Nucleophilic substitution reaction of 3-acetyl-1-methoxyindole and its application for the synthesis of novel 2-substituted methyl 2,3-dihydro-1-methyl-3-oxo-5H-pyrido-[4,3-b]indole-4-carboxylates

NUCLEOPHILIC SUBSTITUTION REACTION OF 3-ACETYL-1-METHOXYINDOLE AND ITS APPLICATION FOR THE SYNTHESIS OF NOVEL 2-SUBSTITUTED METHYL 2,3-DIHYDRO-1-METHYL-3-OXO-5*H*-PYRIDO-[4,3-*b*]INDOLE-4-CARBOXYLATES[1]

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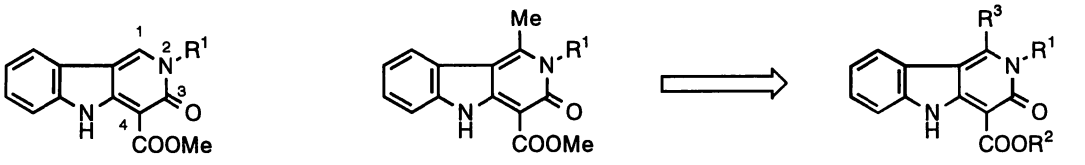
Abstract — A simple synthetic route was established for 3-acetyl-1-methoxyindole, which was found to undergo nucleophilic substitution reactions selectively at the 2-position. Applying the reaction, novel 2-substituted methyl 2,3-dihydro-1-methyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylates were prepared.

In our project to find biologically active compounds,[2] we have focused our attention to 5*H*-pyrido[4,3-*b*]indoles[3] (γ-carboline) and reported synthetic method for methyl 2,3-dihydro-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylates (**1**, Figure 1).[4] For extending structure-activity relationship study, we needed 1-substituted derivatives of **1**, but the introduction of a substituent into the 1-position was not easily attained as far as **1** was used as a starting material.

Figure 1 R^1~ R^3 = an appropriate substituent



1 **2** **3**

To meet the above demand, we attempted to prepare methyl 2,3-dihydro-1-methyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylates (**2**), because the methyl group at the 1-position would be expected to react with various reagents providing a lot of 1-substituted derivatives such as **3**. In this report, we wish to describe a simple synthetic method for novel compounds (**2**) relied on the nucleophilic substitution reaction of 1-hydroxyindoles.[5]

We first tried to produce 3-acetyl-1-methoxyindole[6] (**4**) as a key synthetic intermediate. Although Acheson and co-workers[6] reported its synthesis in 42% yield from 1-methoxyindole[7] (**5**) by applying Vilsmeier-Haack reaction using *N*,*N*-dimethylacetamide, the yield was lower in our hand (around 14%) (Scheme 1). Direct acetylation of **5** with either refluxing Ac_2O or AcCl afforded poorer results. We therefore attempted to develop an alternative approach.

