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SIMPLE SYNTHESES OF ANALOGS OF A WASABI PHYTOALEXIN[1]

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Abstract — Preparations of 5-nitroindol-1-yl (**5a**), 6-nitroindol-1-yl (**5b**), and 1,2,3-benzotriazol-1-yl 1-methoxyindole-3-carboxylates (**9**) are reported. These are active esters and proved to be useful intermediates for the preparations of ester and amide analogs of methyl 1-methoxyindole-3-carboxylate, a wasabi phytoalexin.

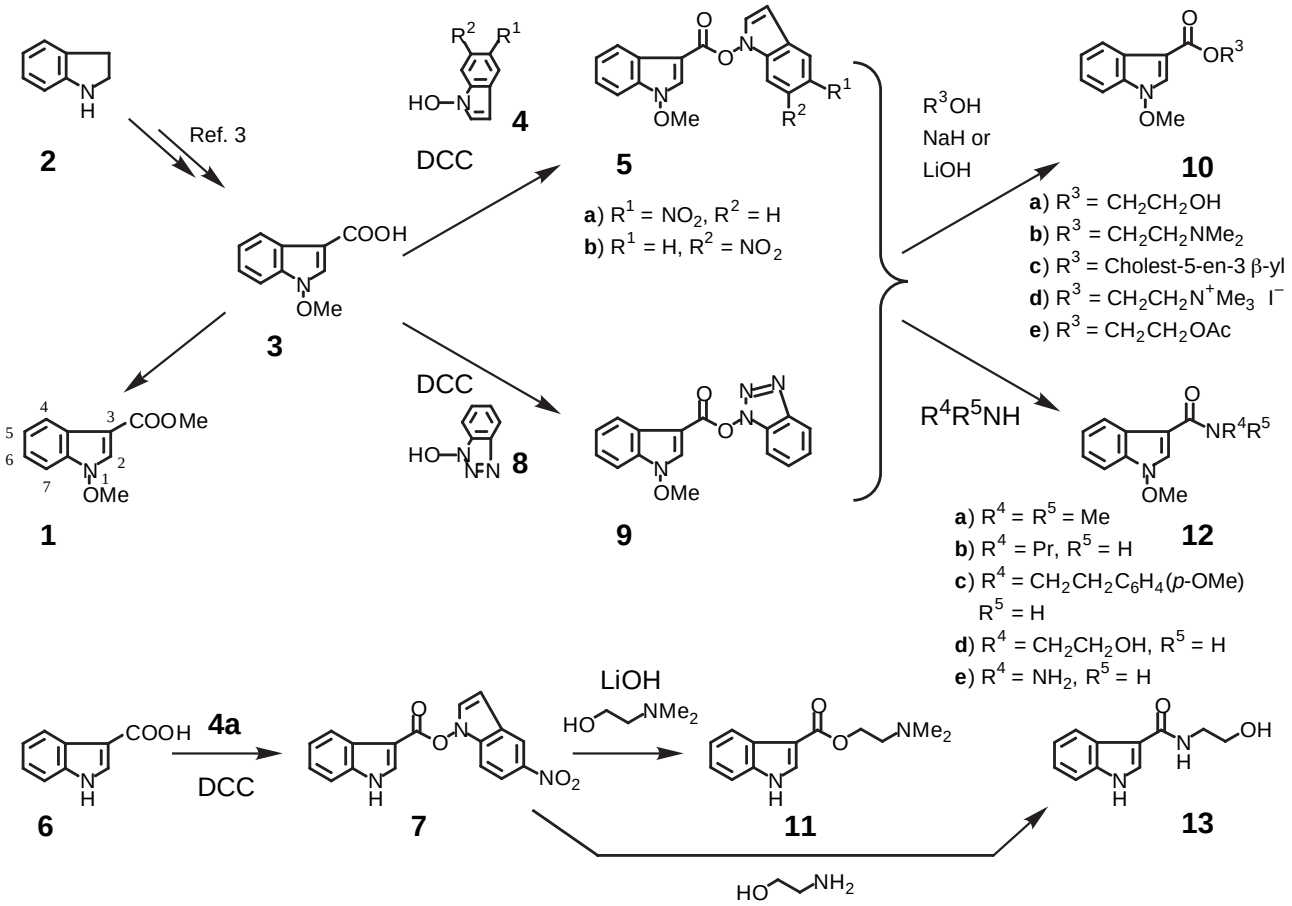
Pedras and co-workers[2] isolated methyl 1-methoxyindole-3-carboxylate[2,3] (**1**) from Wasabi (*Wasabia japonica*, syn. *Eutrema wasabi*) as a phytoalexin (Scheme 1). In our project to determine the effect of 1-hydroxy and 1-methoxy moieties on the chemical reactivities[4,5] and biological activities of indole compounds,[6] we have much interested in the syntheses of various analogs of **1**. In this paper, we wish to describe a widely applicable and simple method for producing many kinds of ester and amide analogs of **1**.

