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NUCLEOPHILIC SUBSTITUTION REACTION OF 1-METHOXY-6-NITRO-INDOLE[1]

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Abstract – Nucleophilic substitution reaction of 1-methoxy-6-nitroindole (**1**) was examined. In the reaction with sodium methoxide or sodium cyanide as a nucleophile, 2- and 3-methoxy-6-nitroindoles, and 7-cyano-6-nitroindole were obtained, respectively. A novel methylene homologation at the 3-position was found in the reaction of **1** with sodium methyl sulfide or potassium salt of diethyl malonate to give 3-methylthiomethyl-6-nitroindole and its 2-methylthio derivative, and diethyl 2-(6-nitroindol-3-yl)methylmalonate, respectively. Possible reaction mechanism is discussed.

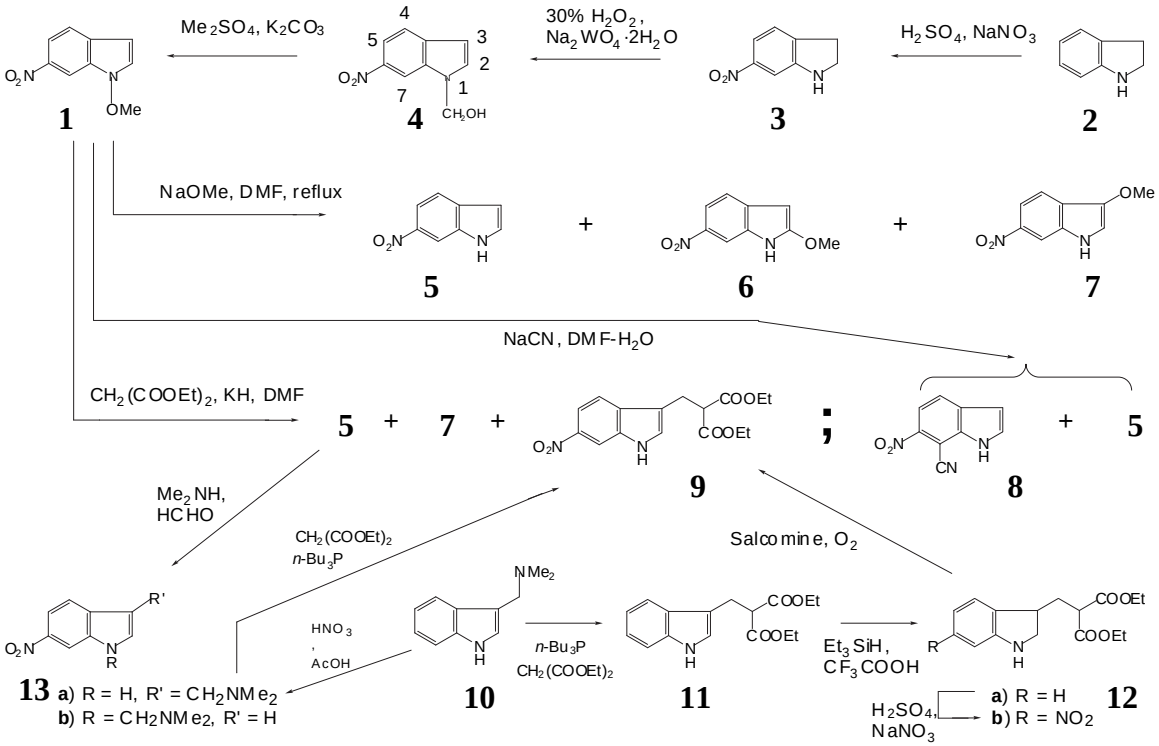
1-Hydroxyindoles are interesting compounds.[2] They undergo nucleophilic substitution reactions and provide various kinds of products depending on the structures of substrates, nucleophiles, and reaction conditions.[3] In this paper, we have focused our attention to the reactivity of 1-methoxy-6-nitroindole (**1**) with an expectation that nucleophilic substitution would occur more readily than other 1-methoxyindoles owing to the presence of a strong electron withdrawing nitro group on the indole nucleus.