Scheme 1

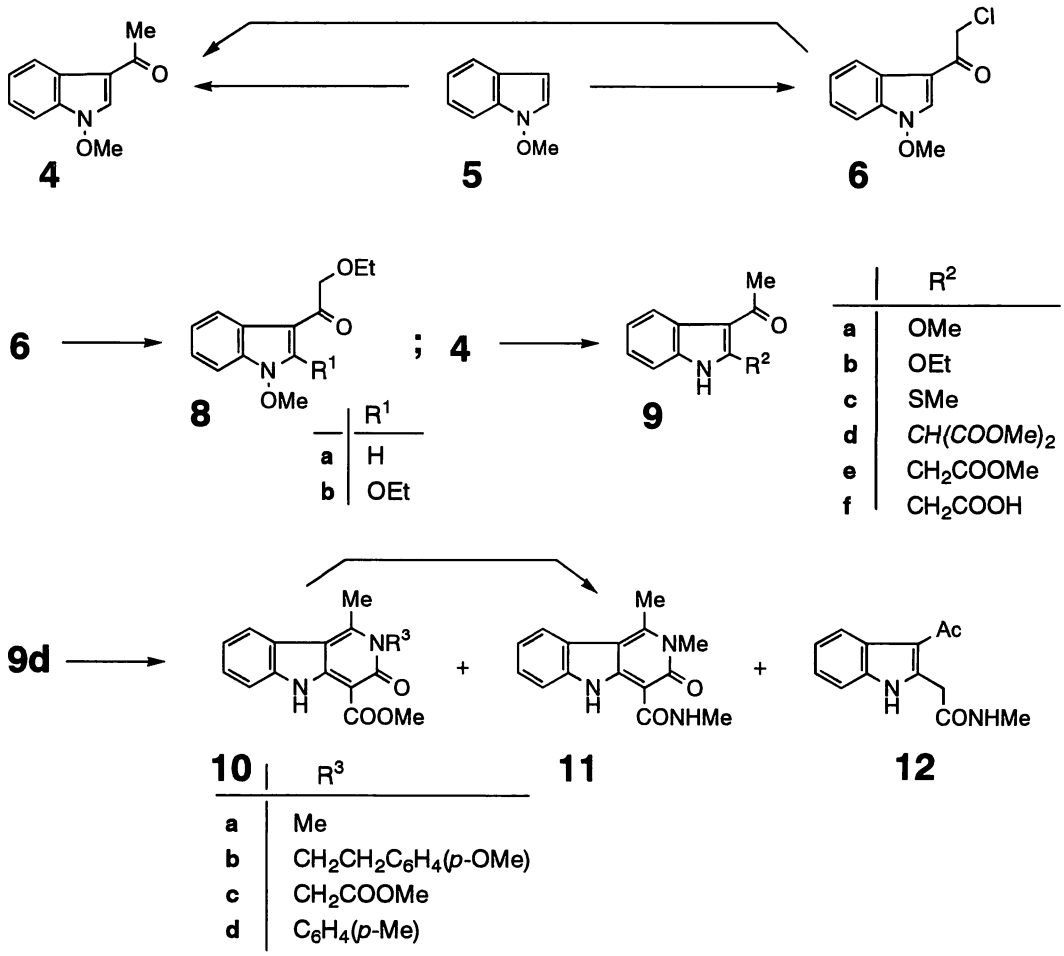
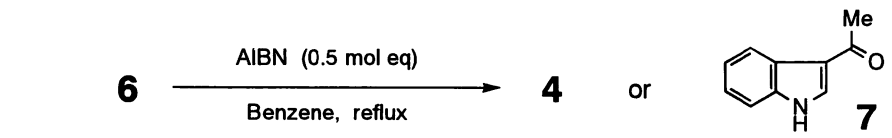


Table 1



Entry	$(n\text{-Bu})_3SnH$ (mol eq)	Reaction Time (min)	Yield (%) 4	7
1	3	30	0	100
2	1	40	69	0
3	1	30	77	0
4	1	20	95	0

We have already observed that **5** reacts with chloroacetyl chloride in refluxing benzene to give 3-chloroacetyl-1-methoxyindole[8] (**6**) in 91% yield. Chlorine-hydrogen exchange reaction of **6** proceeded successfully with (n-Bu)$_3$SnH in the presence of AIBN affording the desired **4**. In this reaction, the amount of (n-Bu)$_3$SnH and the reaction time were crucial factors as shown in Table 1. Thus, the reaction employing 3 mol eq. of (n-Bu)$_3$SnH for 30 min transformed **6** to 3-acetylindole (**7**) quantitatively (Entry 1). In the reaction of **6** with 1 mol eq. of (n-Bu)$_3$SnH, 20 min was the reaction time of choice and 95% yield of **4** was attained, while the longer reaction time decreased the yield (compare Entries 2~4).