We have already established a five-step synthetic method for **1** from indoline (**2**) in 51% overall yield.[5] Among synthetic intermediates involved in the route, we selected 1-methoxyindole-3-carboxylic acid (**3**) as a starting material to meet our end. When we examined the reaction of **3** with 1-hydroxy-5-nitroindole (**4a**) and 1-hydroxy-6-nitroindole (**4b**) in the presence of DCC, 5-nitroindol-1-yl (**5a**) and 6-nitroindol-1-yl 1-methoxyindole-3-carboxylates (**5b**) were found to be isolated as crystallines in 84 and 76% yields, respectively. Similar reaction of indole-3-carboxylic acid (**6**) with **4a** provided **7** in 31% yield. By the reaction with 1-hydroxy-1,2,3-benzotriazole (**8**), **3** afforded 1,2,3-benzotriazol-1-yl 1-methoxyindole-3-carboxylate (**9**) in 89% yield.

Compounds (**5a**), (**5b**), and (**9**) are stable compounds and easy to handle. They can be stored at room temperature for months without decomposition in the absence of nucleophiles. In spite of these facts, they have intrinsic reactive nature as active esters, being suggested by the absorption band at 1760, 1751, and 1764 cm^{-1}, respectively, in their IR spectra. On the other hand, **7** has an absorption band at 1727 with a shoulder at 1756 cm^{-1}.

In accord with the expectations, alcohols reacted with **5a**, **5b**, and **9** in the presence of an appropriate base to give ester analogs of **1** in excellent yields. For example, 2-hydroxyethyl (**10a**) and 2-(*N*,*N*-dimethylamino)ethyl 1-methoxyindole-3-carboxylate (**10b**) were prepared by the reaction of **5a** either with ethylene glycol in the presence of NaH or with 2-(*N*,*N*-dimethylamino)ethanol in the presence of LiOH in 99 and 98% yields, respectively. The reaction of **5b** with 2-(*N*,*N*-dimethylamino)ethanol in the presence of LiOH also provided **10b** in 98% yield. Although the reaction of **3** with cholesterol in the presence of DCC did not afford cholest-5-en-3β-yl 1-methoxyindole-3-carboxylate (**10c**) at all, **5a** reacted with cholesterol using NaH as a base to produce **10c**, but in only 38% yield

Scheme 1



The reaction of **9** with 2-(*N*,*N*-dimethylamino)ethanol in the presence of LiOH provided **10b** in 95% yield, while the same reaction of **7** afforded **11** in only 43% yield. Comparison of these results with those of **5a** and **5b** shows that the presence of 1-methoxy group plays an important role on enhancing the reactivities of **5a**, **5b**, and **9**. Among these three compounds, **5a** and **5b** seem to be superior to **9** from the point of recycling of the activators (**4a**, **4b**, and **8**). In fact, recovery of orange-colored and acidic **4a** and **4b** can be more easily carried out from the reaction mixture compared with that of **8**.

On the other hand, an acetylcholine analog, [2-(1-methoxyindol-3-yl)ethyl]trimethylammonium iodide (**10d**), could be produced by the treatment of **10b** with excess MeI in a quantitative yield. Acetylation of **10a** with Ac_2O-pyridine afforded **10e** in 94% yield, while **10a** was reproduced by alkaline hydrolysis of **10e** in 94% yield. Thus, preparations of various ester analogs of **1** would be possible from **5a**, **5b**, and **9**.

Amide analogs of **1** can also be obtained utilizing **5a**, **5b**, and **9** as starting materials. Reactions of **5a** in MeOH with dimethylamine, propylamine, *p*-methoxyphenethylamine, 2-aminoethanol, and hydrazine produced **12a**, **12b**, **12c**, **12d**, and **12e** in 82, 74, 84, 91, and 92% yields, respectively. The reaction of **5b** and **9** with 2-aminoethanol provided **12d** in 91 and 98% yields, respectively, while the same reaction of **7** afforded **13** in 37% yield. These results again prove the enhancing effect of a 1-methoxy group on the nucleophilic substitution reaction. A function of 1-hydroxyindoles as an activator of carboxylic acids is also demonstrated.

In conclusion, we have succeeded in isolating active esters (**5a**, **5b**, and **9**). They can be stored and used,

if need be, as useful reagents for preparing both ester and amide analogs of **1**. Biological evaluations of new compounds are now under investigation.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a 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.

