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

Received, 7th April, 2003, Accepted, 19th May, 2003, Published online, 21st May, 2003

NUCLEOPHILIC SUBSTITUTION REACTION AT THE 1-POSITION OF 1-HYDROXYTRYPTAMINE AND -TRYPTOPHAN DERIVATIVES[1]

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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_N2 mechanism on the indole nitrogen (1-position) is proposed.

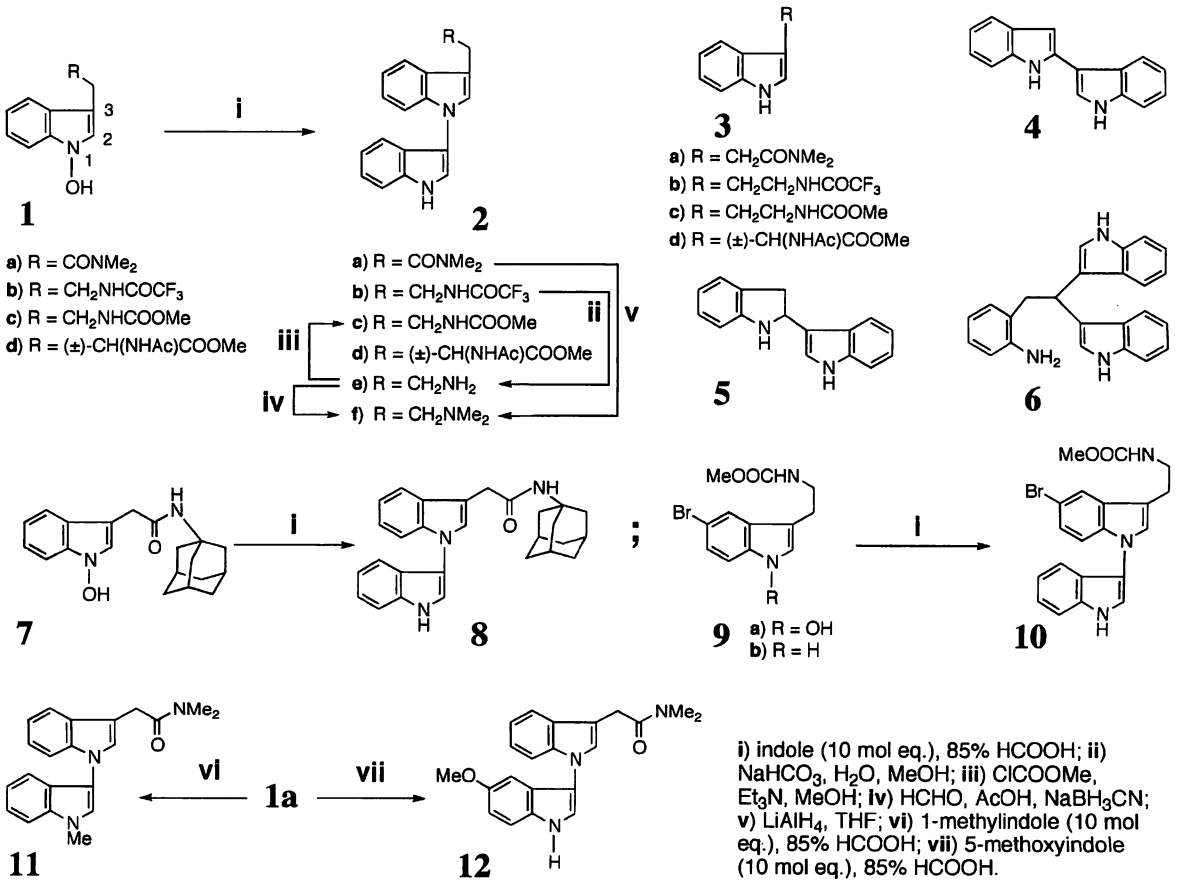
Indole is an electron rich aromatic heterocycle.[2] Indoles can therefore react with various kinds of electrophiles,[2] as is well known both chemically and as common knowledge. In contrast to the accepted wisdom, no one has challenged to realize a nucleophilic substitution reactions on the indole nucleus.

About 30 years ago,[3] 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.[3] 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.[4] 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.[5] 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.[4]

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**,[6] **5**,[7] and **6**,[7] 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 *N*b-trifluoroacetyl- (**1b**) and *N*b-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 *N*b nitrogen did not alter the reaction pathway, providing a 73% yield of **8**.