According to our previous synthetic method,[4] **1** was prepared by the following sequence of reactions as shown in Scheme 1: 1) nitration of indoline[5] (**2**) with H_2SO_4 and $NaNO_3$ giving 6-nitroindoline (**3**) in 92% yield, 2) oxidation of **3** with $NaWO_4 \cdot 2H_2O$ and 30% H_2O_2 affording 1-hydroxy-6-nitroindole[4] (**4**) in 79% yield, and 3) methylation of **4** with Me_2SO_4 and K_2CO_3 or CH_2N_2 providing **1** in 100 and 96% yields, respectively.

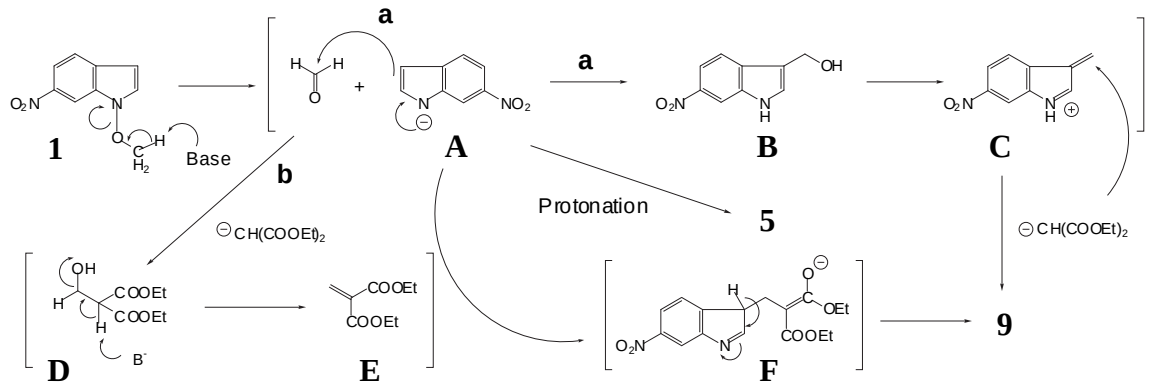
The reaction of **1** with NaOMe in refluxing DMF afforded 6-nitroindole[6] (**5**), 2-methoxy- (**6**), and 3-methoxy-6-nitroindoles (**7**) in 57, 22, and 6% yields, respectively. The result suggested that 2- and/or 3-cyanoindoles could be obtained when NaCN was used as a nucleophile. To our surprise, in fact, the reaction of **1** with NaCN in DMF-H_2O at reflux produced 7-cyano-6-nitroindole (**8**) and **5** as isolable products in 15 and 4% yields, respectively, together with tarry matter. Indoles having a cyano group at other positions were not detected at all. When the reaction was carried out in DMSO at 150°C, only demethoxylation occurred to give **5** in 62% yield.

Upon reaction of **1** with diethyl malonate using KO*t*Bu as a base in DMF at reflux, an interesting methylene homologation reaction took place at the 3-position instead of simple nucleophilic substitution reaction. Thus, diethyl 2-(6-nitroindol-3-yl)methylmalonate (**9**) was obtained in 38% yield in addition to **5** in 47% yield. When KH was used as a base, the yield of **9** was slightly improved to 40% together with **5**