5-Nitroindol-1-yl 1-Methoxyindole-3-carboxylate (5a) from 1-Methoxyindole-3-carboxylic acid (3) — A solution of 1-hydroxy-5-nitroindole (**4a**, 135.6 mg, 0.76 mmol) in anhydrous THF (2.0 mL) was added to a solution of **3** (96.7 mg, 0.51 mmol) and DCC (128.4 mg, 0.62 mmol) in anhydrous THF (3.0 mL), and the mixture was stirred at 62 ℃ for 5.5 h. After addition of H_2O and $CHCl_3$–MeOH (95:5, v/v) to the reaction mixture, the whole was made basic (pH 11) by adding aqueous 2N NaOH under ice cooling, and extracted with $CHCl_3$–MeOH (95:5, v/v). Urea was filtered off and washed with AcOEt. The combined extract and washings were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–hexane (1:1, v/v) to give **5a** (149.4 mg, 84%). The H_2O layer was made acidic (pH 2) with aqueous 2N HCl, 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 a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **4a** (34.1 mg, 25%) and **3** (1.3 mg, 1.3%) in the order of elution. **5a**: mp 186—188 ℃ (yellow powder, recrystallized from $CHCl_3$-hexane). IR (KBr): 1760, 1515, 1344, 1191, 1062, 923, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (3H, s), 6.73 (1H, d, *J*=3.4 Hz), 7.33 (1H, d, *J*=8 Hz), 7.37 (1H, t, *J*=7.5 Hz), 7.42 (1H, d, *J*=3.4 Hz), 7.43 (1H, t, *J*=7.5 Hz), 7.58 (1H, d, *J*=7.5 Hz), 8.13 (1H, dd, *J*=8, 2.5 Hz), 8.17 (1H, d, *J*=8 Hz), 8.25 (1H, s), 8.63 (1H, d, *J*=2.5 Hz). MS (FAB$^+$) *m*/*z*: 352 (M^++1). *Anal*. Calcd for $C_{18}H_{13}N_3O_5 \cdot 1/4H_2O$: C, 60.76 ; H, 3.82; N, 11.81. Found: C, 60.69 ; H, 3.63 ; N, 11.82 .

6-Nitroindol-1-yl 1-Methoxyindole-3-carboxylate (5b) from 3 — A solution of 1-hydroxy-6-nitroindole (**4b**, 276.8 mg, 1.55 mmol) in anhydrous THF (4.0 mL) was added to a solution of **3** (198.5 mg, 1.04 mmol) and DCC (258.4 mg, 1.25 mmol) in anhydrous THF (6.0 mL), and the mixture was stirred at 65 ℃ for 4.5 h. After the same work-up as described in the case of **5a** from **3** using $CHCl_3$ for extraction, **5b** (278.9 mg, 76%) was obtained. The same work-up of the H_2O layer as described above afforded **4b** (64.7 mg, 24%). **5b**: mp 166—169 ℃ (black prisms, recrystallized from AcOEt–hexane). IR (KBr): 1751, 1513, 1338, 1186, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.27 (3H, s), 6.66 (1H, dd, *J*=3.5, 1.1 Hz), 7.37 (1H, ddd, *J*=7.9, 7.5, 1.1 Hz), 7.43 (1H, ddd, *J*=7.9, 7.5, 1.1 Hz), 7.55 (1H, d, *J*=3.5 Hz), 7.58 (1H, dt, *J*=7.9, 1.1 Hz), 7.71 (1H, d, *J*=8.8 Hz), 8.05 (1H, dd, *J*=8.8, 1.9 Hz), 8.16 (1H, dt, *J*=7.9, 1.1 Hz), 8.26 (1H, br d, *J*=1.9 Hz), 8.28 (1H, s). *Anal*. Calcd for $C_{18}H_{13}N_3O_5$: C, 61.54; H, 3.73; N, 11.96. Found: C, 61.52; H, 3.71; N, 11.72.

5-Nitroindol-1-yl Indole-3-carboxylate (7) from Indole-3-carboxylic Acid (6) — A solution of **4a** (166.8 mg, 0.93 mmol) in anhydrous THF (2.0 mL) was added to a solution of **6** (101.0 mg,