With **4** and **6** in hand, we next examined their nucleophilic substitution reactions expecting that they would show similar reactivities as in the case of 1-methoxyindole-3-carbaldehyde.[5] However, **6** gave **8a** instead of **8b** in 17% yield in the reaction with NaOEt in refluxing EtOH. On the other hand, **4** provided the expected 2-substituted products (**9a**) and (**9b**) in 93 and 94% yields, respectively, by the treatments with NaOMe and NaOEt in the corresponding refluxing alcohol. Stronger nucleophiles such as NaSMe provided **9c** in a quantitative yield. Based on these data, the reaction of **4** with sodium methyl malonate was examined using KOtBu as a base resulting in the formation of dimethyl 2-(3-acetylindol-2-yl)malonate (**9d**) in 51% yield together with 47% recovery of unreacted **4**. Subsequent treatment of **9d** with NaOMe in refluxing MeOH afforded methyl 2-(3-acetylindol-2-yl)acetate (**9e**) and 2-(3-acetylindol-2-yl)acetic acid (**9f**) in 42 and 42% yields, respectively. The ester compound (**9e**) was also prepared in 98% yield by methylation of **9f** with diazomethane.

The compound (**9d**) was found to be an useful building block for our purpose. The reaction of **9d** with an excess amount of methylamine in refluxing MeOH for 15 min produced the desired methyl 2,3-dihydro-1,2-dimethyl-3-oxo-5H-pyrido[4,3-b]indole-4-carboxylate (**10a**), 2,3-dihydro-1,2,N-trimethyl-3-oxo-5H-pyrido[4,3-b]indole-4-carboxamide (**11**), and N-methyl-2-(3-acetylindol-2-yl)acetamide (**12**) in 62, 7, and 19% yields, respectively. The compound (**11**) was obtained in 87% yield when **10a** was treated with methylamine in refluxing MeOH for 15 h.

The reaction of **9d** with 4-methoxyphenethylamine in refluxing MeOH for 2 h produced **10b** in 64% yield. Similarly, glycine methyl ester hydrochloride reacted in the presence of Et$_3$N to afford methyl 2,3-dihydro-3-oxo-2-methoxycarbonylmethyl-1-methyl-5H-pyrido[4,3-b]indole-4-carboxylate (**10c**) in 44% yield. When p-toluidine was used as an amine component, the reaction proceeded slowly and even after 48 h in refluxing MeOH, **10d** was produced in only 12 % yield together with 37% yield of methyl 2-(3-acetylindol-2-yl)acetate (**9e**) and 28% yield of recovery.

In conclusion, we have found that 3-acetyl-1-methoxyindole reacts with nucleophiles selectively at the 2-position. The reaction is successfully applied to simple syntheses of novel 2-substituted methyl 2,3-dihydro-1-methyl-3-oxo-5H-pyrido[4,3-b]indole-4-carboxylates.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 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. Preparative thin-layer chromatography (P-TLC) was performed on Merck

Kiesel-gel GF_{254} (Type 60)(SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.).

3-Chloroacetyl-1-methoxyindole (6) from 1-Methoxyindole (5)— Chloroacetyl chloride (6.470 g, 57.3 mmol) was added to a solution of **5** (842.7 mg, 5.73 mmol) in anhydrous benzene (20.0 mL) and the mixture was refluxed for 24 h with stirring. Aqueous 2N NaOH was added to the reaction mixture until the water layer became basic and benzene layer was separated. The water layer was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract and benzene layer were combined and the whole was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a solid, which was recrystallized from MeOH to give **6**[8] (729.1 mg). Mother liquor was column-chromatographed on SiO_2 with $CHCl_3$ to give further crop of **6** (371.3 mg). Total yield of **6** was 1.1004 g (91%). **6**: mp 103.0—104.5 °C (colorless needles). IR (KBr): 1661, 1513, 1225, 1197, 958, 741 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.08 (3H, s), 4.37 (2H, s), 7.01–7.51 (3H, m), 7.84 (1H, s), 8.01–8.34 (1H, m). MS *m/z*: 225 (M^+), 223 (M^+). *Anal.* Calcd for $C_{11}H_{10}NO_2Cl$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.13; H, 4.38; N, 6.34.

