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

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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. Indoles can therefore react with various kinds of electrophiles, 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, 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. 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. 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. 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.
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, 5, and 6, 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.

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.

\[ \text{Figure 1} \]

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\(_3\)N afforded a 99% yield of \(2c\), which was identical to the sample obtained from \(1c\). Dimethylation of \(2e\) with HCHO and NaBH\(_3\)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\(_4\) 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-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\(^8,9\) 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 \(S_N2\) mechanism of the transition state (B-1 and/or B-2), resulting in the formation of \(2a–d\).

**Figure 2**

\[
\begin{align*}
\text{A} & \quad \text{Y = an appropriate substituent} \\
\text{B-1} & \quad \text{H}^+ \\
\text{B-2} & \quad \text{Nu}
\end{align*}
\]

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\(^8\) 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 \(S_N2\) 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$_2$O, the whole was extracted with CHCl$_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na$_2$SO$_4$, 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-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 cm$^{-1}$. $^1$H-NMR (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 D$_2$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 D$_2$O). MS $m/z$: 317 (M$^+$). Anal. Calcd for C$_{20}$H$_{19}$N$_3$O·1/4H$_2$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 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%), 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 CHCl$_3$–hexane). IR (KBr): 3153, 1635, 744 cm$^{-1}$. $^1$H-NMR (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 D$_2$O), 6.45 (1H, br s, disappeared on addition of D$_2$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 D$_2$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 D$_2$O). Anal. Calcd for C$_{20}$H$_{19}$N$_3$OF$_3$: C, 64.69; H, 4.34; N, 11.32. Found: C,
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\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)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\(^+\)). Anal. Calcd for C\(_{20}\)H\(_{19}\)N\(_3\)O\(_2\)·1/8H\(_2\)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\(_2\) with CHCl\(_3\)–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\(^{-1}\). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)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\(_2\)O). HRMS: Calcd for C\(_{22}\)H\(_{21}\)N\(_3\)O\(_3\): 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.\(^1\)c

1-(Indol-3-yl)-N\(_2\)N\(_2\)-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\(_2\)SO\(_4\), 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. ¹H-NMR (CD₃OD) [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 C₂₀H₂₁N₃: 303.1735. Found: 303.1738.

1-(Indol-3-yl)-Nb-methoxycarbonyltrpytamine (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 Et₃N (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 H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave oil, which was column-chromatographed on SiO₂ 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% NaBH₃CN (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 CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave oil, which was column-chromatographed on SiO₂ with AcOEt–hexane (1:2, 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 SiO₂ with CHCl₃ 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. ¹H-NMR (CDCl₃) [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 D₂O), 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 D₂O). HRMS: Calcd for C₂₈H₂₉N₃O: 423.2311. Found: 423.2314.

Reaction of 5-bromo-1-hydroxy-Nb-methoxycarbonyltrpytamine (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\textsubscript{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\textsubscript{2} with CHCl\textsubscript{3}–hexane (1:1, v/v) to give 5-bromo-1-(indol-3-yl)-N\textsubscript{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\textsuperscript{-1}. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 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\textsubscript{2}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\textsubscript{2}O). HRMS: Calcd for C\textsubscript{20}H\textsubscript{18}N\textsubscript{3}O\textsubscript{2}\textsuperscript{81}Br: 413.0562. Found: 413.0572. Calcd for C\textsubscript{20}H\textsubscript{18}N\textsubscript{3}O\textsubscript{2}\textsuperscript{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 CHCl\textsubscript{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\textsubscript{3}–hexane). IR (KBr): 1635, 1493, 1456, 742 cm\textsuperscript{-1}. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 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\textsubscript{2}O). MS \( m/z \) : 347 (M\textsuperscript{+}). Anal. Calcd for C\textsubscript{21}H\textsubscript{21}N\textsubscript{3}O\textsubscript{2}·1/2H\textsubscript{2}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\textsubscript{2} 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\textsuperscript{-1}. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \): 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\textsubscript{21}H\textsubscript{21}N\textsubscript{3}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 CuKα radiation ($\lambda=1.54178$ Å) and the $\omega-2\theta$ scan method at a $2\theta$ scan speed of 6°/min. The structure of 2a was solved by the direct method using MITHRIL11) 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 Rw-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$_3$O; $M=317.39$; monoclinic; space group, P2$_1$/n (#14); $a=11.043$ (1) Å, $b=13.675$ (2) Å, $c=11.712$ (1) Å; $\beta=99.924$ (9)°; $V=1742.2$ (4) Å$^3$, $Z=4$, $D_{\text{calc.}}=1.210$ g/cm$^3$.

| Table 1. Positional Parameters and B (eq) for 2a |
|---|---|---|---|
| atom | $x$ | $y$ | $z$ | $B$ (eq) |
| O (1) | 0.2074 (2) | 0.7574 (2) | 0.4475 (2) | 6.5 (1) |
| N (1) | 0.2840 (2) | 0.4442 (2) | 0.5274 (2) | 3.9 (1) |
| N (2) | 0.0271 (2) | 0.7978 (2) | 0.3388 (2) | 4.8 (1) |
| N (3) | 0.5464 (3) | 0.2908 (2) | 0.5238 (3) | 5.4 (1) |
| C (1) | 0.2152 (3) | 0.4971 (2) | 0.4383 (3) | 3.9 (1) |
| C (2) | 0.1430 (2) | 0.5632 (2) | 0.4814 (3) | 3.7 (1) |
| C (3) | 0.1656 (2) | 0.5510 (2) | 0.6038 (3) | 3.6 (1) |
| C (4) | 0.1166 (3) | 0.5035 (3) | 0.6946 (3) | 4.7 (2) |
| C (5) | 0.1541 (4) | 0.5003 (3) | 0.8054 (4) | 5.9 (2) |
| C (6) | 0.2413 (4) | 0.4862 (3) | 0.8293 (4) | 5.8 (2) |
| C (7) | 0.2927 (3) | 0.4429 (3) | 0.7434 (3) | 4.8 (2) |
| C (8) | 0.2533 (3) | 0.4762 (2) | 0.6306 (3) | 3.6 (1) |
| C (9) | 0.0540 (3) | 0.6317 (2) | 0.4127 (4) | 4.1 (1) |
| C (10) | 0.1026 (3) | 0.7337 (2) | 0.4018 (3) | 4.2 (1) |
| C (11) | 0.0989 (4) | 0.7755 (3) | 0.2875 (4) | 5.7 (2) |
| C (12) | 0.0728 (5) | 0.8957 (3) | 0.3188 (7) | 7.8 (3) |
| C (13) | 0.4927 (3) | 0.3763 (3) | 0.5487 (3) | 5.1 (2) |
| C (14) | 0.3701 (3) | 0.3703 (2) | 0.5139 (3) | 3.9 (1) |
| C (15) | 0.3431 (3) | 0.2766 (2) | 0.4620 (3) | 3.7 (1) |
| C (16) | 0.2370 (3) | 0.2285 (3) | 0.4104 (3) | 4.9 (2) |
| C (17) | 0.2466 (5) | 0.1355 (3) | 0.3693 (3) | 6.3 (2) |
| C (18) | 0.3597 (5) | 0.0887 (3) | 0.3791 (3) | 6.3 (2) |

REFERENCES AND NOTES


9. Acheson and co-workers have reported that 1-benzoyloxyindole has also a pyramidal nitrogen atom (N-1); R. M. Acheson, M. H. Benn, J. Jacyno, and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 2*, 1983, 497.