0.63 mmol) and DCC (155.4 mg, 0.75 mmol) in anhydrous THF (3.0 mL), and the mixture was stirred at 60 ℃ for 24 h. The same work-up as described in the case of **5a** from **3**, using $CHCl_3$ for extraction and $CHCl_3$–hexane (2:1, v/v) as an eluent, afforded 5-nitroindole (21.5 mg, 14%) and **7** (62.4 mg, 31%) in the order of elution. After the same work-up of the H_2O layer as described above, **4a** (48.4 mg, 29%) and **6** (25.8 mg, 26%) were obtained in the order of elution. **7**: mp 209—212 ℃ (brown prisms, recrystallized from AcOEt–hexane). IR (KBr): 1756 (sh), 1727, 1521, 1438, 1330 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.87 (1H, dd, *J*=4.1, 1.3 Hz), 7.28 (1H, t, *J*=8 Hz), 7.31 (1H, t, *J*=8 Hz), 7.54 (1H, d, *J*=9 Hz), 7.61 (1H, d, *J*=8 Hz), 7.97—8.00 (2H, m), 8.09 (1H, dd, *J*=9, 2.2 Hz), 8.60 (1H, dd, *J*=4.1, 1.3 Hz), 8.69 (1H, d, *J*=2.2 Hz). 12.40 (1H, br s). *Anal*. Calcd for $C_{17}H_{11}N_3O_4$: C, 63.55 ; H, 3.45 ; N, 13.08. Found: C, 63.42 ; H, 3.66 ; N, 12.73.

1,2,3-Benzotriazol-1-yl 1-Methoxyindole-3-carboxylate (9) from 1-Methoxyindole-3-carboxylic acid (3) — A solution of 1-hydroxy-1,2,3-benzotriazole (**8**, 105.5 mg, 0.78 mmol) in anhydrous THF (2.0 mL) was added to a solution of **3** (99.2 mg, 0.52 mmol) and DCC (130.0 mg, 0.62 mmol) in anhydrous THF (4.0 mL), and the mixture was stirred at rt for 28.5 h, and then at 60 ℃ for 4 h. After the same work-up as described in the case of **5a** from **3**, using benzene–$CHCl_3$ (2:1, v/v) as an eluent, **9** (143.5 mg, 89%) was obtained. The same work-up of the H_2O layer as described above, using $CHCl_3$ for extraction, afforded **3** (7.1 mg, 7%). **9**: mp 132— 134 ℃ (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 1764, 1627, 1575, 904 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.25 (3H, s), 7.37 (1H, t, *J*=7.5 Hz), 7.41—7.45 (2H, m), 7.49—7.56 (2H, m), 7.58 (1H, d, *J*=8 Hz), 8.09 (1H, d, *J*=8 Hz), 8.17 (1H, d, *J*=7.5 Hz), 8.33 (1H, s). MS (FAB$^+$) *m/z*: 309 (M^++1). *Anal*. Calcd for $C_{16}H_{12}N_4O_3 \cdot 1/4H_2O$: C, 61.43; H, 4.03; N, 17.91. Found: C, 61.66 ; H, 3.87; N, 17.91 .

2-Hydroxyethyl 1-Methoxyindole-3-carboxylate (10a) i) from 5a — A solution of ethylene glycol (0.07 mL, 1.3 mmol) in DMF (2.0 mL) was added to 60% NaH (287.0 mg, 7.10 mmol) at 0 ℃, and the mixture was stirred at rt for 15 min. To the mixture, a solution of **5a** (50.0 mg, 0.14 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 30 min. 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 an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **10a** (33.2 mg, 99%). The H_2O layer was made acidic by adding aqueous 2N HCl 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 give **4a** (23.1 mg, 91%). **10a**: colorless viscous oil. IR (film): 3400 (br), 1698, 1523, 1209, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (1H, br s), 3.96—3.99 (2H, m), 4.15 (3H, s), 4.47—4.50 (2H, m), 7.29 (1H, ddd, *J*=8.1, 7, 1 Hz), 7.33 (1H, ddd, *J*=8.1, 7, 1 Hz), 7.48 (1H, dd, *J*=8.1, 1 Hz), 7.99 (1H, s), 8.16 (1H, dd, *J*=8.1, 1 Hz). High-resolution MS *m/z*: Calcd for $C_{12}H_{13}NO_4$: 235.0845. Found: 235.0850.

ii) from 10e — 40% Aqueous Na_2CO_3 (1.5 mL) was added to a solution of **10e** (13.7 mg, 0.05 mmol) in MeOH (1.5 mL) and the mixture was stirred at rt for 30 min. After addition of ice and 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 an oil, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **10a** (10.9 mg, 94%).

