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journal or publication title	Heterocycles
volume	57
number	9
page range	1627-1634
year	2002-09-01
URL	http://hdl.handle.net/2297/4372

doi: <https://doi.org/10.3987/com-02-9533>

SYNTHESIS OF ANALOGS OF WASABI PHYTOALEXIN (METHYL 1-METHOXYINDOLE-3-CARBOXYLATE)¹

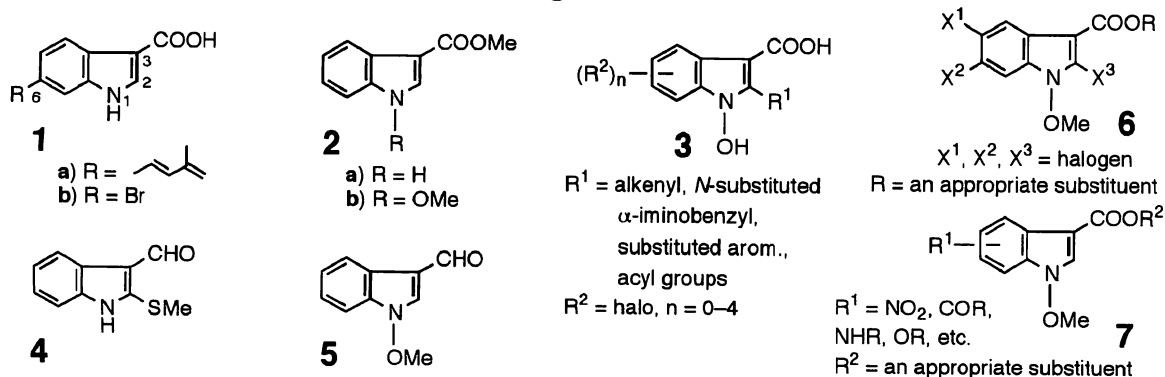
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Abstract — Syntheses of wasabi phytoalexin analogs, such as 6-bromo-5-iodo, 2-bromo-5-iodo, 6-nitro, 5-chloroacetyl, and 6-chloroacetyl congeners, are reported. An interesting effect of the 1-methoxy group on the regioselectivity of electrophilic substitution reactions on indole nucleus is observed.

Indoles having a carboxy or a formyl group at the 3-position, including 1-hydroxy- or 1-methoxyindole derivatives, exhibit marked physiological activities in spite of their simple chemical structures.² Compounds (**1–3**)^{2a–d} are a few representative examples (Scheme 1). Brassicanal A³ (**4**) and 1-methoxyindole-3-carbaldehyde^{3a} (**5**) are additional examples isolated by Takasugi³ and co-workers as phytoalexins of plant family, *Cruciferae*. Recently, Pedras⁴ and co-workers determined methyl 1-methoxyindole-3-carboxylate (**2b**) as a phytoalexin of Wasabi (*Wasabia japonica*, syn. *Eutrema wasabi*).

We have been much interested in determining the effect of 1-methoxy and 1-hydroxy groups on both the chemical reactivities⁵ and biological activities⁶ of indole compounds, aiming at preparing our own biologically active substances. From these points of view, we needed various kinds of analogs⁷ of wasabi phytoalexin like **6** and **7** as shown in general formula.