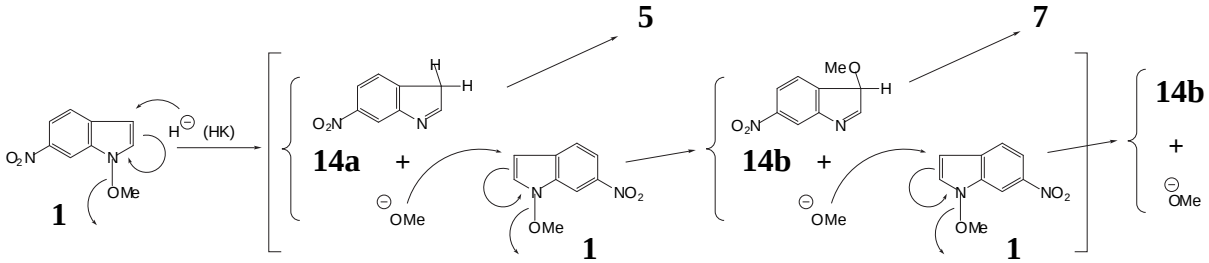
Scheme 1



Scheme 2



Scheme 3



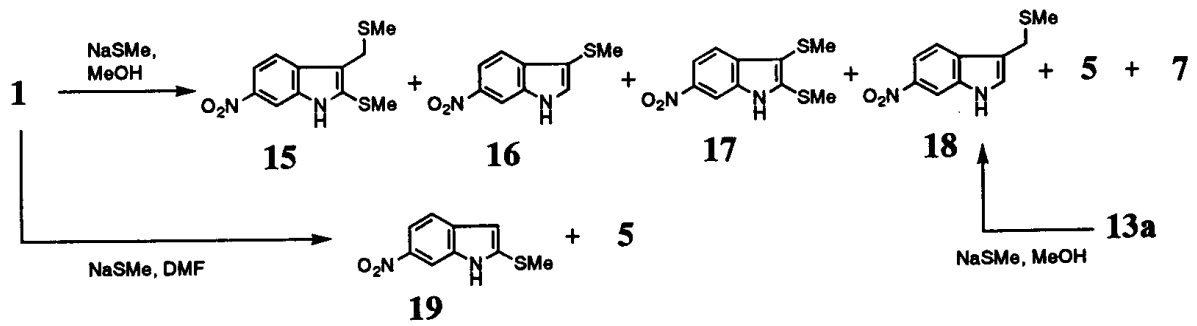
and **7** in the respective yields of 20 and 5%.

The structure of **9** was proved by the following two alternative syntheses. In the first route, gramine (**10**) was converted to diethyl 2-(indol-3-yl)methylmalonate (**11**) in 83% yield by our reaction[7] with diethyl malonate using tri-*n*-butylphosphine[7] as a catalyst. Reduction of **11** to the corresponding 2,3-dihydroindole (**12a**) with triethylsilane[8] and trifluoroacetic acid proceeded in 82% yield. Nitration of **12a** with $NaNO_3$ and H_2SO_4 provided 2,3-dihydro-6-nitroindole derivative (**12b**) in 92% yield. Then, its oxidation with bubbling oxygen in MeOH in the presence of a catalytic amount of salcomine[9] afforded **9** in 56% yield. All spectral data were identical with those of **9** obtained from **1**. The second synthetic trial used 6-nitrogramine[10] (**13a**) as a substrate, which was available either from **10** by nitration[10a] or from **5** by Mannich reaction.[10b] The reaction of **13a** with diethyl malonate and tri-*n*-butylphosphine[7] afforded **9** in 67% yield. It is interesting to note that when the reaction of **5** with HCHO-Me_2NH was carried out in MeOH, **13b** was obtained in 62% yield without any formation of **13a**.

The mechanism for the formation of **9** could be explained as illustrated in Scheme 2. Initial deprotonation of the 1-methoxy group of **1** liberates formaldehyde and indolyl anion (**A**). Then, following the reaction path **a**, **A** reacts with formaldehyde to produce indol-3-ylmethanol (**B**). Under the reaction conditions, unstable **B** transforms to 3-methyleneindolenine (**C**), which adds dimethyl malonate to give **9**. Another possibility is the reaction path **b**. Addition of diethyl malonate to formaldehyde gives the intermediate (**D**), which collapses to methylenemalonate (**E**). Subsequent Michael addition of **A** to **E** affords **9** through **F**.

The formations of **6** and **7** in the reaction of **1** with NaOMe in DMF can be explained by the S_N2' type nucleophilic substitution reaction at the 2- and 3-positions, respectively, with 1-methoxy moiety as a leaving group. On the other hand, formation of **7** without using NaOMe, thus upon reaction of **1** with KH in DMF, might be explained in terms of the initial hydride addition to **1** at the 3-position forming **14a** and a methoxide ion, which then adds to another molecule of **1** to generate **14b** and a new methoxide ion as shown in Scheme 3. The process is repeated as chain reaction, while **14a** and **14b** collapse to **5** and **7**, respectively.