3-Acetyl-1-methoxyindole (4) from 6— AIBN (64.7 mg, 0.394 mmol) was added to a solution of $(n\text{-}Bu)_3SnH$ (229.4 mg, 0.788 mmol) and **6** (166.7 mg, 0.788 mmol) in anhydrous benzene (8.0 mL) and the mixture was refluxed for 20 min with stirring. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed on SiO_2 with $CHCl_3$ to give **4** (141.9 mg, 95%). **4**: mp 77.0—77.5 °C (decomp, colorless prisms, recrystallized from CH_2Cl_2–hexane, lit.,[6] mp 76-77 °C). IR (KBr): 3110, 1634, 1510, 1376, 1210, 1078, 945, 754 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 4.32 (3H, s), 7.26–7.38 (2H, m), 7.43–7.50 (1H, m), 7.90 (1H, s), 8.36–8.42 (1H, m). MS *m/z*: 189 (M^+), 174, 159. *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.76; H, 5.81; N, 7.36.

3-Ethoxyacetyl-1-methoxyindole (8a) from 6 — A solution of **6** (101.1 mg, 0.452 mmol) in anhydrous EtOH (3.0 mL) was added to a solution of NaOEt [prepared with sodium (308.2 mg, 13.6 mmol) and anhydrous EtOH (5.0 mL)] and the mixture was stirred for 20 min at rt. After addition of H_2O, the whole was made acidic by adding aqueous 2N HCl and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by P-TLC on SiO_2 with $CHCl_3$ as a developing solvent. Extraction of the band having a Rf value of 0.49—0.29 with $CHCl_3$–MeOH (95:5, v/v) gave **8a** (17.5 mg, 17%). **8a**: pale brown oil. IR (film): 2980, 2875, 1648, 1509, 1450, 1367, 1339, 1328, 1199, 1123, 1108, 956, 748 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.30 (3H, t, *J*=7.0 Hz), 3.65 (2H, q, *J*=7.0 Hz), 4.18 (3H, s), 4.46 (2H, s), 7.31 (1H, dt, *J*=1.2 and 7.2 Hz), 7.35 (1H, dt, *J*=1.2 and 7.2 Hz), 7.47 (1H, dt, *J*=7.2 and 1.2 Hz), 8.30 (1H, s), 8.41 (1H, dt, *J*=7.2 and 1.2 Hz). High-resolution MS *m/z*: Calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1048.

3-Acetyl-2-methoxyindole (9a) from 4— A solution of **4** (30.8 mg, 0.173 mmol) in anhydrous MeOH (3.0 mL) was added to a solution of NaOMe [prepared with sodium (171.0 mg, 7.43 mmol) and anhydrous MeOH (2.0 mL)] and the mixture was refluxed for 5 h with stirring. After evaporation of the solvent under reduced pressure, sat. aq. NH_4Cl was added to the residue and 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 a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **9a** (28.7 mg, 93%). **9a**: mp 143.0—145.0℃ (colorless needles, recrystallized from MeOH). IR

(KBr): 2920, 2770, 1597, 1547 (br), 1478, 1440, 1349, 1268, 1217, 1190, 1103, 1024, 900, 737 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.35 (3H, s), 4.16 (3H, s), 7.04–7.09 (2H, m), 7.26–7.29 (1H, m), 8.05–8.08 (1H, m). MS *m/z*: 189 (M^+). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.92; H, 5.90; N, 7.29.

3-Acetyl-2-ethoxyindole (9b) from 4 — A solution of **4** (50.2 mg, 0.266 mmol) in anhydrous EtOH (2.0 mL) was added to a solution of NaOEt [prepared with sodium (189.7 mg, 7.98 mmol) and anhydrous EtOH (3.0 mL)] and the mixture was refluxed for 40 min with stirring. After evaporation of the solvent, sat. aq. NH_4Cl was added and 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 a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **9b** (50.5 mg, 94%). **9b**: mp 235.5—237.0 °C (pale yellow powder, recrystallized from MeOH–H_2O). IR (KBr): 3080, 1596, 1564, 1482, 1375, 1355, 1343, 1259, 1246, 1099, 1030, 748 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.46 (3H, t, *J*=7.0 Hz), 2.37 (3H, s), 4.45 (2H, q, *J*=7.0 Hz), 7.03–7.09 (2H, m), 7.23–7.28 (1H, m), 8.04–8.09 (1H, m). MS *m/z*: 203 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_2 \cdot 1/8H_2O$: C, 70.14; H, 6.50; N, 6.82. Found: C, 70.22; H, 6.42; N, 6.73.

