

# Nucleophilic substitution reaction at the 1-position of 1-hydroxytryptamine and -tryptophan derivatives

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## NUCLEOPHILIC SUBSTITUTION REACTION AT THE 1-POSITION OF 1-HYDROXYTRYPTAMINE AND -TRYPTOPHAN DERIVATIVES<sup>1</sup>

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**Abstract** – A novel nucleophilic substitution reaction at the 1-position of indole nucleus was discovered by reacting 1-hydroxytryptamine and -tryptophan derivatives with indoles in 85% formic acid yielding 1-(indol-3-yl)indoles. Their structures were determined by X-Ray crystallographic analysis and chemical correlations. An *S<sub>N</sub>2* mechanism on the indole nitrogen (1-position) is proposed.

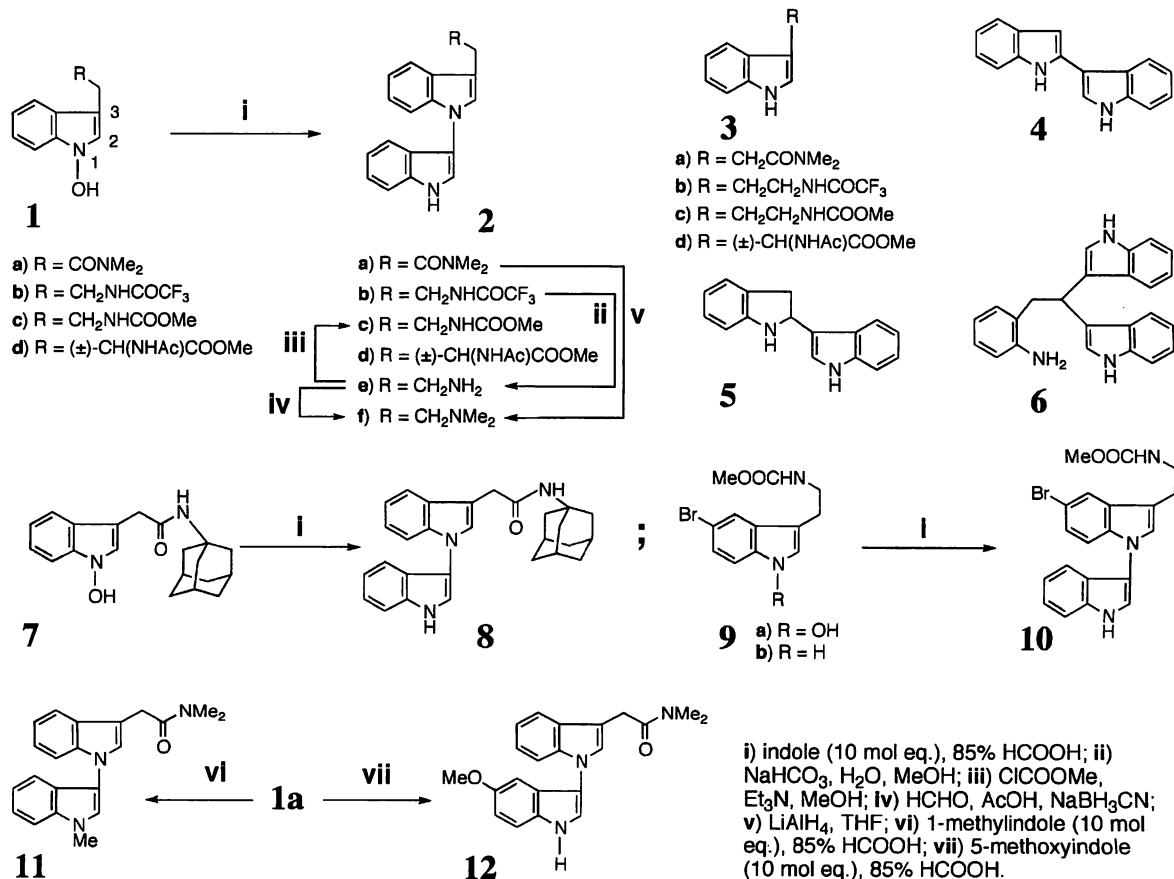
Indole is an electron rich aromatic heterocycle.<sup>2</sup> Indoles can therefore react with various kinds of electrophiles,<sup>2</sup> as is well known both chemically and as common knowledge. In contrast to the accepted wisdom, no one has challenged to realize a nucleophilic substitution reactions on the indole nucleus.