Figure 1



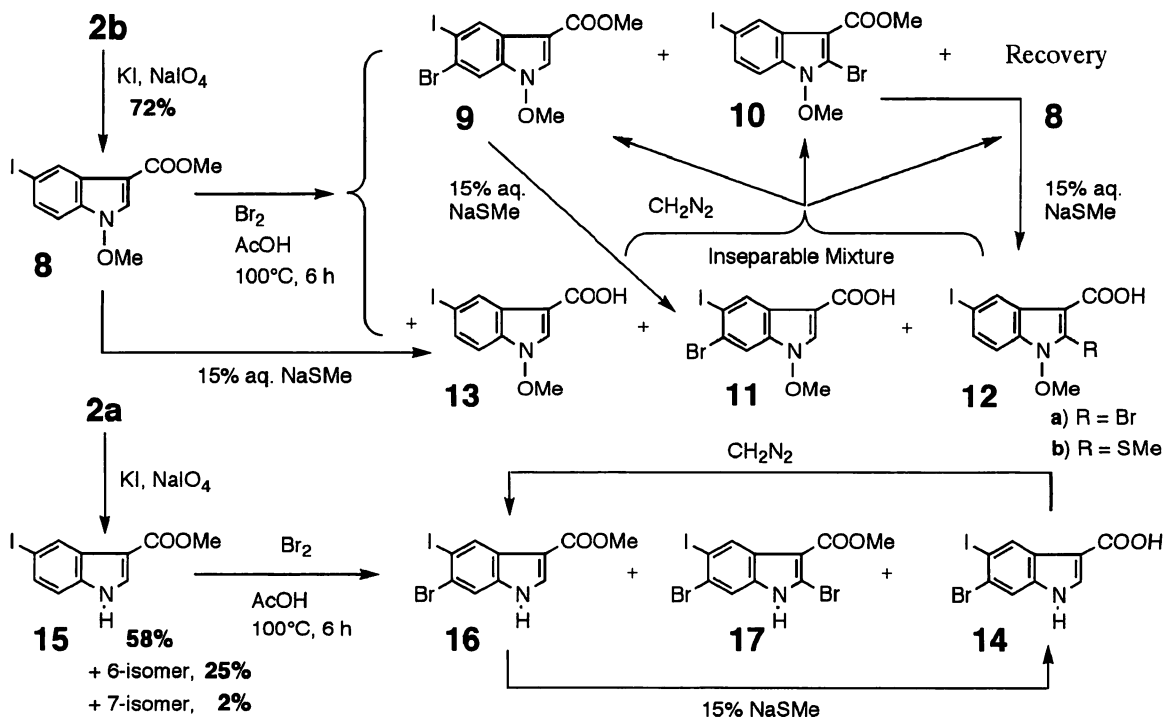
In the previous papers,⁷ we established simple synthetic method for **2b** and its regioselective iodination to give methyl 5-iodo-1-methoxyindole-3-carboxylate^{7a} (**8**). Based on these results, synthesis of methyl 6-bromo-5-iodo-1-methoxyindole-3-carboxylate (**9**), a representative of **6**, seemed to be easy. In fact, however, bromination of **8** gave complex mixtures of products under various reaction conditions.

Relatively clean reaction took place with Br_2 (1.3 mol eq.) in AcOH at 100°C to provide **9**, methyl 2-bromo-5-iodo-1-methoxyindole-3-carboxylate (**10**), 6-bromo- (**11**), 2-bromo-5-iodo-1-methoxyindole-3-carboxylic acid (**12a**), and 5-iodo-1-methoxyindole-3-carboxylic acid (**13**) in 17, 33, 6, 5, and 7% yields, respectively, together with 16% yield of unreacted **8**. Since the carboxylic acids (**11**, **12a**, and **13**) were inseparable, the mixture was methylated with diazomethane (CH_2N_2) to give **9**, **10**, and **8** in 6, 5, and 7% yields, respectively. Assuming that the methylation proceeded in a quantitative yield, the yields of **11**, **12a**, and **13** in the initial bromination products were estimated. Pure compound (**13**) was obtained in 38% yield by reacting **8** with 15% aq. NaSMe. Under similar reaction conditions, **9** provided **11** and **14** in 45 and 38% yields, respectively. In the same reaction of **10**, the expected compound (**12a**) was not produced at all, instead nucleophilic substitution reaction by methyl sulfide occurred at the 2-position to afford **12b** in 83% yield. As a result, pure **12a** has not been obtained yet.

On the other hand, bromination (1.3 mol eq.) of methyl 5-iodoindole-3-carboxylate (**15**) in AcOH at 100°C provided methyl 6-bromo- (**16**), 2,6-dibromo-5-iodoindole-3-carboxylate (**17**), and 6-bromo-5-iodoindole-3-carboxylic acid (**14**) in 48, 8, and 17% yields, respectively. In the same reaction, when 0.85 mol eq. of bromine was employed, **16** and **14** were produced in 56 and 18% yields, respectively, without formation of **17**. The structure of **14** was confirmed by the direct comparison with the sample obtained in 92% yield by the treatment of **16** with 15% NaSMe under reflux. Furthermore, methylation of **14** with CH_2N_2 in MeOH provided **16** in 90% yield.