***N*,*N*-Dimethylaminoethyl 1-Methoxyindole-3-carboxylate (10b) i) from 5a —** Lithium

hydroxide (35.2 mg, 1.47 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 60 ℃ for 10 min. To the mixture, a solution of **5a** (51.5 mg, 0.15 mmol) in DMF (3.0 mL) was added and the whole was stirred at rt for 1.5 h. After the same work-up as described in the case of **10a** from **5a**, using $CHCl_3$–MeOH (97:3, v/v) as an eluent, **10b** (36.8 mg, 96%) was obtained. The same work-up of the H_2O layer as described above, using $CHCl_3$ for extraction, afforded **4a** (25.1 mg, 97%). **10b**: colorless oil. IR (KBr): 1698, 1207, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (6H, s), 2.76 (2H, t, *J*=6 Hz), 4.14 (3H, s), 4.44 (2H, t, *J*=6 Hz), 7.28 (1H, ddd, *J*=8, 7.7, 1.2 Hz), 7.31 (1H, ddd, *J*=8, 7.7, 1.2 Hz), 7.46 (1H, dt, *J*=8, 1.2 Hz), 7.99 (1H, s), 8.19 (1H, br d, *J*=8 Hz). High-resolution MS *m/z*: Calcd for $C_{14}H_{18}N_2O_3$: 262.1317. Found: 262.1316.

ii) from 5b — Lithium hydroxide (35.1 mg, 1.47 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol) and the mixture was stirred at 60 ℃ for 10 min and at rt for additional 10 min. To the mixture, a solution of **5b** (51.3 mg, 0.15 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 30 min. After the same work-up as described above, **10b** (37.4 mg, 98%) was obtained. The same work-up of H_2O layer as described above gave **4b** (24.9 mg, 95%).

iii) from 9 — Lithium hydroxide (37.2 mg, 1.55 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 63 ℃ for 10 min. To the mixture, a solution of **9** (46.5 mg, 0. 15 mmol) in DMF (3.0 mL) was added and the whole was stirred at rt for 1 h. After the same work-up as described above, **10b** (37.0 mg, 95%) was obtained. The same work-up of H_2O layer as described above, using $CHCl_3$–MeOH (95:5, v/v) for extraction, afforded **8** (7.9 mg, 40%).

Cholest-5-en-3β-yl 1-Methoxyindole-3-carboxylate (10c) from 5a — A solution of cholesterol (558.1 mg, 1.44 mmol) in DMF (8.0 mL) was added to 60% NaH (64.6 mg, 1.6 mmol), and the mixture was stirred at rt for 15 min. To the mixture, a solution of **5a** (101.5 mg, 0.29 mmol) in DMF (2.5 mL) was added, and the whole was stirred at rt for 3.5 h. After the same work-up as described in the case of **10a** from **5a** using $CHCl_3$–hexane (1:2, v/v) as an eluent, **10c** (59.7 mg, 38%) and cholesterol (459.1 mg) were obtained in the order of elution. The same work-up of H_2O layer as described above, using $CHCl_3$ for extraction and as an eluent, afforded an additional cholesterol (21.9 mg), **4a** (45.3 mg, 87%), and **3** (5.2 mg, 9%) in the order of elution. **10c**: viscous hard oil. IR (KBr): 2944, 1691, 1523, 1207, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 0.87 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz), 0.92 (3H, d, *J*=6.6 Hz), 1.08 (3H, s), 0.97—2.06 (26H, m), 2.45—2.54 (2H, m), 4.14 (3H, s), 4.84—4.91 (1H, m), 5.43 (1H, br d, *J*=4.9 Hz), 7.26 (1H, ddd, *J*=8, 7.6, 1 Hz), 7.31 (1H, ddd, *J*=8, 7.6, 1 Hz), 7.45 (1H, d, *J*=7.6 Hz), 7.95 (1H, s), 8.17 (1H, d, *J*=7.6 Hz). High-resolution MS (FAB^+) *m/z*: Calcd for $C_{37}H_{53}NO_3Na$: 582.3923. Found: 582.3922 $(M+Na)^+$.

[2-(1-Methoxyindol-3-carboxy)ethyl]trimethylammonium Iodide (10d) from 10b — Methyl iodide (1.0 mL, 16 mmol) was added to a solution of **10b** (36.8 mg, 0.14 mmol) in MeOH (2.0 mL) and the mixture was stirred at rt for 30 min. Solvent was evaporated under reduced pressure to leave a solid (**10d**, 50.3 mg, 99.7%). **10d**: mp 181—183 ℃ (colorless powder, recrystallized from $CHCl_3$–MeOH). IR (KBr): 1683, 1201, 746 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.20 (9H, s), 3.78—3.82 (2H, m), 4.17 (3H, s), 4.69 (2H, br s), 7.29 (1H, br t, *J*=7.8 Hz), 7.36 (1H, br t, *J*=7.8 Hz), 7.60 (1H, br d, *J*=7.8 Hz), 8.08 (1H, br d, *J*=7.8 Hz), 8.53 (1H, s). High-resolution MS (FAB^+) *m/z*: 277 (M^+–I). *Anal.* Calcd for $C_{15}H_{21}N_2O_3I \cdot 1/4H_2O$: C, 44.07; H, 5.30; N, 6.85. Found: C, 44.19; H, 5.11; N,

6.64.

