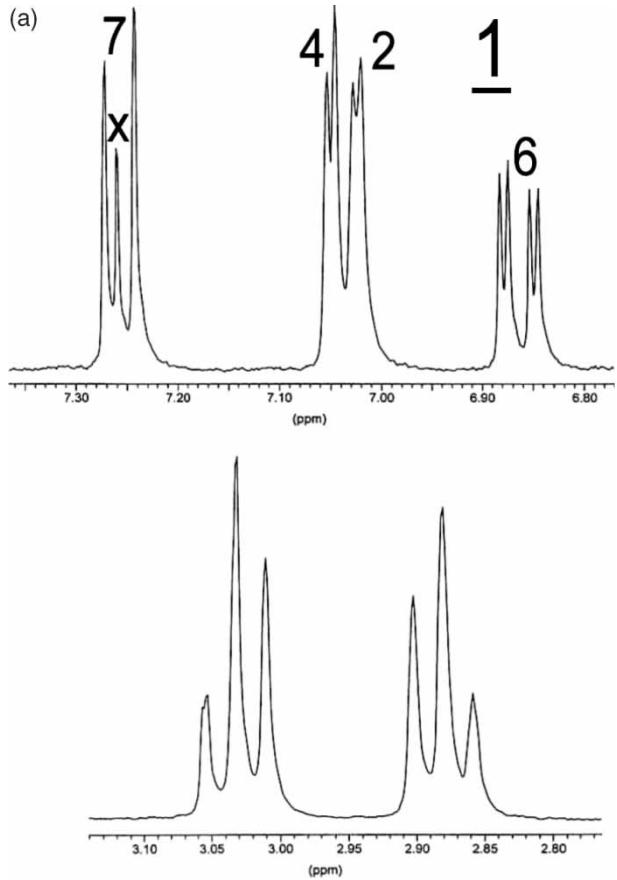

Figure 2. Expansions of 300 MHz ^{1}H-NMR spectra ($CDCl_3$, ambient temperature). Note that different vertical and horizontal scales are used for the various expansions. For clarity, some signals are omitted from the selected traces. The low field indole NH signals are not shown for any of the compounds, and the NH_2 signal is omitted for **1** and **2**. The CH_3O signal is not shown for **1**, **2**, or **3**. The $CHCl_3$ peak from the solvent is marked "X." (a) 5-methoxytryptamine, **1**: the lower trace shows the signal of the CH_2CH_2 moiety; (b) 6-methoxytryptamine, **2**: the lower trace shows the signal of the CH_2CH_2 moiety; (c) *N,N*-diisopropyl-5-methoxytryptamine, **3**: in the aryl region, the $CHCl_3$ peak coincides with the low field branch of the H7 doublet. In the lower trace, the 2H septet at ca. 3.1 ppm is assigned to the methines from the two isopropyl groups. (The single high field 12H doublet from the methyls of the two isopropyl groups is not shown.) The multiplets at ca. 2.65–2.8 ppm are from the CH_2CH_2 moiety; (d) *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide, **4**: an impurity peak of benzene (ca. 7.37 ppm) is marked "B" in the upper trace. Lower left trace: the intense CH_3O peak (3H, singlet) appears at 3.86 ppm and the two multiplets at ca. 3.54 and 3.94 ppm are the methine signals from the nonequivalent *syn* and *anti* amide isopropyl groups. Lower right trace: the two 6H doublets result from the *geminal* methyls of each of the nonequivalent *syn* and *anti* amide isopropyl groups.