Scheme 1

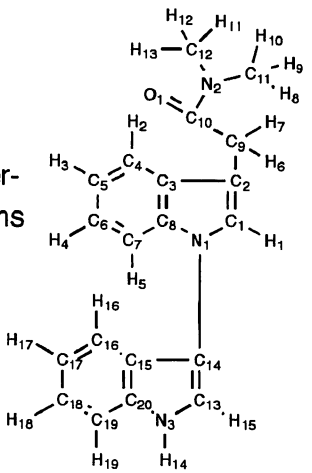


On the other hand, an extra ester group on the tryptamine side chain retarded the reaction and increased dehydroxylation. Thus, 1-hydroxytryptophan derivative (**1d**) produced a 16% yield of **3d** together with a

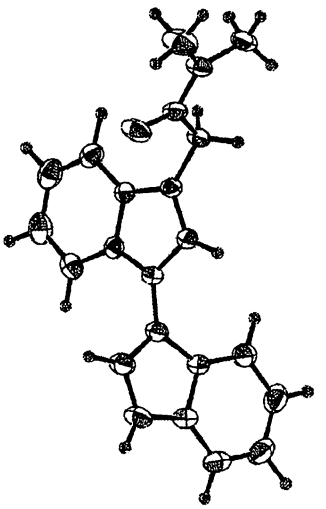
61% yield of the desired **2d**. The presence of the bromine atom at the 5-position of the indole nucleus further retarded the reaction. As observed in the case of **9a**, the initial material (**9a**) was recovered unchanged with a 24% yield after the reaction for 1 h, while **10** and the dehydroxylated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

Figure 1

(**a**) Numbering of Atoms of **2a**



(**b**) ORTEP Drawing of **2a** (R = 0.038)



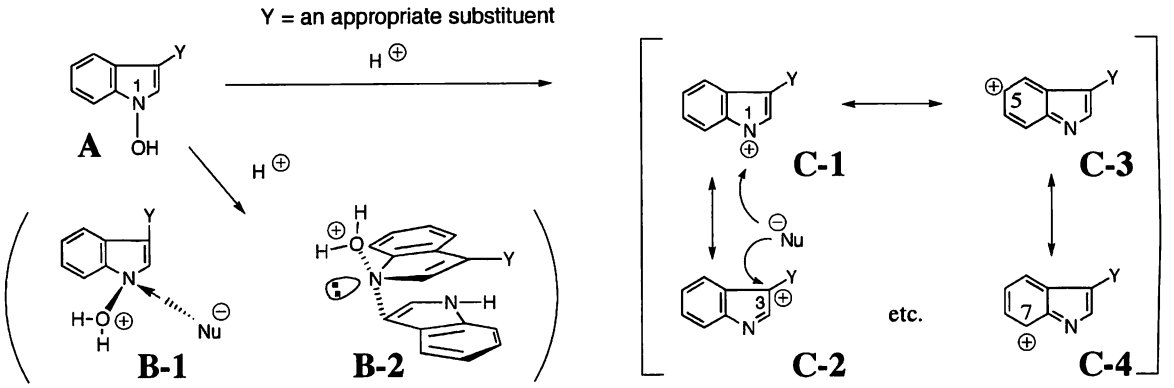
The structure of **2a** was unequivocally determined by X-Ray single crystallographic analysis. The results shown in Figure 1-**b** prove the presence of a covalent bond connecting the *N*-1 of indole to the *C*-3 (C_{14} in Figure 1-**a**) of the other indole molecule. Positional parameters are shown 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% $NaHCO_3$ provided tryptamine (**2e**) with a 99% yield. Methoxycarbonylation of **2e** with methyl chloroformate in the presence of Et_3N afforded a 99% yield of **2c**, which was identical to the sample obtained from **1c**. Dimethylation of **2e** with HCHO and $NaBH_3CN$ 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 $LiAlH_4$ 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-methoxylindol-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[8,9] by about 15°, as shown by X-Ray single crystallographic analysis of the tryptophan derivative[8] (**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 *SN2* mechanism of the transition state (**B-1** and/or **B-2**), resulting in the formation of **2a–d**.

Figure 2



An *SN1* 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[8] products.

In fact, neither 5- nor 7-substituted indoles[4] were obtained at all, nor was even a trace amount of the formation of pyrrolo[2,3-*b*]indoles[8] observed. Eventually, we might have found the first example of the *SN2* reaction on the indole nitrogen.[10]

In summary, we have discovered[5] 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[8] 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}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 (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

Reaction of *N,N*-dimethy-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 H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave oil, which was column-chromatographed repeatedly on SiO_2 sequentially with $CHCl_3$–hexane (1:1, v/v), $CHCl_3$, and $CHCl_3$–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*-dimethyl1-(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 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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 D_2O), 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 D_2O). MS *m/z*: 317 (M^+). *Anal.* Calcd for $C_{20}H_{19}N_3O \cdot 1/4H_2O$: C, 74.63; H, 6.11; N, 13.05. Found: C, 74.83; H, 5.99; N, 12.99.