Scheme 4



We next examined the reaction of **1** with 15% aqueous NaSMe in refluxing MeOH (Scheme 4). Products were 2-methylthio-3-methylthiomethyl-6-nitroindole (**15**), **5**, 3-methylthio- (**16**), 2,3-dimethylthio- (**17**), 3-methylthiomethyl-6-nitroindoles (**18**) and **7** in 17, 39, 4, 2, 2, and 4% yields, respectively. When the

reaction was carried out in DMF, 2-methylthio-6-nitroindole (**19**) was produced in 13% yield in addition to 54% yield of **5**, while the formations of **15** and **18** were not observed. The structure of **18** was confirmed by direct comparison with the authentic sample prepared in 94% yield by the reaction of **13a** with NaSMe.

For the formations of **15** and **18**, formaldehyde generated from **1** as shown in Scheme 3 also plays an important role. The extra presence of methylthio group in the products (**15** and **17**) might be accounted for by either a methylthiyl radical addition and/or an electrophilic addition of methanesulfenyl ion generated by air oxidation of methyl sulfide ion.

In conclusion, the present synthetic route provides a ready access to 6-nitroindole derivatives including 6-nitroindole itself from cheap indoline. The reactions of **1** with various carbon nucleophiles are in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (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 JMS-SX102A or JEOL JMS-AX5 spectrometer. Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) or activated alumina (Al_2O_3, 300 mesh, from Wako Pure Chemical Industries, Ltd.) throughout the present study. Preparative thin-layer chromatography (P-TLC) was performed on Merck Kiesel-gel GF_{254} (Type 60) (SiO_2).

1-Hydroxy-6-nitroindole (4) from 6-Nitroindoline (3) — 30% Aq. H_2O_2 (0.58 mL, 5.7 mmol) was added to a solution of **3** (101.3 mg, 0.57 mmol) and $Na_2WO_4 \cdot 2H_2O$ (18.8 mg, 0.06 mmol) in MeOH (10 mL) and H_2O (1.0 mL) at 0℃ with stirring. Stirring was continued at rt for 7 h and then the whole was extracted with CH_2Cl_2. 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 CH_2Cl_2–MeOH (99:1, v/v) to give 6-nitroindole (**5**, 6.1 mg, 7%), **3** (10.7 mg, 11%), and **4** (80.1 mg, 79%) in the order of elution. **4**: mp 153—155°C (decomp, orange needles recrystallized from $CHCl_3$). IR (KBr): 3240, 1617, 1586, 1514, 1332, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$: CD_3OD, 95:5, v/v) δ: 6.43 (1H, d, *J*=3.3 Hz, C_3-H), 7.51 (1H, d, *J*=3.3 Hz, C_2-H), 7.61 (1H, d, *J*=8.8 Hz, C_4-H), 7.95 (1H, dd, *J*=8.8 and 2.1 Hz, C_5-H), 8.42 (1H, d, *J*=2.1 Hz, C_7-H). MS *m*/*z*: 178 (M^+). *Anal*. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found: C, 54.03; H, 3.45; N, 15.73.

1-Methoxy-6-nitroindole (1) from 4 — Method 1: A mixture of **4** (1.667 g, 9.37 mmol), K_2CO_3 (6.472 g, 46.8 mmol) and Me_2SO_4 (4.45 mL, 46.9 mmol) in MeOH (25 mL) was stirred at rt for 1 h. After addition of H_2O, the whole was extracted with AcOEt. 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 $CHCl_3$–hexane (1:1, v/v) to give **1** (1.79 g, 100 %). **1**: mp 90—91°C (yellow needles recrystallized from MeOH). IR (KBr): 1613, 1584, 1508, 1339, 1100, 955, 756, 720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.17 (3H, s, CH_3), 6.45 (1H, dd, *J*=3.4, 0.8 Hz, C_3-H), 7.52 (1H, d, *J*=3.4 Hz, C_2-H), 7.60 (1H, d, *J*=8.8 Hz, C_4-H), 7.98 (1H, dd, *J*=8.8 and 2.2 Hz, C_5-H), 8.38 (1H, br

d, *J*=2.2 Hz, C_7-H). MS *m/z*: 192 (M^+). *Anal*. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.21; H, 4.17; N, 14.73.

Method 2: An excess amount of ethereal CH_2N_2 solution was added to a solution of **4** (34.7 mg, 0.20 mmol) in MeOH (3 mL) at rt with stirring. After confirming the disappearence of **4** monitoring with TLC, the solvent was 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 **1** (35.8 mg, 96 %).