3-Acetyl-2-methylthioindole (9c) from 4 — 15% Aqueous NaSMe (2.54 mL) was added to a solution of **4** (102.7 mg, 0.543 mmol) in MeOH (10.0 mL) and stirring was continued for 1 h at reflux. After evaporation of the solvent under reduced pressure , sat. aq. NH_4Cl was added to the residue and 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 a crystalline solid, which was recrystallized from MeOH to give **9c** (111.1 mg, 99.8%). **9c**: mp 203.0—203.5 °C (colorless needles). IR (KBr): 3250, 1596, 1424, 1328, 1222, 1015, 980, 965, 745, 738 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 2.70 (3H, s), 7.21 (1H, dt, *J*=1.2 and 7.9 Hz), 7.26 (1H, dt, *J*=1.2 and 7.9 Hz), 7.37 (1H, d, *J*=7.9 Hz), 7.93 (1H, d, *J*=7.9 Hz). MS *m/z*: 205 (M^+). *Anal.* Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.39; H, 5.39; N, 6.83.

Dimethyl 2-(3-acetylindol-2-yl)malonate (9d) from 4— A solution of **4** (425.5 mg, 2.251 mmol) in anhydrous DMF (15 mL) was added to a solution of KO*t*Bu (1.021 g, 9.00 mmol) and dimethyl malonate (1.1197 g, 9.06 mmol) in anhydrous DMF (15.0 mL). The mixture was heated at 120°C for 1 h with stirring. After addition of H_2O under ice-cooling, the whole was made neutral by adding sat. aq. NH_4Cl 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 $CHCl_3$–MeOH (99:1, v/v) to give **9d** (328.8 mg, 51%) and unreacted **4** (197.8 mg, 47%) in the order of elution. **9d**: mp 183.5—185.0 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3325, 2959, 1747, 1721, 1645, 1530, 1497, 1438, 1350, 1339, 1187, 1157, 1037, 951, 759 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.73 (3H, s), 3.81 (6H, s), 6.32 (1H, s), 7.26–7.31 (2H, m), 7.45–7.48 (1H, m), 7.89–7.93 (1H, m), 9.84 (1H, s, disappeared on addition of D_2O). MS *m/z*: 289 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.28; H, 5.27; N, 4.85.

Methyl 2-(3-acetylindol-2-yl)acetate (9e) and 2-(3-acetylindol-2-yl)acetic acid (9f) from 9d — A solution of **9d** (100.4 mg, 0.347 mmol) in anhydrous MeOH (5.0 mL) was added to a solution of

NaOMe [prepared with sodium (17.1 mg, 0.743 mmol) and anhydrous MeOH (1.0 mL)] and the mixture was stirred for 1 h at rt and refluxed for 2 h with stirring. After addition of H_2O, the whole 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 leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **9e** (33.3 mg, 42%) and **9f** (31.3 mg, 42%) in the order of elution. **9e**: mp 135.0—136.0 °C (pale brown powder, recrystallized from $CHCl_3$–hexane). IR (KBr): 3170, 3130, 1741, 1623, 1612, 1486, 1460, 1328, 1260, 1201, 978, 736 cm^{-1}. ^1H- NMR ($CDCl_3$) δ: 2.71 (3H, s), 3.81 (3H, s), 4.40 (2H, s), 7.25 (1H, dt, *J*=1.5 and 7.3 Hz), 7.28 (1H, dt, *J*=1.5 and 7.3 Hz), 7.43 (1H, dd, *J*=7.3 and 1.5 Hz), 7.90 (1H, dd, *J*=7.3 and 1.5 Hz), 10.05 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.23; H, 5.69; N, 5.96. **9f**: mp 179.0—180.0 °C (decomp, pale brown powder, recrystallized from MeOH). IR (KBr): 3170, 1719, 1623, 1490, 1454, 1422, 1368, 1324, 1222, 1183, 738 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 2.55 (3H, s), 4.09 (2H, s), 7.16–7.20 (2H, m), 7.42–7.46 (1H, m), 7.92–7.95 (1H, m), 11.98 (1H, s, disappeared on addition of D_2O), 12.59 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 217 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.99; H, 5.07; N, 6.42.