(*continued*)

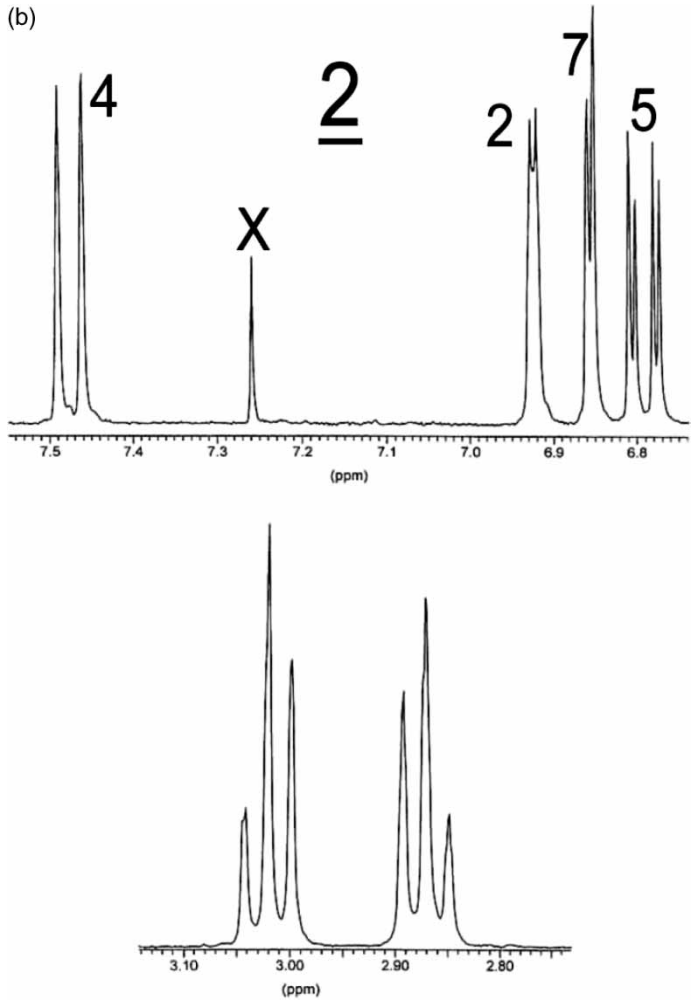

Figure 2. Continued.

114.51; 113.92 Q; 112.96; 103.02; 55.74 (OMe); 50.43 $\underline{C}HMe_2$(a); 45.98 $\underline{C}HMe_2$(b); 20.58 $CH\underline{M}e_2$(a); 20.29 $CH\underline{M}e_2$(b).

RESULTS AND DISCUSSION

The ^{1}H-NMR spectrum in the aryl region of 5-methoxytryptamine, **1**, in $CDCl_3$ appears somewhat puzzling initially, with what appears to be a 2H intensity double doublet (dd) signal at ca. 7.03 ppm and a 1H dd signal at