6-Nitroindole (5), 2-Methoxy- (6), and 3-Methoxy-6-nitroindoles (7) from 1 — A solution of **1** (109.6 mg, 0.57 mmol) in DMF (2 mL) was added to a suspension of NaOMe [prepared with sodium (132.0 mg, 5.74 mg atom) and anhydrous MeOH (5 mL)] in DMF (10 mL). The mixture was refluxed for 5 min with stirring. After addition of ice, the whole was made acidic with 2N HCl, and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on Al_2O_3 with benzene to give the less polar (94.5 mg) and the more polar fractions (33.9 mg). The former was again column-chromatographed on SiO_2 with AcOEt–hexane (1:5, v/v) to give **5**[6] (52.5 mg, 57%). The latter was purified by P-TLC on SiO_2, developed three times with AcOEt–hexane (1:5, v/v). Extraction of the band having an Rf value of 0.47—0.32 with $CHCl_3$–MeOH (95:5, v/v) gave **6** (24.6 mg, 22%). Extraction of the band having an Rf value of 0.32—0.21 with $CHCl_3$–MeOH (95:5, v/v) gave **7** (6.3 mg, 6%). **6**: mp 158—160°C (yellow prisms recrystallized from $CHCl_3$). IR (KBr): 3338, 1548, 1292 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s, CH_3), 5.72 (1H, dd, *J*=2.2, 0.7 Hz, C_3-H), 7.41 (1H, d, *J*=8.7 Hz, C_4-H), 8.00 (1H, dd, *J*=8.7, 2.0 Hz, C_5-H), 8.11 (1H, br s, NH), 8.14 (1H, d, *J*=2.0 Hz, C_7-H). MS *m/z*: 192 (M^+). *Anal*. Calcd for $C_9H_8N_2O_3 \cdot 1/4H_2O$: C, 54.96; H, 4.36; N, 14.24. Found: C, 55.10; H, 4.08; N, 14.27. **7**: mp 176.5— 178.0°C (orange prisms recrystallized from $CHCl_3$-hexane). IR (film): 1556, 1508, 1331, 1300, 1097, 1061 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.29 (3H, s, CH_3), 6.99 (1H, d, *J*=2.7 Hz, collapsed to s on addition of D_2O, C_2-H), 7.70 (1H, d, *J*=8.8 Hz, C_4-H), 7.94 (1H, br s, NH, disappeared on addition of D_2O), 7.98 (1H, dd, *J*=8.8, 2.1 Hz, C_5-H), 8.27 (1H, d, *J*=2.1 Hz, C_7-H). *Anal*. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.98; H, 4.20; N, 14.36.

7-Cyano-6-nitroindole (8) and 5 from 1 — A solution of **1** (101.2 mg, 0.53 mmol) in DMF (5 mL) was added to a solution of NaCN (95%, 818.8 mg, 15.9 mmol) in DMF (5 mL) and H_2O (1 mL). The mixture was refluxed for 1 h with stirring. After cooling, the whole was made acidic with 2N HCl, and stirred at rt for 0.5 h. The resultant mixture 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 residue, which was column-chromatographed on SiO_2 with $CHCl_3$–hexane (4:1, v/v) to give **5** (3.4 mg, 4%) and **8** (14.7 mg, 15%) in the order of elution. **8**: mp 237—240°C (decomp, yellow fine needles recrystallized from AcOEt–hexane). IR (KBr): 3271, 2233, 1520, 1335, 1105, 1101 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.84 (1H, d, *J*=3.2 Hz, C_3-H), 7.90 (1H, d, *J*=3.2 Hz, C_2-H), 8.06 (1H, d, *J*=8.5 Hz, C_4- or C_5-H), 8.09 (1H, d, *J*=8.5 Hz, C_4- or C_5-H), 12.76 (1H, br s, NH, disappeared on addition of D_2O). *Anal*. Calcd for $C_9H_5N_3O_2$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.77; H, 2.69; N, 22.34.