Reaction of *N*b-trifluoroacetyl-1-hydroxytryptamine (1b) with indole in 85% HCOOH — A solution of **1b** (102.2 mg, 0.38 mmol) in $CHCl_3$ (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 SiO_2 with $CHCl_3$–hexane (2:1, v/v) and AcOEt–hexane (1:4, v/v) to give **5** (35.5 mg, 8%), *N*b-trifluoroacetyltryptamine (**3b**, 8.4 mg, 9%), *N*b-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 $CHCl_3$–hexane). IR (KBr): 3390, 3303, 1707, 1178, 748, 739 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.14 (2H, t, *J*=6.4 Hz), 3.77 (2H, q, *J*=6.4 Hz, collapsed to t on addition of D_2O), 6.45 (1H, br s, disappeared on addition of D_2O), 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 D_2O), 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 D_2O). *Anal.* Calcd for $C_{20}H_{16}N_3OF_3$: C, 64.69; H, 4.34; N, 11.32. Found: C,

64.74; H, 4.35; N, 11.34.

Reaction of 1-hydroxy-*N*b-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%), *N*b-methoxycarbonyltryptamine (**3c**, 9.4 mg, 9%), 1-(indol-3-yl)-*N*b-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^{-1}. ^{1}H-NMR ($CDCl_3$) 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_2O), 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^+). *Anal.* Calcd for $C_{20}H_{19}N_3O_2 \cdot 1/8H_2O$: C, 71.57; H, 5.71; N, 12.52. Found: C, 71.69; H, 5.70; N, 12.57.

Reaction of (±)-*N*b-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_2 with $CHCl_3$–MeOH (99:1, v/v) to give (±)-*N*b-acetyl-1-(indol-3-yl)tryptophan methyl ester (**2d**, 41.1 mg, 61%) and (±)-*N*b-acetyltryptophan methyl ester (**3d**, 7.3 mg, 16%) together with **4**, **5**, and **6**. **2d**: colorless gum. IR (film): 1739, 1653, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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_2O), 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_2O). HRMS: Calcd for $C_{22}H_{21}N_3O_3$: 375.1583. Found: 375.1589.

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

1-(Indol-3-yl)-*N*,*N*-dimethyltryptamine (2f) from 2a — $LiAlH_4$ (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 $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% NH_3 (46:3:0.3, v/v) to

give **2f** (16.7 mg, 78%). **2f**: colorless gum. IR (film): 3401, 1456, 739 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 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 $C_{20}H_{21}N_3$: 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 Et_3N (0.6 mL, 4.27 mmol) at 0°C and the mixture was stirred at rt for 30 min. Evaporation of the solvent under reduced pressure afforded a residue. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave oil, which was column-chromatographed on 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% $NaBH_3CN$ (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°C. A solution of 35% HCHO (23.8 mg, 0.28 mmol) in MeOH (0.5 mL) was then added at 0°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 $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–28% 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 SiO_2 with $CHCl_3$ 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 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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 D_2O), 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 D_2O). HRMS: Calcd for $C_{28}H_{29}N_3O$: 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-*N*b-methoxycarbonyltryptamine (**9a**, 53.6 mg, 0.17 mmol), and indole (200.5 mg, 1.7 mmol) were used. Column-chromatography was performed on SiO_2 with $CHCl_3$–hexane (1:1, v/v) to give 5-bromo-1-(indol-3-yl)-*N*b-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^{-1}. ^{1}H-NMR ($CDCl_3$) 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_2O), 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_2O). HRMS: Calcd for $C_{20}H_{18}N_3O_2{}^{81}Br$: 413.0562. Found: 413.0572. Calcd for $C_{20}H_{18}N_3O_2{}^{79}Br$: 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_2 with $CHCl_3$ 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 $CHCl_3$–hexane). IR (KBr): 1635, 1493, 1456, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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_2O). MS *m/z* : 347 (M^+). *Anal.* Calcd for $C_{21}H_{21}N_3O_2 \cdot 1/2H_2O$: 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_2 with AcOEt–hexane (3:1, v/v) to give *N,N*-dimethyl-1-(5-methoxylindol-3-yl)indole-3-acetamide (**12**, 46.1 mg, 58%) together with products originated from 5-methoxylindole. **12**: colorless gum. IR (film): 2935, 1641, 742 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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 $C_{21}H_{21}N_3O$: 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°<2θ<79.98° using Cu$K\alpha$ radiation (λ=1.54178 Å) and the ω–2θ scan method at a 2θ scan speed of 6°/min. The structure of **2a** was solved by the direct method using MITHRIL[11]) 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*w-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**: $C_{20}H_{19}N_3O$; *M*=317.39; monoclinic; space group, $P2_1/n$ (#14); *a*=11.043 (1) Å, *b*=13.675 (2) Å, *c*=11.712 (1) Å; β=99.924 (9)°; *V*=1742.2 (4) Å^3, *Z*=4, *D*calc.=1.210 g/cm^3.

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

atom	*x*	*y*	*z*	*B* (eq)	atom	*x*	*y*	*z*	*B* (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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