Methyl 2-(3-acetylindol-2-yl)acetate (9e) from 9f — An excess of ethereal CH_2N_2 was added to a solution of **9f** (15.2 mg, 0.07 mmol) in MeOH (3.0 mL) and the mixture was stirred for 15 min at rt. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **9e** (15.9 mg, 98%).

Methyl 2,3-dihydro-1,2-dimethyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (10a), 2,3-dihydro-1,2,*N*-trimethyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxamide (11), and *N*-methyl-2-(3-acetylindol-2-yl)acetamide (12) from 9d — 40% Methylamine (2.30 mL, 29.6 mmol) was added to a solution of **9d** (84.1 mg, 0.291 mmol) in MeOH (8.0 mL) and the mixture was refluxed for 15 min with stirring. 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 a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **11** (5.7 mg, 7%), **12** (12.6 mg, 19%) and **10a** (48.9 mg, 62%) in the order of elution. **10a**: mp 276.5—278.0°C (pale yellow needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 3370, 1705, 1655, 1638, 1570, 1437, 1365, 1260, 1095, 801, 719 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.91 (3H, s), 3.70 (3H, s), 4.00 (3H, s), 7.23 (1H, dt, *J*=1.7 and 7.9 Hz), 7.33 (1H, br d, *J*=7.9 Hz), 7.36 (1H, dt, *J*=1.7 and 7.9 Hz), 7.84 (1H, d, *J*=7.9 Hz), 10.49 (1H, br s). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.57; H, 5.23; N, 10.25. **11**: mp 286.5—287.5 °C (colorless fine fibrous crystals, recrystallized from $CHCl_3$–hexane). IR (KBr): 3330, 1658, 1611, 1589, 1535, 1412, 1361, 1261, 801, 718 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.92 (3H, s), 3.02 (3H, d, *J*= 4.9 Hz, collapsed to s on addition of D_2O), 3.73 (3H, s), 7.21 (1H, dt, *J*=1.0 and 7.8 Hz), 7.33 (1H, d, *J*=7.8 Hz), 7.37 (1H, br t, *J*=7.8 Hz), 7.86 (1H, d, *J*=7.8 Hz), 9.90 (1H, br s, disappeared on addition of D_2O), 11.23 (1H, br s). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.83; H, 5.60; N, 15.53. **12**: mp 207.0—209.0℃ (decomp, sealed tube, colorless fine needles, recrystallized from MeOH). IR (KBr): 3295, 3180 (br), 1653, 1620, 1610, 1568, 1484, 1455, 1335, 1191, 975, 741 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.77 (3H, s), 2.81 (3H, d, *J*=4.8

Hz), 4.11 (2H, s), 7.24 (1H, dt, *J*=1.2 and 7.3 Hz), 7.27 (1H, dt, *J*=1.2 and 7.3 Hz), 7.43 (1H, dd, *J*=7.3, 1.2 Hz), 7.68 (1H, br s), 7.83 (1H, br d, *J*=7.3 Hz), 11.14 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 230 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.63; H, 6.12; N, 12.04.

2,3-Dihydro-1,2,*N*-trimethyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxamide (11) from 10a — 40% Methylamine (2.28 mL, 29.4 mmol) was added to a solution of **10a** (19.8 mg, 0.073 mmol) in MeOH (2.0 mL) and the mixture was refluxed for 15 h with stirring. 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 a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) to give **11** (17.1 mg, 87%). The product was identical with the sample obtained from **9d**.