Diethyl 2-(6-Nitroindol-3-yl)methylmalonate (9), 5, and 7 from 1 — A solution of **1** (49.8 mg, 0.26 mmol) in anhydrous DMF (2 mL) was added to a solution of diethyl malonate (0.06 mL, 0.40

mmol) and KH (35% dispersion in mineral oil, 45.7 mg, 0.40 mmol) in anhydrous DMF (3 mL). The mixture was refluxed for 5 min with stirring. After addition of H_2O under ice cooling, the whole was made acidic with 2N HCl, and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was purified by P-TLC on SiO_2 developed twice with AcOEt–hexane (1:4, v/v). Extraction of the band having an Rf value of 0.75—0.59 with $CHCl_3$–MeOH (95:5, v/v) gave **5** (8.4 mg, 20%). Extraction of the band having an Rf value of 0.53—0.31 with $CHCl_3$–MeOH (95:5, v/v) gave a mixture (39.8 mg) of **7** and **9**. The mixture was column-chromatographed on SiO_2 with $CHCl_3$ to give **7** (2.3 mg, 5%) and **9** (34.7 mg, 40%) in the order of elution. **9**: mp 121—122°C (yellow prisms recrystallized from $CHCl_3$-hexane). IR (KBr): 3350, 1718 (br), 1504, 1342, 1329, 1309, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, t, *J*=7.3 Hz, $C\underline{H}_3CH_2$), 3.40 (2H, d, *J*=7.6 Hz, $C\underline{H}_2CH$), 3.72 (1H, t, *J*=7.6 Hz, $CH_2C\underline{H}$), 4.11—4.21 (4H, m, $CH_3C\underline{H}_2$), 7.37 (1H, d, *J*=2.5 Hz, C_2-H), 7.67 (1H, d, *J*=8.8 Hz, C_4-H), 8.03 (1H, dd, *J*=8.8, 2.0 Hz, C_5-H), 8.32 (1H, d, *J*=2.0 Hz, C_7-H), 8.53 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 334 (M^+). *Anal*. Calcd for $C_{16}H_{18}N_2O_6 \cdot 1/4H_2O$: C, 56.72; H, 5.50; N, 8.27. Found: C, 56.80; H, 5.37; N, 8.22.

Diethyl 2-(Indol-3-yl)methylmalonate (11) from gramine (10) — A mixture of **10** (1.037 g, 5.96 mmol), diethyl malonate (1.09 mL, 7.19 mmol) and tri-*n*-butylphosphine[7] (0.44 mL, 1.79 mmol) in MeCN (50 mL) was refluxed for 1 day with stirring. After evaporation of the solvent, H_2O and $CHCl_3$ was added and the whole was made acidic with 2N HCl, and the organic layer was separated. The water layer was further extracted with $CHCl_3$–MeOH (95:5, v/v). The combined 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 AcOEt–hexane (1:4, v/v) to give **11** (1.425 g, 83%) and unreacted **10** (188.0 mg, 15%) in the order of elution. **11**: mp 66°C (colorless fine needles recrystallized from $CHCl_3$–hexane). IR (film): 3352, 1747, 1716, 1344, 1298, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, t, *J*=7.1 Hz, $C\underline{H}_3CH_2$), 3.39 (2H, d, *J*=7.6 Hz, $C\underline{H}_2CH$), 3.76 (1H, t, *J*=7.6 Hz, $CH_2C\underline{H}$), 4.11—4.21 (4H, m, $CH_3C\underline{H}_2$), 7.05 (1H, d, *J*=2.2 Hz, C_2-H), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz, C_5 or C_6-H), 7.19 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz, C_5 or C_6-H), 7.34 (1H, dt, *J*=8.1, 1.0 Hz, C_4 or C_7-H), 7.61 (1H, dt, *J*=8.1, 1.0 Hz, C_4 or C_7-H), 7.98 (1H, br s, NH). MS *m/z*: 289 (M^+). *Anal*. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.69; N, 4.76.