About 30 years ago,<sup>3</sup> we proposed the 1-hydroxyindole hypothesis, in which we posited the presence of imaginary 1-hydroxytryptamines and -tryptophans in living organisms, and hypothesized unprecedented nucleophilic substitution reactions.<sup>3</sup> After many trials, we have found that the nucleophilic substitution reaction actually takes place on the 5-position of the indole nucleus when 1-hydroxytryptamines and -tryptophans are employed as substrates.<sup>4</sup> In our ongoing effort to determine the scope and limitations of this reaction, we have discovered another, new type of nucleophilic substitution reaction which occurs regioselectively on the indole nitrogen (1-position), as reported in the previous communications.<sup>5</sup> This paper represents a full report of this reaction.

Generally speaking, in the presence of such good nucleophiles as indole derivatives (10 mol eq.), 1-hydroxytryptamines and -tryptophans can produce 1-(indol-3-yl)indole compounds in 85% formic acid (HCOOH) at room temperature within 2 h, instead of undergoing regioselective nucleophilic introduction of the hydroxy group into the 5-position.<sup>4</sup>

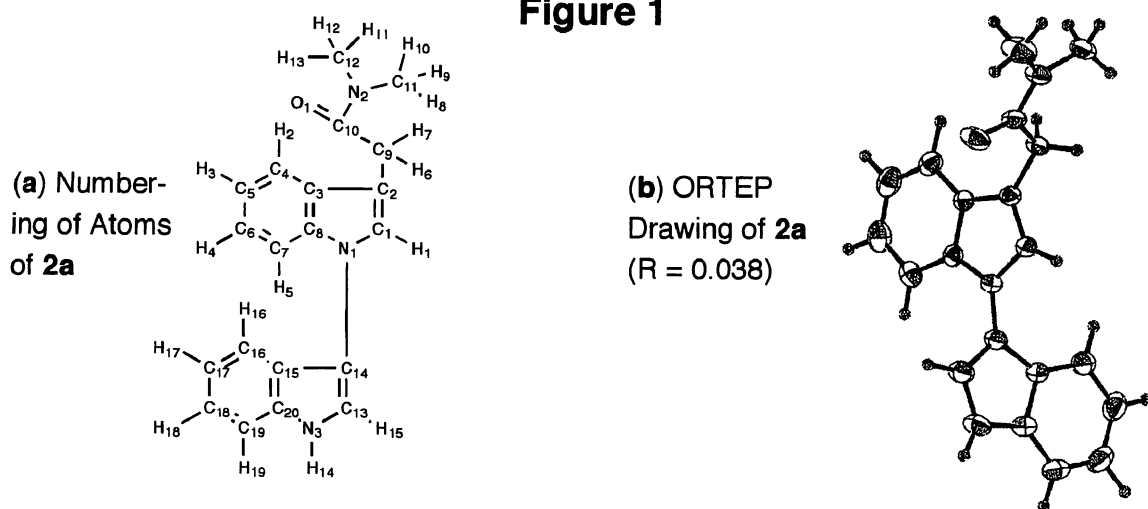
When *N,N*-dimethyl-1-hydroxyindole-3-acetamide (**1a**) was reacted with indole (10 mol eq.) in 85% HCOOH at room temperature, rapid nucleophilic substitution reaction on the indole nitrogen occurred, yielding *N,N*-dimethyl-1-(indol-3-yl)indole-3-acetamide (**2a**) together with the dehydroxylated *N,N*-dimethylindole-3-acetamide (**3a**) in 84 and 8% yields, respectively (Scheme 1). In addition, **4**,<sup>6</sup> **5**,<sup>7</sup> and **6**,<sup>7</sup> which are well known products originating from an excess amount of indole under acidic reaction conditions, were also isolated with respective yields of 1, 11, and 37%. Further examples are *Nb*-trifluoroacetyl- (**1b**) and *Nb*-methoxycarbonyl-1-hydroxytryptamine (**1c**), which generated a set of products, **2b** and **3b**, with 55 and 9% yields, or **2c** and **3c** with 47 and 9% yields, respectively. In both reactions, concomitant formations of **4**, **5**, and **6** were also observed. As can be seen in the reaction of **7** with indole, the existence of a large substituent on the *Nb* nitrogen did not alter the reaction pathway, providing a 73% yield of **8**.

## Scheme 1



On the other hand, an extra ester group on the tryptamine side chain retarded the reaction and increased dehydroxylation. Thus, 1-hydroxytryptophan derivative (**1d**) produced a 16% yield of **3d** together with a

61% yield of the desired **2d**. The presence of the bromine atom at the 5-position of the indole nucleus further retarded the reaction. As observed in the case of **9a**, the initial material (**9a**) was recovered unchanged with a 24% yield after the reaction for 1 h, while **10** and the dehydroxylated **9b** were produced in 34 and 7% yields, respectively.