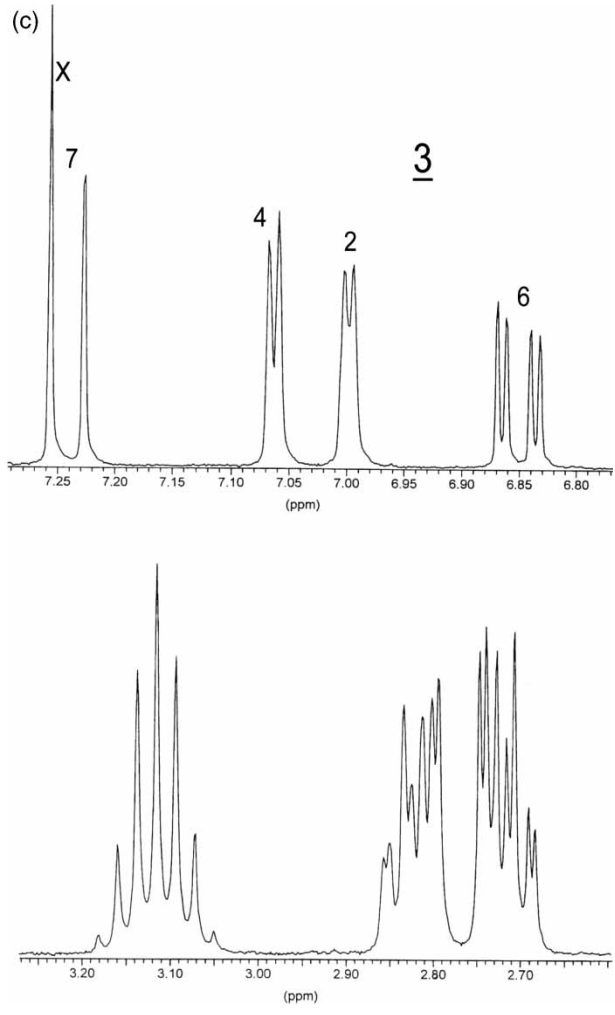

Figure 2. Continued.

6.86 ppm. In addition, three lines are seen from 7.23–7.28 ppm; the central of these three lines is due to $CHCl_3$ inpurity in the solvent (see Fig. 2a). Irradiation at 6.86 ppm cleanly collapses the ca. 7.25 ppm region to a singlet (plus the $CHCl_3$ peak) and transforms the apparent 2H dd near 7.03 ppm to a 1H singlet (s) at 7.05 ppm with a remaining 1H d ($J = 2.2$ Hz) at 7.02 ppm. The 7.02 ppm signal is assigned to H2, slightly split by vicinal coupling to the indole NH; the latter signal appears as a broad singlet at 7.95 ppm, broadened by the nitrogen-14 quadrupole moment. The irradiated 6.86 ppm dd signal may then be assigned to H6,

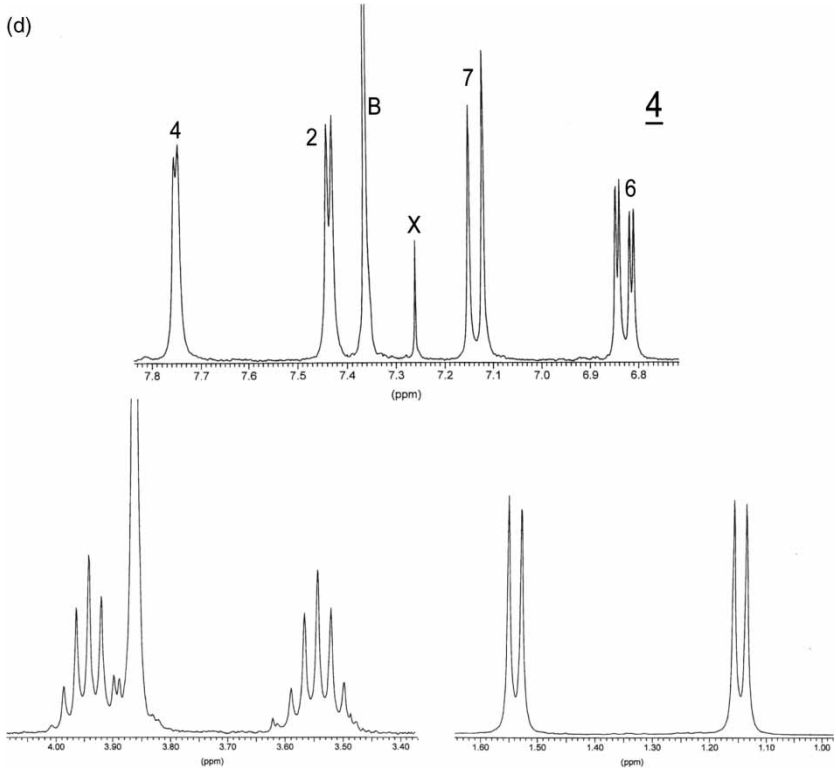

Figure 2. Continued.

with vicinal ^{3}J coupling of 8.8 Hz to H7 and small ^{4}J ("W") coupling of 2.6 Hz to H4. The narrow H4 doublet must be the 7.05 ppm absorption, with the wide 7.26 ppm doublet attributed to H7. Centered at 3.03 and 2.88 ppm are approximate 2H triplets (t) for the CH_2CH_2 sidechain. We cannot rigorously distinguish the aryl-CH_2 from the NCH_2, although the higher field triplet is very slightly broader (lower peak heights) which might be consistent with proximity to, and weak splitting by, the NH_2. For the ^{13}C-NMR, the highfield signals have been assigned to MeO (55.96 ppm), NCH_2 (42.32 ppm), and aryl-CH_2 (29.54 ppm) on chemical shift grounds [11,12]. The nonprotonated quaternary aryl carbons (Q) give much weaker signals than the aryl methine carbons when shorter relaxation delays are used (e.g., 1 s).