2-Acetoxyethyl 1-Methoxyindole-3-carboxylate (10e) from 10a — Ac_2O (1.75 mL, 18.5 mmol) was added to a solution of **10a** (35.2 mg, 0.15 mmol) in anhydrous pyridine (3.5 mL) and the mixture was stirred at rt for 1.5 h. Solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$ to give **10e** (39.4 mg, 94%). **10e**: colorless oil. IR (film): 1739, 1704 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 4.15 (3H, s), 4.42—4.45 (2H, m), 4.51—4.54 (2H, m), 7.28 (1H, br t, *J*=7.9 Hz), 7.32 (1H, br t, *J*=7.9 Hz), 7.47 (1H, d, *J*=7.9 Hz), 7.97 (1H, s), 8.16 (1H, d, *J*=7.9 Hz). High-resolution MS *m/z*: Calcd for $C_{14}H_{15}NO_5$: 277.0956. Found: 277.0950.

***N*,*N*-Dimethylaminoethyl Indole-3-carboxylate (11) from 7 —** Lithium hydroxide (39.3 mg, 1.64 mmol) was added to dimethylaminoethanol (2.0 mL, 20 mmol), and the mixture was stirred at 60 ℃ for 10 min. To the mixture, a solution of **7** (53.4 mg, 0.17 mmol) in DMF (3.0 mL) was added, and the mixture was stirred at rt for 4.5 h. After the same work-up as described in the case of **10a** from **5a**, using $CHCl_3$ for extraction and $CHCl_3$–MeOH (97:3, v/v) as an eluent, 5-nitroindole (1.8 mg, 7%), **4a** (2.1 mg), **7** (10.1 mg, 19%), and **11** (16.4 mg, 43%) were obtained in the order of elution. The same work-up of H_2O layer as described above, using $CHCl_3$ for extraction, afforded additional **4a** (25.2 mg, total 27.3 mg, 92%). **11:** 129—131 ℃ (colorless needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 1695, 1182 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s), 2.78 (2H, t, *J*=5.9 Hz), 4.46 (2H, t, *J*=5.9 Hz), 7.23—7.27 (2H, m), 7.37—7.41 (1H, m), 7.89 (1H, d, *J*=3.1 Hz), 8.15—8.19 (1H, m), 8.89 (1H, br s). *Anal*. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.95; N, 11.96.

General Procedure for Amide Analogs of Methyl 1-Methoxyindole-3-carboxylate: Amine was added to a solution of an active ester (**5a**, **5b**, **7**, or **9**) in an appropriate solvent and the mixture was stirred. After addition of H_2O to the reaction mixture, the whole was extracted with an organic solvent. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product, which was column-chromatographed on SiO_2 with an eluent to give an amide product (**12**). The H_2O layer was made acidic by adding aqueous 2N HCl and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and evaporated under reduced pressure to give **4a**, **4b**, or **8**.

***N*,*N*-Dimethyl 1-Methoxyindole-3-carboxamide (12a) i) from 5a —** In the general procedure, 50% aqueous Me_2NH (1.0 mL, 9.6 mmol) and **5a** (35.1 mg, 0.1 mmol) in MeOH (3.0 mL) were used. The mixture was stirred at rt for 2 h and $CHCl_3$ was used for extraction. Using $CHCl_3$ as an eluent, **12a** (17.8 mg, 82%) was obtained. After the same work-up of H_2O layer as described in the general procedure, **4a** (16.9 mg, 95%) was obtained. **12a**: pale yellow oil. IR (film): 1612, 1533, 1452, 1394, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.16 (6H, s), 4.12 (3H, s), 7.21 (1H, ddd, *J*=7.8, 7.4, 1 Hz), 7.29 (1H, ddd, *J* =7.8, 7.4, 1 Hz), 7.45 (1H, dt, *J*=7.8, 1 Hz), 7.57 (1H, s), 7.78 (1H, dt, *J*=7.4, 1 Hz). High-resolution MS *m/z*: Calcd for $C_{12}H_{14}N_2O_2$: 218. 1055. Found: 218. 1061.

ii) from 9 — In the general procedure, 50% aqueous Me_2NH (1.0 mL, 9.6 mmol) and **9** (23.6 mg, 0.073 mmol) in MeOH (3.0 mL) were used. The mixture was stirred at rt for 2 h and $CHCl_3$ was used for extraction. Using $CHCl_3$ as an eluent, **12a** (13.1 mg, 82%) was obtained.