Above results exhibited that the bromination of **15** proceeds regioselectively at the 6-position, while the

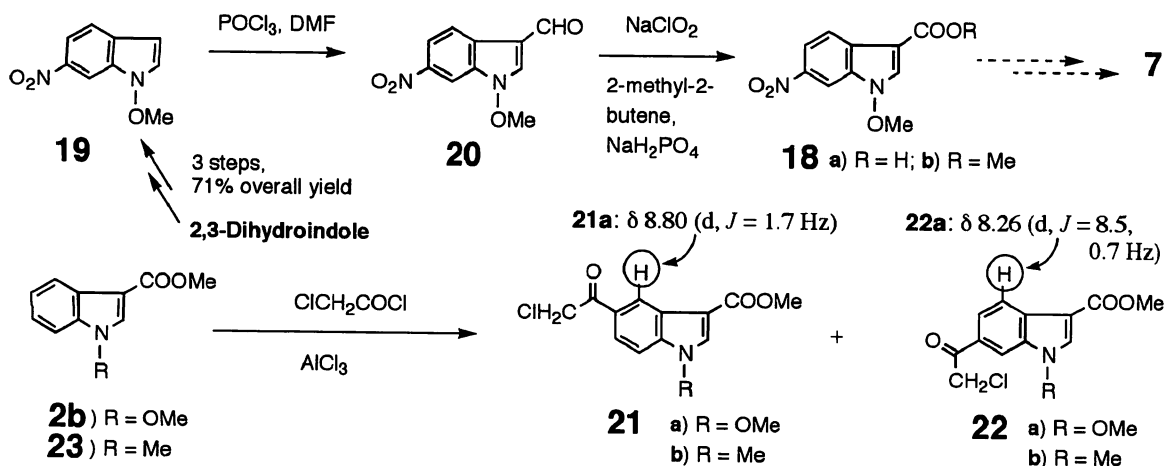
Scheme 1



introduction of methoxy group into the 1-position of **15** alters the reaction site and tends to favor the 2-position. These observations are quite interesting considering the initial iodination of **2a** and **2b**. Thus, **2b** produced **8** exclusively in 72% yield,^{7a} while **2a** afforded **15** together with 6- and 7-iodo isomers in 58, 25, and 2% yields.^{7a} Further reaction examples would be needed for clarifying the effect of 1-methoxy group on the regioselectivity of electrophilic substitution reactions.

We next tried the preparation of methyl 1-methoxy-6-nitroindole-3-carboxylate (**18b**, Scheme 2) as a common intermediate for **7**, because the nitro group can easily be transformed into other functional groups such as amino, halogen, hydroxy, etc. According to our procedure,⁸ 1-methoxy-6-nitroindole (**19**) was prepared from an industrial raw material, 2,3-dihydroindole, in three steps in 71% overall yield. Subsequent Vilsmeier reaction of **19** with POCl₃ and *N,N*-dimethylformamide provided a 94% yield of 1-methoxy-6-nitroindole-3-carbaldehyde (**20**), an analog of daikon phytoalexin^{3a} (**5**). Oxidation of **20** to 1-methoxy-6-nitroindole-3-carboxylic acid (**18a**) was achieved in 92% yield by the treatment with NaClO₂⁹ in the presence of 2-methyl-2-butene. Methylation of **18a** with CH₂N₂ in MeOH provided the desired **18b** in 99% yield.

Scheme 2



For the preparation of wasabi phytoalexin analogs having an acyl group, direct acylation of **2b** was examined. Thus, Friedel-Crafts acylation using chloroacetyl chloride and AlCl₃ in nitrobenzene at 100°C provided cleanly methyl 5-chloroacetyl- (**21a**) and 6-chloroacetyl-1-methoxyindole-3-carboxylate (**22a**) in 52 and 20% yields, respectively, and the ratio of **21a** to **22a** was 2.5:1. The acylated position of **21a** is determined by the presence of C4-H signal at 8.80 ppm (d, $J=1.7$ Hz) in its ¹H-NMR spectrum, while the corresponding C4-H signal of **22a** is observed at 8.26 ppm (d, $J=8.5, 0.7$ Hz) proving the 6-substituted indole structure.