For 6-methoxytryptamine, **2**, the $CHCl_3$ solvent impurity peak is well separated from the aryl proton peaks. The two narrow doublets (J ca. 2.2 Hz) at 6.93 and 6.86 ppm are quite different in appearance, with the 6.93 ppm signal displaying some broadening, based on a valley height of

about 80% of the doublet peaks. For the 6.86 ppm doublet, the valley height is ca. 45% of the doublet peaks (see Fig. 2b). Irradiation of the H5 dd signal at 6.79 ppm leaves the slightly broad 6.93 ppm d signal unchanged but collapses the 6.86 ppm signal to a sharp singlet signal and identifying the latter as H7. The 6.93 ppm signal must be H2, slightly split by the NH and slightly broadened by the ^{14}N quadrupole moment. The H4 d ($^3J = 8.6$ Hz) at 7.48 ppm is thus assigned, collapsing to a singlet on irradiation at 6.79 ppm. Two approximate triplets for the CH_2CH_2 are seen at 3.02 and 2.87 ppm, but selective broadening is not obvious for either signal. The three higher field carbon-13 signals are assignable on chemical shift grounds, as for the 5-methoxy isomer.[11,12]

5-Methoxyindole reacts with oxalyl chloride at the 3-position, and subsequent reaction with diisopropylamine gives the *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide, compound **4**. Hindered rotation about the N–C═O amide bond is slow on the proton and carbon-13 NMR timescales under our conditions, resulting in slow exchange limit (SEL) spectra showing sharp separate signals for each isopropyl group, *syn* or *anti* to the amide oxygen[13,14] (see Fig. 2d). Irradiation of the H6 dd signal at 6.83 ppm collapses the H7 doublet ($^3J = 8.9$ Hz) at 7.14 ppm to a singlet, and similarly collapses the H4 doublet ($^4J = 2.1$ Hz) at 7.75 ppm. The H2 doublet at 7.44 ppm is unchanged by the decoupling. The indole NH appears highly deshielded at 10.34 ppm; it may be considered a "vinylogous amide." For the ^{13}C-NMR spectrum, the lowest field signal at 186.27 ppm is assigned to the aryl C═O and the 168.31 ppm signal to the amide N–C═O, based on chemical shift arguments. We also assign the MeO signal at 55.74 ppm, the two isopropyl NCH methines at 50.43 and 45.98 ppm, and the pairs of methyls at 20.58 and 20.29 ppm, based on chemical shifts (and higher peak areas for the methyls).[11,12]

Lithium aluminum hydride reduction of the amide gives the *N,N*-diisopropyl-5-methoxytryptamine, **3**, (5-MeO-DIPT) as reference material. The peak of $CHCl_3$ solvent impurity is coincidentally partly overlapped with the H7 doublet ($^3J = 8.7$ Hz) centered at 7.24 ppm (see Fig. 2c). Irradiation of the H6 dd at 6.85 ppm collapses the H7 doublet and also the H4 doublet ($^4J = 2.5$ Hz) at 7.06 ppm, leaving the H2 doublet at 7.00 ppm unchanged. In the amine, **3**, the two isopropyl groups are effectively averaged on the NMR timescales so that fast exchange limit (FEL) spectra are observed, with the pair of NCH methines appearing as a clean 2H septet at 3.12 ppm, and all four methyls of the isopropyl groups resonating as a 12H doublet at 1.08 ppm. The CH_2CH_2 moiety gives rise to a pair of complex 2H multiplets (seven lines seen in each multiplet), with the lower field multiplet at 2.82 ppm distinctly broadened compared to the 2.72 ppm; we might attribute the broadened absorption to the NCH_2 signal. COSY45 spectra confirmed coupling between the CH_2CH_2 multiplets, and between the isopropyl methine and methyl signals. A distinct crosspeak was also observed correlating the indole NH and H2 signals. The H6 dd strongly