Diethyl 2-(2,3-Dihydroindol-3-yl)methylmalonate (12a) from 11 — A mixture of **11** (1.035 g, 3.58 mmol) and Et_3SiH (1.14 mL, 7.14 mmol) in TFA (8 mL) was refluxed for 3 day with stirring. After evaporation of the solvent, H_2O and $CHCl_3$ were added and the whole was made alkaline with 2N NaOH. After separating organic layer, the water layer was extracted with $CHCl_3$–MeOH (95:5, v/v). The combined 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 AcOEt–hexane (1:4, v/v) to give **12a** (854.9 mg, 82%). **12a**: colorless oil. IR (film): 3383, 2981, 1747, 1728, 1608, 1242 (br), 1028, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=6.8 Hz, $C\underline{H}_3CH_2$), 1.28 (3H, t, *J*=6.8 Hz, $C\underline{H}_3CH_2$), 2.10—2.17 (1H, m), 2.36—2.43 (1H, m), 3.22—3.28 (2H, m), 3.47 (1H, t, *J*=6.8 Hz), 3.67—3.71 (1H, m), 4.17—4.23 (4H, m, $CH_3C\underline{H}_2$), 6.64 (1H, d, *J*=7.6 Hz, C_4 or C_7-H), 6.73 (1H, dt, *J*=1.0, 7.6 Hz,

C_5 or C_6-H), 7.04 (1H, dt, *J*=1.0, 7.6 Hz, C_5 or C_6-H), 7.14 (1H, d, *J*=7.6 Hz, C_4 or C_7-H). HR-MS *m/z*: Calcd for $C_{16}H_{21}NO_4$: 291.1470. Found: 291.1473.

Diethyl 2-(2,3-Dihydro-6-nitroindol-3-yl)methylmalonate (12b) from 12a — $NaNO_3$ (18.2 mg, 0.21 mmol) was added to a solution of **12a** (51.3 mg, 0.18 mmol) in conc. H_2SO_4 (1 mL) under ice cooling with stirring. Stirring was continued at 0°C for 30 min. After addition of ice, the whole was made alkaline with 2N NaOH and extracted with AcOEt. 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 $CHCl_3$–hexane (2:1, v/v) to give **12b** (54.4 mg, 92%). **12b**: orange viscous oil. IR (KBr): 3392, 2983, 1745, 1728, 1520, 1344 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J*=7.1 Hz, $C\underline{H}_3CH_2$), 1.29 (3H, t, *J*=7.1 Hz, $C\underline{H}_3CH_2$), 2.13—2.20 (1H, m), 2.38—2.44 (1H, m), 3.30—3.38 (2H, m), 3.43 (1H, t, *J*=7.3 Hz), 3.80 (1H, t, *J*=8.3 Hz), 4.01 (1H, br s, NH, disappeared on addition of D_2O), 4.17—4.27 (4H, m, $CH_3C\underline{H}_2$), 7.21 (1H, d, *J*=8.1 Hz, C_4-H), 7.37 (1H, d, *J*=2.0 Hz, C_7-H), 7.59 (1H, dd, *J*=8.1, 2.0 Hz, C_5-H). HR-MS *m/z*: Calcd for $C_{16}H_{20}N_2O_6$: 336.1322. Found: 336.1306.

Diethyl 2-(6-Nitroindol-3-yl)methylmalonate (9) from 12b — Oxygen was bubbled into the suspension of **12b** (102.9 mg, 0.31 mmol) and salcomine (56.3 mg, 0.17 mmol) in MeOH (10 mL) at rt for 8 h with vigorous stirring. The solvent was evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:3, v/v) to give **9** (57.4 mg, 56%). All spectral data were identical with those of **9** from **1**.

Diethyl 2-(6-Nitroindol-3-yl)methylmalonate (9) from 6-Nitrogramine (13a) — A mixture of **13a**[10] (54.0 mg, 0.25 mmol), diethyl malonate (0.056 mL, 0.37 mmol) and tri-*n*-butylphosphine[7] (0.03 mL, 0.12 mmol) in DMF (1.5 mL) was heated at 60°C for 4 h with stirring. Then, diethyl malonate (0.37 mL, 0.37 mmol) and tri-*n*-butylphosphine[7] (0.03 mL, 0.12 mmol) were added to the reaction mixture and stirred at 60°C for additional 7 h with stirring. After evaporation of the solvent, the residue was column-chromatographed on SiO_2 with AcOEt–hexane (2:1, v/v) to give **9** (55.2 mg, 67%).