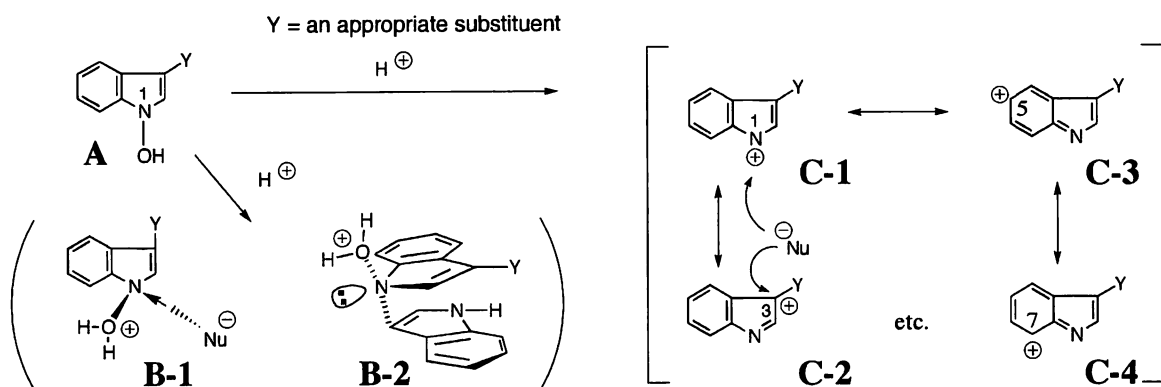
The structure of **2a** was unequivocally determined by X-Ray single crystallographic analysis. The results shown in Figure 1-**b** prove the presence of a covalent bond connecting the *N*-1 of indole to the *C*-3 (*C*<sub>14</sub> in Figure 1-**a**) of the other indole molecule. Positional parameters are shown in Table 1.

In order to establish the structures of 1-(indol-3-yl)indoles (**2b**, **2c**, **2e**, and **2f**), their chemical correlations with **2a** were examined. Hydrolysis of **2b** with 8% NaHCO<sub>3</sub> provided tryptamine (**2e**) with a 99% yield. Methoxycarbonylation of **2e** with methyl chloroformate in the presence of Et<sub>3</sub>N afforded a 99% yield of **2c**, which was identical to the sample obtained from **1c**. Dimethylation of **2e** with HCHO and NaBH<sub>3</sub>CN proceeded smoothly to produce a 92% yield of dimethyltryptamine (**2f**), which was identical to the sample prepared in 78% yield by the reduction of **2a** with LiAlH<sub>4</sub> in THF. The structure of **2d** was determined by spectral data.

On the basis of these novel findings, we next tried to change the nucleophile's structure by employing *N,N*-dimethyl-1-hydroxyindole-3-acetamide (**1a**) as the 1-hydroxyindole component in order to determine its effect on the nucleophilic substitution reaction. When 1-methylindole was chosen as the nucleophile, the expected reaction occurred in 85% HCOOH to generate *N,N*-dimethyl-1-(1-methylindol-3-yl)indole-3-acetamide (**11**) and **3a** in 65 and 8% yields, respectively. Employing 5-methoxyindole as the nucleophile resulted in the production of *N,N*-dimethyl-1-(5-methoxyindol-3-yl)indole-3-acetamide (**12**) with a 58% yield.

The substitution mechanism for the 1-hydroxy group by indole can be explained as follows. We have already shown that the hydroxy oxygen at the 1-position and lying above the plane of the indole nucleus, deviated<sup>8,9</sup> by about 15°, as shown by X-Ray single crystallographic analysis of the tryptophan derivative<sup>8</sup> (**1d**). This finding suggests that the indole nitrogen in 1-hydroxyindoles is no longer exactly  $sp^2$  hybridized. Upon protonation of 1-hydroxy oxygen of 1-hydroxyindoles (**A**, Figure 2), the nitrogen may become more  $sp^3$  hybridized as shown in formula (**B-1**). Therefore, when water leaves from the nitrogen, a nucleophile (indole) could approach from the back side of the group which is leaving as seen in the  $S_N2$  mechanism of the transition state (**B-1** and/or **B-2**), resulting in the formation of **2a-d**.

**Figure 2**



An  $S_N1$  mechanism through resonance-stabilized cation (**C-1** to **C-4**) is another possibility. The contribution of **C-1** would be poor, however, because a positive charge is placed on the electron negative nitrogen, while **C-3** and **C-4**, leading to 5- and 7-substitution, are less important due to the lack of aromaticity of the benzene component. The resonance structure (**C-2**) would thus be more responsible for the reaction resulting in the formation of pyrrolo[2,3-*b*]indole<sup>8</sup> products.