correlated with the H7 signal (vicinal ^3J) and was also correlated with H4 (^4J). No cross-peak was seen between H4 and H7 (a potential long-range five-bond coupling). However, a weak crosspeak for this long-range coupling was observed in a "long range" COSY90 using a low (sensitive) contour level. Some expansions of proton NMR spectra of these compounds are shown in Fig. 2.

Comparing the proton NMR shifts for the three amines, **1**, **2**, and **3**, as shown in Table 1, the chemical shifts for the carbon-bound protons of the indole system are seen to be virtually identical for both 5-methoxy compounds, **1** and **3**. This is indicative of identical attachment of the CH_3O group. Appreciably different shifts are seen for the benzo ring protons of the 6-methoxy isomer, allowing easy distinction of the different substitution series. In contrast, compounds **1** and **2** have identical shifts for the CH_2CH_2 group, with noticeably different shifts for **3**, associated with the bulky diisopropylamino moiety. For the carbon-13 spectra, the aryl carbon shifts of **1** and **3** appear remarkably similar. With the exception of the peaks of **1** at 122.78 and 113.64 (Q) ppm versus the peaks of **3** at 122.08 and 115.07 (Q) ppm, which differ from each other by ca. 1.4 ppm or less, the other aryl carbon peaks appear in the spectra of both **1** and **3** within about 0.2 ppm of each other. In contrasting **1** with **2**, however, carbon shifts seem to differ by as much as ca. 6 ppm. Again, the different methoxy substitution positions is readily detected.

Although the 2D carbon-proton heteronuclear chemical shift correlation spectra (e.g., HETCOR) would presumably have permitted assignments for most protonated carbons, this data is not included here. We are aware that most forensic labs and crime labs typically have enormous case loads, meaning that it would be very unusual (and rather unlikely) for NMR experiments with long acquisition times to actually be performed. We have, therefore, emphasized proton assignments via 1D and 2D NMR experiments, and presented (as supplements) basic 1D carbon-13 spectral data.

Ab Initio Computational Studies

Geometry optimizations for each of the four compounds of interest were performed at the Hartree–Fock level with the 6-31G* basis set. This method is considered to provide reasonable accuracy for energy and conformational structures in terms of computational "expense" (i.e., calculation times), and better accuracy would be expected using the 6-31G* than the 3-21G* basis set.[15–18] Details of the 6-31G* basis set are described for first-row elements, e.g., carbon–fluorine[19] and for second-row elements.[20] Hehre[18] has rather clearly illustrated the superiority of the HF/6-31G* calculations versus the 3-21G basis set, *especially for calculations on amines*, where small-basis-set Hartree–Fock models can produce poor