***N*-Propyl 1-Methoxyindole-3-carboxamide (12b) from 5a —** In the general procedure,

n-propylamine (1.0 mL, 12.2 mmol) and **5a** (50.4 mg, 0.13 mmol) in $CHCl_3$ (3.0 mL) were used. The mixture was stirred at rt for 3.5 h and $CHCl_3$ was used for extraction. Using $CHCl_3$ as an eluent, **12b** (27.5 mg, 74%) was obtained. After the same work-up of H_2O layer as described in the general procedure, **4a** (20.2 mg, 86%) was obtained. **12b**: mp 82—85 ℃ (colorless needles, recrystallized from $CHCl_3$-hexane). IR (KBr): 1612, 1548 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, *J*=7.2 Hz), 1.67 (2H, sext, *J*=7.2 Hz), 3.46 (2H, br q, *J*=7.2 Hz), 4.12 (3H, s), 5.91 (1H, br t, *J*=7.2 Hz, disappeared on addition of D_2O), 7.26 (1H, ddd, *J*=8.1, 7.8, 1 Hz), 7.31 (1H, ddd, *J*=8.1, 7.8, 1 Hz), 7.48 (1H, dt, *J*=8.1, 1 Hz), 7.83 (1H, s), 7.92 (1H, dt, *J*=8.1, 1 Hz). MS *m/z*: 232 (M^+). *Anal*. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22 ; H, 6.94 ; N, 12.06 . Found: C, 67.00 ; H, 7.01; N, 11.97.

***N*-*p*-Methoxyphenethyl 1-Methoxyindole-3-carboxamide (12c) from 5a —** In the general procedure, *p*-methoxyphenethylamine (1.0 mL, 6.8 mmol) and **5a** (50.4 mg, 0.14 mmol) in $CHCl_3$ (4.0 mL) were used. The mixture was stirred at rt for 3 h and $CHCl_3$ was used for extraction. Using $CHCl_3$ and $CHCl_3$–MeOH (99:1, v/v) successively as eluents, **4a** (2.0 mg) and **12c** (39.0 mg, 84%) were obtained in the order of elution. After the same work-up of H_2O layer as described in the general procedure, **4a** (6.0 mg, total 8.0 mg, 40%) was obtained. **12c**: colorless oil. IR (film): 1621, 1544, 1511, 1245, 1228 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (2H, t, *J*=6.7 Hz), 3.73 (2H, q, *J*=6.7 Hz), 3.80 (3H, s), 4.10 (3H, s), 6.86—6.89 (2H, m), 7.16—7.20 (3H, m), 7.29 (2H, ddd, *J*=8, 7.5, 1 Hz), 7.45 (1H, dt, *J*=8, 1 Hz), 7.68 (1H, dt, *J*=8, 1 Hz), 7.78 (1H, s). High-resolution MS *m/z*: Calcd for $C_{19}H_{20}N_2O_3$: 324.1514. Found: 324.1491.

***N*-(2-Hydroxy)ethyl 1-Methoxyindole-3-carboxamide (12d) i) from 5a —** In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **5a** (51.5 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 1.5 h and $CHCl_3$–MeOH (95:5, v/v) was used for extraction. Using $CHCl_3$–MeOH (99:1, v/v) as an eluent, **4a** (23.0 mg) and **12d** (31.7 mg, 92%) were obtained in the order of elution. After the same work-up of H_2O layer as described in the general procedure, **4a** (1.8 mg, total 24.8 mg, 95%) was obtained. **12d**: oil. IR (film): 1623, 1544, 1228 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, br s, disappeared on addition of D_2O), 3.64 (2H, q, *J*=5.2 Hz), 3.83 (2H, t, *J*=5.2 Hz), 4. 09 (3H, s), 6.52 (1H, br t, *J*=5.2 Hz), 7.22—7.26 (1H, m), 7.30 (1H, ddd, *J*=7.9, 7.5, 1 Hz), 7.46 (1H, dt, *J*=7.9, 1 Hz), 7.85 (1H, s), 7.97 (1H, dt, *J*=7.9, 1 Hz). High-resolution MS *m/z*: Calcd for $C_{12}H_{14}N_2O_3$: 234.1004. Found: 234.1003.

ii) from 5b — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **5b** (50.1 mg, 0.14 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 30 min and $CHCl_3$–MeOH (95:5, v/v) was used for extraction. Using $CHCl_3$–MeOH (95:5, v/v) as an eluent, **4b** (24.8 mg, 98%) and **12d** (28.8 mg, 91%) were obtained in the order of elution.

iii) from 9 — In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **9** (46.3 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 1.5 h and $CHCl_3$–MeOH (95:5, v/v) was used for extraction. Using $CHCl_3$–MeOH (95:5, v/v) as an eluent, **12d** (34.4 mg, 98%) was obtained. After the same work-up of the H_2O layer as described in the general procedure, using $CHCl_3$–MeOH (95:5, v/v) for extraction, **8** (10.8 mg, 53%) was obtained.