In fact, neither 5- nor 7-substituted indoles<sup>4</sup> were obtained at all, nor was even a trace amount of the formation of pyrrolo[2,3-*b*]indoles<sup>8</sup> observed. Eventually, we might have found the first example of the  $S_N2$  reaction on the indole nitrogen.<sup>10</sup>

In summary, we have discovered<sup>5</sup> the first nucleophilic substitution reaction on the indole nitrogen (1-position) when 1-hydroxytryptamines and -tryptophans are allowed to react with indole derivatives under acidic conditions. This means that a novel and simple synthetic method for 1-(indol-3-yl)tryptamines<sup>8</sup> has been developed. Utilizing various types of nucleophiles, studies are in progress to establish the scope and limitations of this type of reaction. Results will be reported in due course.

## EXPERIMENTAL

IR spectra were determined with a Shimadzu IR-420 or HORIBA FT-720 spectrophotometer and  $^1\text{H-NMR}$  spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel ( $\text{SiO}_2$ , 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

**Reaction of *N,N*-dimethyl-1-hydroxyindole-3-acetamide (1a) with indole in 85% HCOOH** — A powdered **1a** (52.3 mg, 0.24 mmol) was added to a solution of indole (288.1 mg, 2.46 mmol) in 85% HCOOH (4.5 mL) and the mixture was stirred at rt for 2 h. After addition of  $\text{H}_2\text{O}$ , the whole was extracted with  $\text{CHCl}_3$ -MeOH (95:5, v/v). The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave oil, which was column-chromatographed repeatedly on  $\text{SiO}_2$  sequentially with  $\text{CHCl}_3$ -hexane (1:1, v/v),  $\text{CHCl}_3$ , and  $\text{CHCl}_3$ -MeOH (99:1, v/v) to give 2-(indol-3-yl)-2,3-dihydroindole (**5**, 32.1 mg, 11%), 2-(indol-3-yl)indole (**4**, 3.3 mg, 1%), 2-(2-bisindol-3-yl)ethylaniline (**6**, 105.3 mg, 37%), *N,N*-dimethyl-1-(indol-3-yl)indole-3-acetamide (**2a**, 63.6 mg, 84%), and *N,N*-dimethylindole-3-acetamide (**3a**, 3.7 mg, 8%) in the order of elution. **2a**: mp 160.0–161.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3153, 1635, 744  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.02 (3H, s), 3.12 (3H, s), 3.93 (2H, s), 7.10 (1H, ddd,  $J=8.1, 7.1, 0.9$  Hz), 7.14–7.18 (2H, m), 7.21 (1H, d,  $J=2.7$  Hz, collapsed to s on addition of  $\text{D}_2\text{O}$ ), 7.24 (1H, s), 7.22–7.29 (2H, m), 7.42 (2H, m), 7.69–7.72 (1H, m), 8.69 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 317 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}\cdot 1/4\text{H}_2\text{O}$ : C, 74.63; H, 6.11; N, 13.05. Found: C, 74.83; H, 5.99; N, 12.99.

**Reaction of *Nb*-trifluoroacetyl-1-hydroxytryptamine (1b) with indole in 85% HCOOH** — A solution of **1b** (102.2 mg, 0.38 mmol) in  $\text{CHCl}_3$  (1.0 mL) was added to a solution of indole (438.9 mg, 3.75 mmol) in 85% HCOOH (9.0 mL) and the mixture was stirred at rt for 1 h. After the same work-up as described in the reaction of **1a**, the resultant residue was column-chromatographed repeatedly on  $\text{SiO}_2$  with  $\text{CHCl}_3$ -hexane (2:1, v/v) and AcOEt-hexane (1:4, v/v) to give **5** (35.5 mg, 8%), *Nb*-trifluoroacetyltryptamine (**3b**, 8.4 mg, 9%), *Nb*-trifluoroacetyl-1-(indol-3-yl)tryptamine (**2b**, 77.2 mg, 55%), **4** (3.3 mg, 1%), and **6** (171.5 mg, 39%) in the order of elution. **2b**: mp 134.0–136.0°C (pale brown prisms, recrystallized from  $\text{CHCl}_3$ -hexane). IR (KBr): 3390, 3303, 1707, 1178, 748, 739  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.14 (2H, t,  $J=6.4$  Hz), 3.77 (2H, q,  $J=6.4$  Hz, collapsed to t on addition of  $\text{D}_2\text{O}$ ), 6.45 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 7.15 (1H, ddd,  $J=8.1, 7.1, 1.0$  Hz), 7.17–7.25 (2H, m), 7.21 (1H, s), 7.30 (1H, ddd,  $J=8.1, 7.1, 1.0$  Hz), 7.33–7.37 (1H, m), 7.38 (1H, d,  $J=2.7$  Hz, collapsed to s on addition of  $\text{D}_2\text{O}$ ), 7.44 (1H, d,  $J=8.1$  Hz), 7.48 (1H, d,  $J=8.1$  Hz), 7.64–7.67 (1H, m), 8.27 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_3\text{OF}_3$ : C, 64.69; H, 4.34; N, 11.32. Found: C,

64.74; H, 4.35; N, 11.34.