Similar results were already reported by Nakatsuka¹⁰ and co-workers in the chloroacetylation of methyl 1-methylindole-3-carboxylate (**23**). In their experiment, however, **21b** and **22b** were obtained as an

inseparable mixture. Based on the ratio of the following Baeyer-Villiger oxidation products, the ratio of **21b** to **22b** could be estimated to be 3:1. Similar Friedel-Crafts acylation of indoles having an electron withdrawing group has been reported by several researchers.¹¹ Comparing these results, it would be safe to say that the introduction of a methoxy group into the 1-position prefers the 6-substitution to 5-substitution in Friedel-Crafts acylation.

In conclusion, introduction of a methoxy group into the 1-position is found to influence significantly the regiochemistry of electrophilic substitution reactions on indole nucleus. With key building blocks such as **9**, **10**, **15**, **18**, **21a**, and **22a** in hand, preparations of various kinds of wasabi phytoalexin analogs are now in progress to conduct structure-activity relationship study.

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 ¹H-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 (SiO₂, 100-200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

Methyl 6-Bromo- (9), 2-Bromo-5-iodo-1-methoxyindole-3-carboxylate (10), 6-Bromo- (11), 2-Bromo- (12a), and 5-iodo-1-methoxyindole-3-carboxylic acid (13) from Methyl 5-Iodo-1-methoxyindole-3-carboxylate (8) — A solution of Br₂ (3.8 mL, 0.76 mmol) in AcOH was added to a solution of **8** (192.7 mg, 0.58 mmol) in AcOH (10 mL) and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃-MeOH (9:1, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO₂ with CHCl₃-hexane (1:1, v/v) and then with CHCl₃ to give **10** (80 mg, 33%), **9** (40.7 mg, 17%), **8** (30.1 mg, 16%), and a mixture fraction (**11**, **12a**, and **13**, 45.6 mg) in the order of elution. **9**: mp 142.5–143.0°C (colorless fine needles, recrystallized from CHCl₃-hexane). IR (KBr): 1695, 1517, 1446, 1205 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.91 (3H, s), 4.14 (3H, s), 7.79 (1H, s), 7.90 (1H, s), 8.69 (1H, s). MS *m/z*: 410 (M⁺: Br⁸¹), 408 (M⁺: Br⁷⁹). *Anal.* Calcd for C₁₁H₉NO₃BrI: C, 32.22; H, 2.21; N, 3.42. Found: C, 32.28; H, 2.22; N, 3.43. **10**: mp 158–159°C (colorless fine needles, recrystallized from CHCl₃-hexane). IR (KBr): 1722, 1498, 1195, 1178, 1016 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.96 (3H, s), 4.14 (3H, s), 7.22 (1H, d, *J*=8.5 Hz), 7.59 (1H, dd, *J*=8.5, 1.5 Hz), 8.50 (1H, d, *J*=1.5 Hz). MS *m/z*: 410 (M⁺: Br⁸¹), 408 (M⁺: Br⁷⁹). *Anal.* Calcd for C₁₁H₉NO₃BrI·1/2H₂O: C, 31.53; H, 2.17; N, 3.34. Found: C, 31.21; H, 2.19; N, 3.28. Pure samples, (**11**) and (**13**), were obtained from **9** and **8**, respectively, by the reaction with 15% aq. NaSMe as shown below.

Separation of 11, 12a, and 13 as Methylated Products, (9), (10), and (8) — Excess CH₂N₂ in Et₂O was added to a solution of the mixture fraction (**11**, **12a**, and **13**, 45.6 mg), obtained in the above experiment, in MeOH (5.0 mL) and the whole was stirred at rt for 10 min. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃-hexane (1:2, v/v) to give **10** (11.9 mg, 5%), **9** (14.0 mg, 6%), and **8** (12.6 mg, 7%).

6-Bromo-5-Iodo-1-methoxyindole-3-carboxylic acid (11) and 14 from 9 — Excess 15% aq. NaSMe (8 mL) was added to a solution of **9** (51.8 mg, 0.13 mmol) in MeOH (3 mL) and the mixture was refluxed for 2 h with stirring under Ar atmosphere. After addition of H₂O under ice cooling, the whole was made acidic (pH 1) by adding 8% HCl and extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃-MeOH-AcOH (46:1:0.1, v/v) to give **11** (22.5 mg, 45%) and **14** (17.8 mg, 38%) in the order of elution. **11**: mp 275–280°C (decomp, colorless fine needles, recrystallized from CHCl₃-MeOH). IR (KBr): 1658, 1520, 1217 cm⁻¹. ¹H-NMR (5% CD₃OD in CDCl₃) δ: 4.14 (3H, s), 7.80 (1H, s), 7.93 (1H, s), 8.71 (1H, s). MS *m/z*: 397 (M⁺: Br⁸¹), 395 (M⁺: Br⁷⁹). *Anal.* Calcd for C₁₀H₇NO₃Br: C, 30.33; H, 1.78; N, 3.54. Found: C, 30.54; H, 1.85; N, 3.52.