geometries, potentially leading to bond angles which are several degrees too large. We have routinely used a "three-step optimization" (see "Experimental") in calculating our equilibrium structures, with the Merck Molecular Force Field (MMFF94) followed by semiempirical AM-1 before the final HF/6-31G*. Wavefunction, Inc. has indicated that by starting with MMFF minima (and in the absence of symmetry), geometry optimization with HF/6-31G* is very unlikely to give a transition state as opposed to a true local minimum.[21] ["In principle, geometry optimization carried out in the absence of symmetry. . .must result in a local minimum. . .".[18]] Nevertheless, for each of our final optimized structures, we have also calculated the infrared vibrational frequencies. All of the calculated frequencies were positive (real) numbers, no negative (imaginary) frequencies, providing verification that the optimized structures were true minima and not transition states. While we cannot rigorously state that our structures are actually global minima, the structures may reasonably be regarded as important lower energy conformers. For the substituted tryptamines **1**–**3**, the most important geometric considerations were the orientations of: (a) the CH_2CH_2N sidechain on the indole nucleus; (b) the methoxy conformation; and, for **3**, the orientations of the diisopropylamino moiety. For compound **4**, the orientation of the O═C–C═O portion was of special interest, as well as the diisopropylamino group. The calculated geometric parameters are summarized in Tables 2 and 3. Representative views of the calculated optimized structures for each compound are shown in Fig. 3. Some general observations are presented here. Compounds **1** and **3** were very similar with respect to the orientation of the 5-methoxy group, directed toward the indole H4, with the two hydrogens, H(x) and H(y), of the CH_3O group proximal to H4 almost identically positioned and almost symmetrically oriented relative to H4. For amide **4**, the long-range effect of the sidechain is apparent, with the 5-methoxy twisted about 3° from the indole plane based on the C4–C5–O–C dihedral angle, and the hydrogens, H(x) and H(y), less symmetrically disposed toward H4. For the 6-methoxy **2**, the CH_3O group is directed to H5, with the proximal hydrogens, H(x) and H(y), symmetrically positioned about H5. The different methoxy attachments in **1** and **2** have some long-range influence in modifying the dihedral angles of the pendant sidechain, C2–C3–Cβ–Cα by about 1.7° and about 0.7° for the C3–Cβ–Cα–N. Both of these dihedrals are altered, the latter by about 3° in 5-MeO DIPT, **3**, reflecting the severe hindrance of the $N[CH(CH_3)_2]_2$ moiety. The changes are especially notable in the increased distance of the sidechain nitrogen from the indole plane (as defined by C2, C4, and C7) in **3** versus **1** or **2**, and the greater N–H4 distance in **3** compared to **1**.

Profound calculated geometric differences are found for the amide, **4**, versus **3**. The main factors defining the conformation in **4** would likely include the following: (a) preference for conjugation and coplanarity of the carbonyl O═Cβ with the indole system; (b) strong preference for coplanarity of the amide system and a near-trigonal amide nitrogen; and (c) electrostatic

Table 2. Calculated geometric parameters and energies based on Hartree–Fock/6-31G* geometry optimization (see notes below and Discussion section)

Energy (au)	5-MeO T (**1**) −608.4377624	6-MeO T (**2**) −608.4384928	5-MeO DIPT (**3**) −842.6263634	5-MeO amide (**4**) −990.0558364
Dihedrals				
C2–C3–Cβ – Cα	−102.30	−103.97	−101.97	−175.16
C3–Cβ–Cα–N	−176.23	−176.93	−179.57	116.66
C4–C5–O–C	0.65		0.35	3.04
C5-C6-O-C		0.62		
C5–O–C–H(x)	−61.54		−61.31	−63.12
C6-O-C-H(x)		−61.59		
C5–O–C–H(y)	60.75		61.02	59.15
C6-O-C-H(y)		60.99		
Distances				
H(x)-H4	2.354		2.355	2.347
H(x)-H5		2.338		
H(y)-H4	2.357		2.358	2.342
H(y)-H5		2.343		
N–H4	4.260	4.308	4.351	3.545
N–H2	4.987	4.995	4.962	5.111
N-(C2,C4,C7)	1.339	1.329	1.428	1.354

Notes: Distances are in angstroms (Å), dihedral angles and angles are in degrees. Signs of dihedral angles reflect chirality of optimized structure. Calculated energies are in hartrees (1 au = 627.5 Kcal/mol). The distance from the side-chain nitrogen to the plane of the indole ring is given as N–(C2,C4,C7) where C2, C4, and C7 define the plane.