**Reaction of 1-hydroxy-Nb-methoxycarbonyltryptamine (1c) with indole in 85% HCOOH** — In the same procedure and column-chromatography as described in the reaction of **1b** with indole, **1c** (107.4 mg, 0.49 mmol) and indole (577.2 mg, 4.93 mmol) were used to give **5** (52.3 mg, 9%), **4** (3.2 mg, 1%), Nb-methoxycarbonyltryptamine (**3c**, 9.4 mg, 9%), 1-(indol-3-yl)-Nb-methoxycarbonyltryptamine (**2c**, 77.2 mg, 47%), and **6** (296.0 mg, 51%) in the order of elution. **2c**: mp 118.0—119.5°C (pale brown prisms, recrystallized from AcOEt–hexane). IR (KBr): 3338, 3305, 1678, 1464, 1282, 748, 737 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.06 (2H, br t, *J*=6.6 Hz), 3.59 (2H, br q, *J*=6.6 Hz), 3.67 (3H, s), 4.83 (1H, br s), 7.13—7.21 (4H, m), 7.29 (1H, ddd, *J*=8.2, 7.0, 1.0 Hz), 7.32—7.34 (1H, m), 7.38 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.47 (2H, d, *J*=9.0 Hz), 7.67 (1H, br d, *J*=7.0 Hz), 8.27 (1H, br s). MS *m/z* : 333 (M<sup>+</sup>). *Anal.* Calcd for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>·1/8H<sub>2</sub>O: C, 71.57; H, 5.71; N, 12.52. Found: C, 71.69; H, 5.70; N, 12.57.

**Reaction of (±)-Nb-acetyl-1-hydroxytryptophan methyl ester (1d) with indole in 85% HCOOH** — 85% HCOOH (4.0 mL) was added to a mixed powder consisted of **1d** (49.9 mg, 0.18 mmol) and indole (211.5 mg, 1.8 mmol) and the resultant solution was stirred at rt for 3.5 h. After the same work-up as described in the reaction of **1a**, the resultant residue was column-chromatographed repeatedly on SiO<sub>2</sub> with CHCl<sub>3</sub>–MeOH (99:1, v/v) to give (±)-Nb-acetyl-1-(indol-3-yl)tryptophan methyl ester (**2d**, 41.1 mg, 61%) and (±)-Nb-acetyltryptophan methyl ester (**3d**, 7.3 mg, 16%) together with **4**, **5**, and **6**. **2d**: colorless gum. IR (film): 1739, 1653, 742 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.99 (3H, s), 3.39 (1H, dd, *J*=14.0, 5.0 Hz), 3.44 (1H, dd, *J*=14.0, 5.5 Hz), 3.72 (3H, s), 5.00—5.04 (1H, m), 6.07 (1H, br d, *J*=7.8 Hz), 7.13 (1H, s), 7.14—7.20 (3H, m), 7.28—7.33 (2H, m), 7.38 (1H, d, *J*=2.5 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.44 (1H, d, *J*=7.5 Hz), 7.48 (1H, d, *J*=7.5 Hz), 7.58—7.61 (1H, m), 8.28 (1H, br s, disappeared on addition of D<sub>2</sub>O). HRMS: Calcd for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>: 375.1583. Found: 375.1589.

**1-(Indol-3-yl)tryptamine (2e) from Nb-trifluoroacetyl-1-(indol-3-yl)tryptamin (2b)** — The experimental procedure and spectral data of **2e** were already reported in the previous paper.<sup>1c</sup>

**1-(Indol-3-yl)-N,N-dimethyltryptamine (2f) from 2a** — LiAlH<sub>4</sub> (32.4 mg, 0.85 mmol) was added to a solution of **2a** (22.8 mg, 0.07 mmol) in anhydrous THF (3.0 mL) and the mixture was stirred at rt for 1 h. After addition of MeOH and aqueous Rochelle salt under ice cooling, the whole was extracted with CHCl<sub>3</sub>. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>–MeOH–28% NH<sub>3</sub> (46:3:0.3, v/v) to

give **2f** (16.7 mg, 78%). **2f**: colorless gum. IR (film): 3401, 1456, 739  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 2.38 (6H, s), 2.73—2.78 (2H, m), 3.01—3.06 (2H, m), 7.03 (1H, ddd,  $J=8.1, 7.1, 1.0$  Hz), 7.07—7.12 (2H, m), 7.18—7.21 (2H, m), 7.21 (1H, s), 7.29 (1H, d,  $J=7.1$  Hz), 7.43 (1H, s), 7.46 (1H, d,  $J=8.1$  Hz), 7.61—7.64 (1H, m). HRMS: Calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_3$ : 303.1735. Found: 303.1738.