5-Iodo-1-methoxy-2-methylthioindole-3-carboxylic acid (12b) from 10 — Excess 15% aq. NaSMe (2 mL) was added to a solution of **10** (23.8 mg, 0.06 mmol) in MeOH (2 mL) and the mixture was refluxed for 1 h with stirring under Ar atmosphere. After addition of H₂O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with EtOAc-MeOH (9:1, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃-MeOH-AcOH (46:1:0.5, v/v) to give **12b** (17.4 mg, 83%). **12b**: mp 167–168°C (decomp, colorless fine needles, recrystallized from CHCl₃-hexane). IR (KBr): 1668, 1492, 1205 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.68 (3H, s), 4.16 (3H, s), 7.21 (1H, dd, *J*=8.5, 0.7 Hz), 7.61 (1H, dd, *J*=8.5, 1.5 Hz), 8.62 (1H, dd, *J*=1.5, 0.7 Hz). High-Resolution MS *m/z*:: Calcd for C₁₁H₁₀NO₃IS: 362.9426. Found: 362.9429.

5-Iodo-1-methoxyindole-3-carboxylic acid (13) from 8 — Excess 15% aq. NaSMe (5.0 mL) was added to a solution of **8** (32.2 mg, 0.9 mmol) in MeOH (2 mL) and the mixture was refluxed for 1 h with stirring under Ar atmosphere. After addition of H₂O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with EtOAc-MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO₂ with CHCl₃-MeOH-AcOH (46:1:0.1, v/v) to give **13** (11.7 mg, 38%). **13**: mp 211–213°C (colorless fine needles, recrystallized from CHCl₃-hexane). IR (KBr): 1670, 1525, 1220 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 4.13 (3H, s), 7.42 (1H, d, *J*=8.6 Hz), 7.58 (1H, dd, *J*=8.6, 1.7 Hz), 8.35 (1H, s), 8.39 (1H, d, *J*=1.7 Hz). MS *m/z*: 317 (M⁺). *Anal.* Calcd for C₁₀H₈NO₃·1/2 H₂O: C, 36.83; H, 2.78; N, 4.30. Found: C, 36.95; H, 2.57; N, 4.35.

Methyl 6-Bromo- (16), 2,6-Dibromo-5-iodoindole-3-carboxylate (17), and 6-Bromo-5-iodoindole-3-carboxylic acid (14) from 15 — [Method 1] A solution of Br₂ (2.2 mL, 0.43 mmol) in AcOH was added to a solution of **15** (100.8 mg, 0.33 mmol) in AcOH (5.0 mL), and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃-MeOH (9:1, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO₂ with acetone-benzene (1:9, v/v) and then with CH₂Cl₂-hexane (2:1, v/v) to give **17** (12.7 mg, 8%), **16** (61.5 mg, 48%), and **14** (20.5 mg, 17%) in the order of elution. **16**:

mp 262.5—263°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3270, 1677, 1520, 1441, 1198, 1053 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 3.82 (3H, s), 7.88 (1H, s), 8.12 (1H, s), 8.52 (1H, s), 12.10 (1H, br s, disappeared on addition of D_2O). MS m/z : 381 (M^+ : Br^{81}), 279 (M^+ : Br^{79}). *Anal.* Calcd for $\text{C}_{10}\text{H}_7\text{NO}_2\text{BrI}$: C, 31.61; H, 1.86; N, 3.69. Found: C, 31.74; H, 1.73; N, 3.74. **17**: mp 275—277°C (colorless fine needles, recrystallized from CHCl_3 -MeOH). IR (KBr): 3226, 1681, 1504, 1430, 1382, 1062 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 3.85 (3H, s), 7.74 (1H, s), 8.47 (1H, s), 13.05 (1H, br s, disappeared on addition of D_2O). MS m/z : 460 (M^+ : 2 x Br^{81}), 458 (M^+ : Br^{81} , Br^{79}), 456 (M^+ : 2 x Br^{79}). *Anal.* Calcd for $\text{C}_{10}\text{H}_6\text{NO}_2\text{Br}_2\text{I}\cdot\frac{1}{4}\text{H}_2\text{O}$: C, 25.92; H, 1.41; N, 3.02. Found: C, 25.80; H, 1.44; N, 2.95. **14**: mp 224—226°C (decomp, brown prisms, recrystallized from EtOAc-MeOH). IR (KBr): 3249, 1637, 1531, 1186 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.85 (1H, s), 8.02 (1H, s), 8.54 (1H, s), 11.96 (1H, br s, disappeared on addition of D_2O). MS m/z : 367 (M^+ : Br^{81}), 365 (M^+ : Br^{79}). *Anal.* Calcd for $\text{C}_9\text{H}_5\text{NO}_2\text{BrI}\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 28.82; H, 1.61; N, 3.74. Found: C, 28.68; H, 1.51; N, 3.67.

[Method 2] A solution of Br_2 in AcOH (1.5 mL, 0.30 mmol) was added to a solution of **15** (108.3 mg, 0.36 mmol) in AcOH (5.0 mL), and the mixture was heated at 100°C for 6 h with stirring under Ar atmosphere. After the same work-up and column-chromatography as described in the **[Method 1]**, **16** (76.9 mg, 56%) and **14** (23.8 mg, 18%) were obtained.

Methyl 6-Bromo-5-iodoindole-3-carboxylate (16) from 14 — Excess CH_2N_2 in Et_2O was added to a solution of **14** (13.0 mg, 0.036 mmol) in MeOH (10 mL) and the mixture was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with CHCl_3 -MeOH (95:5, v/v) to give **16** (12.1 mg, 90%).

6-Bromo-5-iodoindole-3-carboxylic acid (14) from 16 — Excess 15% aq. NaSMe (8.0 mL) was added to a suspension of **16** (50.9 mg, 0.13 mmol) in MeOH (3 mL) and the mixture was refluxed for 2 h with stirring under Ar atmosphere. After addition of H_2O under ice cooling, the whole was made acidic (pH 3) by adding 8% HCl and extracted with CHCl_3 -MeOH (9:1, 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 -MeOH (95:5, v/v) to give **14** (45.3 mg, 92%).

1-Methoxy-6-nitroindole-3-carboxylic acid (18a) from 20 — A solution of sodium chlorite (1.186 g, 13.1 mmol) and sodium dihydrogen phosphate (1.535 g, 9.84 mmol) in H_2O (6 mL) was added to a solution of **20** (144.4 mg, 0.66 mmol) and 2-methyl-2-butene (3.0 mL) in DMF (10 mL), and the mixture was stirred at rt for 1.5 h. The whole was made acidic (pH 3) by adding 8% HCl under ice cooling, and extracted with EtOAc. 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 -MeOH-AcOH (46:1:0.1, v/v) to give **18a** (143.2 mg, 92%). **18a**: mp 232.5—233°C (pale yellow fine needles, recrystallized from CHCl_3 -hexane). IR (KBr): 1682, 1516, 1348, 1221 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 4.23 (3H, s), 8.11 (1H, dd, $J=9.0$, 2.0 Hz), 8.24 (1H, d, $J=9.0$ Hz), 8.46 (1H, d, $J=2.0$ Hz), 8.77 (1H, s). MS m/z : 236 (M^+). *Anal.* Calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_5$: C, 50.85; H, 3.41; N, 11.86. Found: C, 50.64; H, 3.40; N, 11.83.

Methyl 1-Methoxy-6-nitroindole-3-carboxylate (18b) from 18a — Excess CH_2N_2 in Et_2O was added to a suspension of **18a** (11.1 mg, 0.047 mmol) in MeOH (2.0 mL) and the mixture was

stirred at rt for 15 min. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed on SiO₂ with CHCl₃-hexane (2:1, v/v) to give **18b** (11.6 mg, 99%). **18b**: mp 155.5–156°C (pale yellow fine needles, recrystallized from CHCl₃-hexane). IR (KBr): 1716, 1514, 1352, 1213 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.94 (3H, s), 4.23 (3H, s), 8.16 (1H, dd, *J*=9.0, 2.0 Hz), 8.18 (1H, s), 8.28 (1H, d, *J*=9.0 Hz), 8.43 (1H, d, *J*=2.0 Hz). MS *m/z*: 250 (M⁺). *Anal.* Calcd for C₁₁H₁₀N₂O₅·1/8H₂O: C, 52.33; H, 4.09; N, 11.10. Found: C, 52.21; H, 4.05; N, 11.11.