Table 3. Supplemental calculated geometric parameters for **3** and **4** (see notes in table 2 and notes below)

Angles	5-MeO-DIPT (**3**)	5-MeO amide (**4**)	
$Me_2\underline{C}H-\underline{N}-\underline{C}HMe_2$	118.03	118.53	
$\underline{C}\alpha-\underline{N}-\underline{C}HMe_2$	114.96, 117.12	119.21, 122.21	
Dihedrals			
$C\beta-C\alpha-N-\underline{C}HMe_2$	81.27, −133.57	168.13, −9.46	
$Me_2\underline{C}H-N-C\underline{H}(z)$	−23.37	1.68	
N planarity	0.268 (N down)	0.017	
Additional parameters of **4**:			
Dihedrals			
C2–C3–Cβ–O	$\underline{O}$=C–C=$\underline{O}$	$\underline{O}$=C–N–$\underline{C}$	$\underline{O}$=C–N–$\underline{C}$
7.69	110.33	(syn) −7.91	(anti) 174.50
Distances	H4–C$\underline{O}\alpha$	H2–C$\underline{O}\beta$	
	2.451	2.669	

Notes: See "Discussion" section and notes to Table 2. Side-chain nitrogen pyramidalization is expressed as N planarity, the distance from the nitrogen to the plane defined by the three directly bonded atoms. For **3**, the N atom is positioned "down" (back) relative to this plane, as viewed in the figure of the calculated structure.

repulsions between the two carbonyl oxygens. Reflecting (a), dihedral angles C2–C3–Cβ–Cα of -175.16° and C2–C3–Cβ–O of 7.69° are seen, showing a nearly coplanar system; the carbonyl O=Cβ is proximal to H2 with a distance H2-C$\underline{O}\beta$ of only 2.67 Å. As examples of the requisite coplanarity for (b), dihedral angles $\underline{O}$=C–N–C(syn) of −7.91° and $\underline{O}$=C–N–$\underline{C}$(anti) of 174.50° are calculated; the amide nitrogen is nearly planar, only 0.017 Å from the plane of the three directly bonded carbons. Item (c) is reflected by the $\underline{O}$=C–C=$\underline{O}$ dihedral angle of 110.33°. In compound **4**, the sidechain nitrogen is much closer to H4 (only 3.55 Å distance) compared to NH4 distances of ca. 4.3 Å for **1**, **2**, or **3**. A short H4–C$\underline{O}\alpha$ distance of 2.45 Å is seen. In addition to conjugative (through-bond) electronic effects, the proximities of the carbonyl oxygens to H2 and H4 may contribute to the deshielding of these protons in the NMR spectrum of **4**, by anisotropic (through-space) interactions.[22]

The steric bulk of the isopropyl groups on nitrogen is exemplified in **3** by the large $(CH_3)_2\underline{C}H-\underline{N}-\underline{C}H(CH_3)_2$ bond angle of 118.03°, nearly equal to the corresponding angle for the amide, **4**. (In the amide, an sp^2 trigonal nitrogen should have ca. 120° bond angle.) In the amine, **3**, the sidechain nitrogen is clearly highly pyramidalized, positioned 0.27 Å from the plane defined by the three attached neighboring atoms. Other substantial geometry differences between **3** and **4** are reflected by the dihedral angles Cβ–Cα–N–$\underline{C}H(CH_3)_2$,