**1-(Indol-3-yl)-*N*b-methoxycarbonyltryptamine (2c) from 2e** — A solution of ClCOOMe (51.2 mg, 0.54 mmol) in MeOH (2.0 mL) was added to a solution of **2e** (75.8 mg, 0.28 mmol) in MeOH (4.0 mL) and  $\text{Et}_3\text{N}$  (0.6 mL, 4.27 mmol) at  $0^\circ\text{C}$  and the mixture was stirred at rt for 30 min. Evaporation of the solvent under reduced pressure afforded a residue. After addition of  $\text{H}_2\text{O}$ , the whole was extracted with  $\text{CHCl}_3$ -MeOH (95:5, v/v). The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave oil, which was column-chromatographed on  $\text{SiO}_2$  with AcOEt-hexane (1:2, v/v) to give **2c** (90.8 mg, 99%).

**1-(Indol-3-yl)-*N,N*-dimethyltryptamine (2f) from 2e** — A solution of 95%  $\text{NaBH}_3\text{CN}$  (9.2 mg, 0.14 mmol) in MeOH (0.4 mL) was added to a solution of **2e** (17.8 mg, 0.06 mmol) in AcOH (0.1 mL) at  $0^\circ\text{C}$ . A solution of 35% HCHO (23.8 mg, 0.28 mmol) in MeOH (0.5 mL) was then added at  $0^\circ\text{C}$  and the mixture was stirred at rt for 3 h. After evaporation of the solvent, the whole was made alkaline by adding 8% NaOH under ice cooling and extracted with  $\text{CHCl}_3$ -MeOH (95:5, v/v). The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave oil, which was column-chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3$ -MeOH-28%  $\text{NH}_3$  (46:3:0.3, v/v) to give **2f** (18.0 mg, 92%).

**Reaction of *N*-adamantyl-1-hydroxyindole-3-acetamide (7) with indole in 85% HCOOH** — In the same procedure as described in the reaction of **1d** with indole, 85% HCOOH (4.0 mL), **7** (51.8 mg, 0.16 mmol), and indole (189.0 mg, 1.6 mmol) were used. Column-chromatography was performed on  $\text{SiO}_2$  with  $\text{CHCl}_3$  to give *N*-adamantyl-1-(indol-3-yl)indole-3-acetamide (**8**, 49.3 mg, 73%) together with **4**, **5**, and **6**. **8**: colorless gum. IR (film): 3400, 2906, 1653, 741  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.63 (6H, br s), 1.93 (6H, br s), 2.02 (3H, br s), 3.70 (2H, s), 5.52 (1H, s), 7.15 (1H, t,  $J=7.8$  Hz), 7.18—7.23 (2H, m), 7.28 (1H, s), 7.30 (1H, t,  $J=7.8$  Hz), 7.32—7.35 (1H, m), 7.39 (1H, d,  $J=3.0$  Hz, collapsed to s on addition of  $\text{D}_2\text{O}$ ), 7.43 (1H, d,  $J=7.8$  Hz), 7.48 (1H, d,  $J=7.8$  Hz), 7.63—7.66 (1H, m), 8.35 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). HRMS: Calcd for  $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}$ : 423.2311. Found: 423.2314.

**Reaction of 5-bromo-1-hydroxy-*N*b-methoxycarbonyltryptamine (9a) with indole in 85% HCOOH** — In the same procedure as described in the reaction of **1d** with indole, 85% HCOOH (4.0 mL), 5-