1-Methoxyindole-3-carbohydrazide (12e) from 5a — In the general procedure, 100% hydrazine hydrate (0.5 mL, 16 mmol) and **5a** (45.7 mg, 0.10 mmol) in DMF (3.0 mL) were used. The

mixture was stirred at rt for 30 min and $CHCl_3$–MeOH (95:5, v/v) was used for extraction. Using $CHCl_3$–MeOH (99:1, v/v) as an eluent, **4a** (10.1 mg) and **12e** (24.5 mg, 92%) were obtained in the order of elution. After the same work-up of the H_2O layer as described in the general procedure, **4a** (12.8 mg, total 22.9 mg, 99%) was obtained. **12e**: mp 157—159 ℃ (colorless powder, recrystallized from $CHCl_3$-hexane). IR (KBr): 3324, 1616, 1536, 736 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (2H, br s, disappeared on addition of D_2O), 4.13 (3H, s), 7.12 (1H, br s, disappeared on addition of D_2O), 7.27 (1H, br t, *J*=8.2 Hz), 7.32 (1H, br t, *J*=8.2 Hz), 7.48 (1H, dd, *J*=8.2, 0.7 Hz), 7.86 (1H, s), 7.93 (1H, d, *J*=8.2 Hz). MS *m/z*: 205 (M^+). *Anal*. Calcd for $C_{10}H_{11}N_3O_2 \cdot 1/4\ H_2O$: C, 57.27 ; H, 5.28 ; N, 20.03 . Found: C, 57.50 ; H, 5.25 ; N, 19.99.

***N*-(2-Hydroxy)ethyl Indole-3-carboxamide (13) from 7 —** In the general procedure, ethanolamine (0.5 mL, 8.3 mmol) and **7** (47.3 mg, 0.15 mmol) in DMF (3.0 mL) were used. The mixture was stirred at rt for 30 min. Using $CHCl_3$–MeOH (99:3, v/v) and $CHCl_3$–MeOH (99:5, v/v) successively as eluents, **4a** (25.3 mg, 97%) and **13** (11.2 mg, 37%) were obtained in the order of elution. **13**: 189—191 ℃ (brown powder, recrystallized from $CHCl_3$–MeOH–hexane). IR (KBr): 1590, 1573, 1552, 1211 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.32 (2H, q, *J*=5.9 Hz), 3.51 (2H, q, *J*=5.9 Hz, collapsed to t on addition of D_2O), 4.69 (1H, t, *J*=5.9 Hz, disappeared on addition of D_2O), 7.08 (1H, ddd, *J*=7.9, 7.5, 1.1 Hz), 7.13 (1H, ddd, *J*=7.9, 7.5, 1.1 Hz), 7.40 (1H, d, *J*=7.9 Hz), 7.80 (1H, t, *J*=5.9 Hz), 7.99 (1H, d, *J*=2.9 Hz, collapsed to s on addition of D_2O), 8.11 (1H, d, *J*=7.9 Hz), 11.50 (1H, s). MS *m/z*: 204 (M^+). *Anal*. Calcd for $C_{11}H_{12}N_2O_2 \cdot 1/6H_2O$: C, 63.76; H, 5.95; N, 13.52. Found: C, 63.66; H, 5.77; N, 13.53.

REFERENCES AND NOTES

1. This is Part 111 of a series entitled “The Chemistry of Indoles”. Part 110: Y. Fukui and M. Somei, *Heterocycles*, 2001, **55**, 2055.
2. M. S. C. Pedras and J. L. Sorensen, *Phytochemistry*, 1998, **49**, 1959. In the authors' synthesis of methyl 1-methoxyindole-3-carboxylate, our synthetic method[4] for 1-methoxyindole is utilized.
3. R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1117.
4. M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; Review: M. Somei, *ibid.*, 1999, **50**, 1157; M. Somei, F. Yamada, T. Hayashi, A. Goto, and Y. Saga, *ibid.*, 2001, **55**, 457; K. Yamada, T. Kawasaki, Y. Fujita, and M. Somei, *ibid.*, 2001, **55**, 1151 and references cited therein.
5. M. Somei, A. Tanimoto, H. Orita, F. Yamada, and T. Ohta, *Heterocycles*, 2001, **54**, 425.
6. M. Somei, K. Yamada, M. Hasegawa, M. Tabata, Y. Nagahama, H. Morikawa, and F. Yamada, *Heterocycles*, 1996, **43**, 1855; M. Somei, K. Noguchi, and F. Yamada, *ibid.*, 2001, **55**, 1237 and references cited therein.