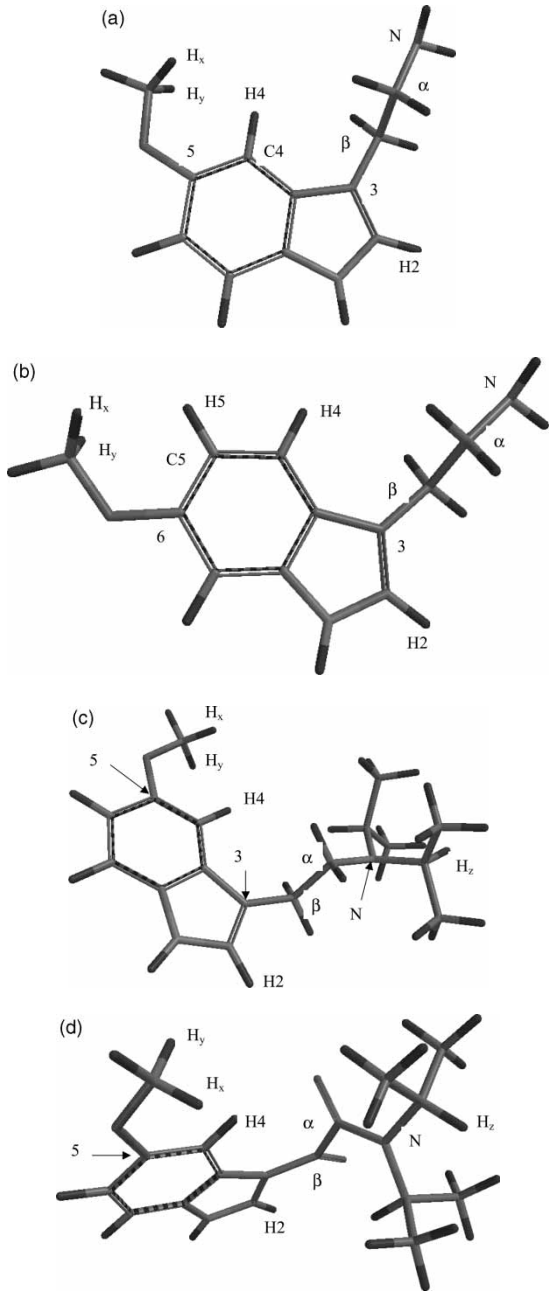

Figure 3. Representative views of optimized structures based on Hartree–Fock level calculation with 6-31G* basis set: (a) compound **1**, 5-methoxytryptamine; (b) compound **2**, 6-methoxytryptamine; (c) compound **3**, *N,N*-diisopropyl-5-methoxytryptamine; (d) compound **4**, *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide.

with nearly coplanar values of 168.1 and -9.5° for amide **4**, versus 81.3 and -133.6° in amine **3**.

We are grateful to a referee for pointing out a recent reference,[23] which included some computational studies of compound **1** and two related 5-methoxytryptamine analogues. Bayari and Ide presented molecular mechanics results (MM3) for optimized geometries and some conformational analysis at the semiempirical PM3 level (together with calculated and experimental Fourier transform infrared data). Our current data provide results from the higher level HF/6-31G* calculations. For the key dihedral angle of the sidechain of **1**, C3–Cβ–Cα–N, our calculated value was 176.23°, compared to 179.2° and 177.5° from the MM3 and PM3 calculations, respectively.

CONCLUSIONS

Proton and carbon-13 NMR spectra for 5-methoxytryptamine, **1**; 6-methoxytryptamine, **2**; *N,N*-diisopropyl-5-methoxytryptamine (5-MeO-DIPT), **3**; and *N,N*-diisopropyl-5-methoxyindole-3-glyoxylamide, **4**, were obtained in $CDCl_3$ at ambient temperature. Proton assignments were assisted with selective homodecoupling and with 2D homonuclear chemical shift correlation spectra, and partial assignments were made for ^{13}C. Distinctive shift differences for aryl protons and carbons for the 5-methoxy compounds, **1** and **3**, compared to the 6-methoxy **2**, should allow facile distinction for the different substitution series. For the 5-methoxy glyoxylamide, **4**, substantial deshielding of several signals was seen. Geometry optimizations for all four compounds were performed at the Hartree–Fock level with the 6-31G* basis set. Notable differences in the calculated structure of **4** (compared with the other compounds) were consistent with preferences for coplanarity within the aryl ketone moiety, and within the amide portion, with repulsions between the oxygens of the O═C–C═O system. Indications of much steric hindrance from the isopropyl groups were seen for the optimized structures of **3** and **4**. Proximity of the carbonyl oxygens in **4** to H2 and H4 is suggested as a possible contributing factor in the deshielding of these protons in the NMR spectrum.

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