bromo-1-hydroxy-*Nb*-methoxycarbonyltryptamine (**9a**, 53.6 mg, 0.17 mmol), and indole (200.5 mg, 1.7 mmol) were used. Column-chromatography was performed on SiO<sub>2</sub> with CHCl<sub>3</sub>–hexane (1:1, v/v) to give 5-bromo-1-(indol-3-yl)-*Nb*-methoxycarbonyltryptamine (**10**, 23.9 mg, 34%), **9b** (3.5 mg, 7%) and unreacted **9a** (13.0 mg, 24%) in the order of elution together with **4**, **5**, and **6**. **10**: colorless gum. IR (film): 3415, 3311, 1701, 1462, 746 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.00 (2H, t, *J*=6.8 Hz), 3.55 (2H, q, *J*=6.8 Hz), 3.68 (3H, s), 4.80 (1H, br s), 7.14 (1H, t, *J*=8.1 Hz), 7.16 (1H, d, *J*=8.8 Hz), 7.17 (1H, s), 7.24 (1H, dd, *J*=8.8, 1.7 Hz), 7.29 (1H, t, *J*=8.1 Hz), 7.35 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D<sub>2</sub>O), 7.40 (1H, d, *J*=8.1 Hz), 7.46 (1H, d, *J*=8.1 Hz), 7.77 (1H, d, *J*=1.7 Hz), 8.32 (1H, br s, disappeared on addition of D<sub>2</sub>O). HRMS: Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub><sup>81</sup>Br: 413.0562. Found: 413.0572. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub><sup>79</sup>Br: 411.0583. Found: 411.0588.

#### Reaction of *N,N*-dimethyl-1-hydroxyindole-3-acetamide (**1a**) with 1-methylindole in 85% HCOOH

— In the same procedure as described in the reaction of **1d** with indole, 85% HCOOH (4.0 mL), **1a** (51.5 mg, 0.24 mmol), and 1-methylindole (319.8 mg, 2.4 mmol) were used. Column-chromatography was performed on SiO<sub>2</sub> with CHCl<sub>3</sub> to give *N,N*-dimethyl-1-(1-methylindol-3-yl)indole-3-acetamide (**11**, 50.6 mg, 65%) and **3a** (3.7 mg, 8%) together with products originated from 1-methylindole. **11**: mp 219.0–221.0°C (pale gray needles, recrystallized from CHCl<sub>3</sub>–hexane). IR (KBr): 1635, 1493, 1456, 742 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.01 (3H, s), 3.11 (3H, s), 3.57 (3H, s), 3.92 (2H, s), 6.82 (1H, d, *J*=2.5 Hz), 6.92 (1H, dd, *J*=8.0, 2.5 Hz), 7.15–7.19 (2H, m), 7.24 (1H, s), 7.27 (1H, d, *J*=3.0 Hz), 7.33 (1H, d, *J*=8.0 Hz), 7.70–7.74 (2H, m), 8.31 (1H, br s, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 347 (M<sup>+</sup>). *Anal.* Calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>·1/2H<sub>2</sub>O: C, 70.78; H, 6.18; N, 11.80. Found: C, 71.04; H, 6.01; N, 11.80.

#### Reaction of *N,N*-dimethyl-1-hydroxyindole-3-acetamide (**1a**) with 5-methoxyindole in 85% HCOOH

— In the same procedure as described in the reaction of **1d** with indole, 85% HCOOH (4.0 mL), **1a** (49.6 mg, 0.23 mmol), and 5-methoxyindole (335.0 mg, 2.3 mmol) were used. Column-chromatography was performed on SiO<sub>2</sub> with AcOEt–hexane (3:1, v/v) to give *N,N*-dimethyl-1-(5-methoxyindol-3-yl)indole-3-acetamide (**12**, 46.1 mg, 58%) together with products originated from 5-methoxyindole. **12**: colorless gum. IR (film): 2935, 1641, 742 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.98 (3H, s), 3.08 (3H, s), 3.88 (3H, s), 3.91 (2H, s), 7.12 (1H, t, *J*=8.0 Hz), 7.15–7.20 (2H, m), 7.23 (1H, s), 7.25 (1H, s), 7.29–7.33 (2H, m), 7.41 (1H, d, *J*=8.0 Hz), 7.44 (1H, d, *J*=8.0 Hz), 7.71–7.74 (1H, m). HRMS: Calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O: 331.1684. Found: 331.1689.

**X-Ray Crystallographic Analysis of 2a** — The reflection data were collected on a Rigaku AFC5R

diffractometer over the range of  $77.79^\circ < 2\theta < 79.98^\circ$  using  $\text{CuK}\alpha$  radiation ( $\lambda = 1.54178 \text{ \AA}$ ) and the  $\omega$ - $2\theta$  scan method at a  $2\theta$  scan speed of  $6^\circ/\text{min}$ . The structure of **2a** was solved by the direct method using MITHRIL<sup>11</sup>) and refined by the full-matrix least-squares method with anisotropic thermal factors for non-hydrogen atoms and with isotropic ones for hydrogen atoms. The final *R*- and *R*<sub>w</sub>-factors were 0.038 and 0.040 for 1456 observed reflections [ $I > 3.00\sigma(I)$ ], respectively. The atomic parameters are listed in Table 1. Crystal data for **2a**:  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}$ ;  $M = 317.39$ ; monoclinic; space group,  $P2_1/n$  (#14);  $a = 11.043$  (1)  $\text{\AA}$ ,  $b = 13.675$  (2)  $\text{\AA}$ ,  $c = 11.712$  (1)  $\text{\AA}$ ;  $\beta = 99.924$  (9)°;  $V = 1742.2$  (4)  $\text{\AA}^3$ ,  $Z = 4$ ,  $D_{\text{calc.}} = 1.210 \text{ g/cm}^3$ .