Methyl 2,3-Dihydro-2-(4-methoxyphenethyl)-1-methyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (10b) from 9d— A solution of 4-methoxyphenethylamine (1.942 g, 12.9 mmol) in MeOH (1.0 mL) was added to a solution of **9d** (41.2mg, 0.143 mmol) in MeOH (3.0 mL) and the mixture was refluxed for 2 h with stirring. 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 successively with $CHCl_3$ and AcOEt–hexane (2:1, v/v) to give **10b** (35.5 mg, 64%). **10b**: mp 120.5 — 121.0 °C (colorless fine fibrous crystals, recrystallized from AcOEt). IR (KBr): 3380, 1710, 1660, 1640, 1610, 1563, 1508, 1441, 1257, 1240, 1100, 1032, 799 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.75 (3H, s), 3.04 (2H, t, *J*=7.6 Hz), 3.79 (3H, s), 4.04 (3H, s), 4.38 (2H, br t, *J*=7.6 Hz), 6.84 (2H, br d, *J*=8.5 Hz), 7.18 (2H, br d, *J*=8.5 Hz), 7.21—7.24 (1H, m), 7.34—7.38 (2H, m), 7.78 (1H, d, *J*=7.8 Hz), 10.58 (1H, br s). *Anal.* Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.63; H, 5.70; N, 6.88.

Methyl 2,3-Dihydro-2-methoxycarbonylmethyl-1-methyl-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (10c) from 9d— Triethylamine (5.0 mL, 17.9 mmol) was added to a solution of glycine methyl ester hydrochloride (1.96 g, 15.6 mmol) in MeOH (10.0 mL). To the resultant solution, a solution of **9d** (49.8 mg, 0.172 mmol) in MeOH (3.0 mL) was added. After the mixture was refluxed for 3 h with stirring, additional triethylamine (5.0 mL, 17.9 mmol) was added to the mixture and refluxing was continued for 2 h with stirring. 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 purified by P-TLC on SiO_2 with $CHCl_3$–MeOH (99:1, v/v) as a developing solvent. Extraction of the band having a Rf value of 0.25—0.13 with $CHCl_3$–MeOH (95:5, v/v) gave **10c** (25.1 mg, 44%). **10c**: mp 234.0 —236.0 °C (decomp, sealed tube, pale yellow powder, recrystallized from $CHCl_3$– AcOEt). IR (KBr): 3270, 1748, 1711, 1625, 1614, 1565, 1365, 1198, 1174, 1099, 798, 734 cm^{-1}. ^1H- NMR ($CDCl_3$) δ: 2.84 (3H, s), 3.79 (3H, s), 3.98 (3H, s), 5.02 (2H, s), 7.23 (1H, dt, *J*=1.2 and 7.5 Hz), 7.34 (1H, d, *J*=7.5 Hz), 7.36 (1H, dt, *J*=1.2 and 7.5 Hz), 7.82 (1H, d, *J*=7.5 Hz), 10.57 (1H, br s). MS *m/z*: 328 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_5 \cdot 1/8H_2O$: C, 61.77; H, 4.95; N, 8.47. Found: C, 61.94; H, 4.93; N, 8.12.

Methyl 2,3-Dihydro-1-methyl-2-(4-methylphenyl)-3-oxo-5*H*-pyrido[4,3-*b*]indole-4-car-

boxylate (10d) from 9d— *p*-Toluidine (1.70 g, 15.9 mmol) was added to a solution of **9d** (50.6 mg, 0.175 mmol) in MeOH (5.0 mL) and the mixture was refluxed for 48 h with stirring. 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 a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$ and acetone–hexane (1:3, v/v) to give **9d** (14.2 mg, 28%), **9e** (14.9 mg, 37%), and **10d** (7.3 mg, 12%) in the order of elution. **10d**: mp 238.5—239.5 °C (pale yellow powder, recrystallized from CH_2Cl_2–hexane). IR (KBr): 3320, 1711, 1620, 1560, 1508, 1468, 1433, 1362, 1254, 1169, 1098 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 2.53 (3H, s), 3.94 (3H, s), 7.10 (2H, br d, *J*=8.1 Hz), 7.21—7.39 (3H, m), 7.36 (2H, br d, *J*=8.1 Hz), 7.77 (1H, d, *J*=7.8 Hz), 10.60 (1H, br s). High-resolution MS *m/z*: Calcd for $C_{21}H_{18}N_2O_3$: 346.1320. Found: 346.1316. *Anal.* Calcd for $C_{21}H_{18}N_2O_3 \cdot 1/8\ H_2O$: C, 72.35; H, 5.28; N, 8.04. Found: C, 72.45; H, 5.25; N, 7.76.

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