1-Methoxy-6-nitroindole-3-carbaldehyde (20) from 1-Methoxy-6-nitroindole (19) — POCl₃ (0.97 mL, 10.4 mmol) was added to dry DMF (5.8 mL, 63 mmol) at 0°C and stirring was continued for 15 min. A solution of **19** (1.00 g, 5.2 mmol) in dry DMF (15 mL) was added to the resultant mixture at 0°C. After stirring at rt for 7 h, H₂O was added to the reaction mixture at 0°C and the whole was made basic (pH 10) by adding sat. aq. NaHCO₃. After stirring at rt for 30 min maintaining pH 10 by adding sat. aq. NaHCO₃, the whole was extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave yellow solid, which was column-chromatographed on SiO₂ with EtOAc-hexane (1:2, v/v) to give **20** (1.08 g, 94%). **20**: mp 180–182°C (yellow prisms, recrystallized from CHCl₃-hexane). IR (KBr): 1664, 1653, 1508, 1342 cm⁻¹. ¹H-NMR (CDCl₃) δ: 4.28 (3H, s), 8.14 (1H, s), 8.22 (1H, dd, *J*=8.8, 2.0 Hz), 8.43 (1H, d, *J*=8.8 Hz), 8.45 (1H, d, *J*=2.0 Hz), 10.02 (1H, s). *Anal.* Calcd for C₁₀H₈N₂O₄: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.32; H, 3.61; N, 12.54.

Methyl 5-Chloroacetyl- (21a) and Methyl 6-Chloroacetyl-1-methoxyindole-3-carboxylate (22a) from 2b — Anhydrous AlCl₃ (392.7 mg, 2.94 mmol) and then a solution of chloroacetyl chloride (166.1 mg, 1.47 mmol) in nitrobenzene (0.4 mL) was added successively to a solution of **2b** (100.5 mg, 0.49 mmol) in nitrobenzene (1 mL) and the mixture was heated at 100°C for 15 min with stirring. After addition of H₂O with stirring under ice cooling, the solvent was evaporated under reduced pressure. The residue was made basic (pH 11) by adding 8% NaOH and extracted with CHCl₃. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO₂ with CH₂Cl₂ and CHCl₃ to give **22a** (26.9 mg, 20%) and **21a** (71.3 mg, 52%) in the order of elution. **21a**: mp 138–139°C (pale brown prisms, recrystallized from CHCl₃-hexane). IR (KBr): 1700, 1610, 1218, 1178 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.95 (3H, s), 4.18 (3H, s), 4.84 (2H, s), 7.55 (1H, dd, *J*=8.7, 1.0 Hz), 8.01 (1H, dd, *J*=8.7, 1.7 Hz), 8.03 (1H, s), 8.80 (1H, d, *J*=1.7 Hz). MS *m/z*: 283 (M⁺: Cl³⁷), 281 (M⁺: Cl³⁵). *Anal.* Calcd for C₁₃H₁₂NO₄Cl·1/8H₂O: C, 54.99; H, 4.35; N, 4.96. Found: C, 54.83; H, 4.29; N, 4.84. **22a**: mp 156–158°C (colorless prisms, recrystallized from CHCl₃-hexane). IR (KBr): 1695, 1616, 1437, 1387, 1197 cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.93 (3H, s), 4.21 (3H, s), 4.79 (2H, s), 7.85 (1H, dd, *J*=8.5, 1.5 Hz), 8.12 (1H, s), 8.16 (1H, dd, *J*=1.5, 0.7 Hz), 8.26 (1H, dd, *J*=8.5, 0.7 Hz). High Resolution MS *m/z*: Calcd. for C₁₃H₁₂NO₄Cl: 283.0425 (M⁺: Cl³⁷) and 281.0455 (M⁺: Cl³⁵). Found: 283.0427 and 281.0427.

REFERENCES AND NOTES

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Received, 12th June, 2002