Table 1. Positional Parameters and *B* (eq) for **2a**

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (eq)	atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (eq)
O (1)	0.2074 (2)	0.7574 (2)	0.4475 (2)	6.5 (1)	C (19)	0.4658 (4)	0.1342 (3)	0.4285 (3)	5.3 (2)
N (1)	0.2840 (2)	0.4442 (2)	0.5274 (2)	3.9 (1)	C (20)	0.4568 (3)	0.2291 (2)	0.4698 (3)	4.2 (1)
N (2)	0.0271 (2)	0.7978 (2)	0.3388 (2)	4.8 (1)	H (1)	0.225 (2)	0.482 (2)	0.357 (2)	4.33 (2)
N (3)	0.5464 (3)	0.2908 (2)	0.5238 (3)	5.4 (1)	H (2)	0.047 (3)	0.648 (2)	0.673 (3)	6.32 (2)
C (1)	0.2152 (3)	0.4971 (2)	0.4383 (3)	3.9 (1)	H (3)	0.120 (4)	0.590 (3)	0.869 (3)	9.05 (4)
C (2)	0.1430 (2)	0.5632 (2)	0.4814 (3)	3.7 (1)	H (4)	0.271 (3)	0.466 (3)	0.909 (3)	7.57 (3)
C (3)	0.1656 (2)	0.5510 (2)	0.6038 (3)	3.6 (1)	H (5)	0.355 (3)	0.388 (2)	0.760 (3)	5.21 (2)
C (4)	0.1166 (3)	0.5935 (3)	0.6946 (3)	4.7 (2)	H (6)	-0.018 (3)	0.639 (2)	0.446 (2)	5.04 (2)
C (5)	0.1541 (4)	0.5601 (3)	0.8054 (4)	5.9 (2)	H (7)	0.024 (3)	0.610 (2)	0.331 (3)	5.67 (2)
C (6)	0.2413 (4)	0.4862 (3)	0.8293 (4)	5.8 (2)	H (8)	-0.128 (4)	0.823 (3)	0.232 (3)	7.78 (3)
C (7)	0.2927 (3)	0.4429 (3)	0.7434 (3)	4.8 (2)	H (9)	-0.146 (3)	0.793 (3)	0.340 (3)	7.44 (3)
C (8)	0.2533 (3)	0.4762 (2)	0.6306 (3)	3.6 (1)	H (10)	-0.111 (3)	0.712 (3)	0.250 (3)	7.35 (3)
C (9)	0.0540 (3)	0.6317 (2)	0.4127 (4)	4.1 (1)	H (11)	0.159 (5)	0.902 (3)	0.342 (5)	13 (2)
C (10)	0.1026 (3)	0.7337 (2)	0.4018 (3)	4.2 (1)	H (12)	0.022 (5)	0.932 (4)	0.263 (5)	14 (2)
C (11)	-0.0989 (4)	0.7755 (3)	0.2875 (4)	5.7 (2)	H (13)	0.039 (5)	0.930 (4)	0.387 (5)	15 (2)
C (12)	0.0728 (5)	0.8957 (3)	0.3188 (7)	7.8 (3)	H (14)	0.628 (3)	0.276 (2)	0.530 (3)	6.44 (2)
C (13)	0.4927 (3)	0.3763 (3)	0.5487 (3)	5.1 (2)	H (15)	0.546 (3)	0.429 (2)	0.586 (3)	6.13 (2)
C (14)	0.3701 (3)	0.3703 (2)	0.5139 (3)	3.9 (1)	H (16)	0.158 (3)	0.263 (2)	0.402 (3)	5.48 (2)
C (15)	0.3431 (3)	0.2766 (2)	0.4620 (3)	3.7 (1)	H (17)	0.170 (4)	0.102 (3)	0.335 (3)	8.61 (4)
C (16)	0.2370 (3)	0.2285 (3)	0.4104 (3)	4.9 (2)	H (18)	0.368 (4)	0.020 (3)	0.345 (3)	8.70 (3)
C (17)	0.2466 (5)	0.1355 (3)	0.3693 (3)	6.3 (2)	H (19)	0.549 (3)	0.106 (2)	0.437 (3)	6.65 (3)
C (18)	0.3597 (5)	0.0887 (3)	0.3791 (3)	6.3 (2)					

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