1-(*N*,*N*-Dimethylaminomethyl)-6-nitroindole (13b) from 5 — A solution of **5** (53.9 mg, 0.33 mmol) in MeOH (2 mL) was added to a solution of HCHO (35% in water, 304.7 mg, 3.39 mmol) and Me_2NH (50% in water, 286.0mg, 3.34 mmol) in MeOH (2 mL). The mixture was stirred at rt for 6 h. After addition of H_2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:2, v/v) to give unreacted **5** (14.5 mg, 27%) and **13b** (45.0 mg, 62%) in the order of elution. **13b**: mp 111—112°C (yellow needles recrystallized from AcOEt–hexane). IR (KBr): 1604, 1583, 1496, 1325 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (6H, s, NMe_2), 4.82 (2H, s, CH_2), 6.62 (1H, d, *J*=3.2 Hz, C_3-H), 7.43 (1H, d, *J*=3.2 Hz, C_2-H), 7.65 (1H, d, *J*=8.8 Hz, C_4-H), 8.02 (1H, dd, *J*=8.8, 2.2 Hz, C_5-H), 8.44 (1H, d, *J*=2.2 Hz, C_7-H). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.33; H, 6.03; N, 19.04.

2-Methylthio-3-methylthiomethyl- (15), 3-Methylthio- (16), 2,3-Dimethylthio- (17), 3-Methylthiomethyl-6-nitroindoles (18), 5, and 7 from 1 — A solution of **1** (201.4 mg, 1.05 mmol) and $NaSCH_3$ (15 % in water, 2 mL, 4.29 mmol) in MeOH (5 mL) was refluxed for 1 h with stirring. After addition of H_2O, the whole was made acidic with 2N HCl and extracted with AcOEt. 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 repeatedly with AcOEt–hexane (1:5, v/v) to give **15** (47.3 mg, 17%), **5** (67.0 mg, 39%), **16** (7.8 mg, 4%), **17** (6.5 mg, 2%), **18** (5.6 mg, 2%), and **7** (7.1 mg, 4%) in the order of elution. **15**: mp 184—186°C (orange needles recrystallized from $CHCl_3$). IR (KBr): 3284, 1614, 1498, 1456, 1425, 1288 (br), 1061 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, CH_3), 2.52 (3H, s, CH_3), 4.00 (2H, s, CH_2), 7.75 (1H, d, *J*=8.8 Hz, C_4-H), 8.04 (1H, dd, *J*=8.8, 2.2 Hz, C_5-H), 8.27 (1H, d, *J*=2.2 Hz, C_7-H), 8.44 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 268 (M^+). *Anal*. Calcd for $C_{11}H_{12}N_2O_2S_2$: C, 49.23; H, 4.51; N, 10.44. Found: C, 49.22; H, 4.45; N, 10.20. **16**: mp 171—172°C (yellow needles recrystallized from $CHCl_3$). IR (KBr): 3325, 1612, 1587, 1504, 1325, 1300, 1275, 1065 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 7.58 (1H, d, *J*=2.4 Hz, collapsed to s on addition of D_2O, C_2-H), 7.82 (1H, d, *J*=8.8 Hz, C_4-H), 8.11 (1H, dd, *J*=8.8, 2.0 Hz, C_5-H), 8.37 (1H, d, *J*=2.0 Hz, C_7-H), 8.63 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 208 (M^+). *Anal*. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.87; H, 3.79; N, 13.45. **17**: mp 197—198°C (orange needles recrystallized from $CHCl_3$). IR (KBr): 3302, 1606, 1583, 1495, 1435, 1288 (br), 1065 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, CH_3), 2.65 (3H, s, CH_3), 7.73 (1H, d, *J*=8.8 Hz, C_4-H), 8.09 (1H, dd, *J*=8.8, 2.0 Hz, C_5-H), 8.27 (1H, d, *J*=2.0 Hz, C_7-H), 8.58 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 254 (M^+). *Anal*. Calcd for $C_{10}H_{10}N_2O_2S_2$: C, 47.22; H, 3.96; N, 11.01. Found: C, 47.14; H, 3.90; N, 10.93. **18**: mp 142—143°C (yellow needles recrystallized from $CHCl_3$–hexane). IR (KBr): 1619, 1587, 1504, 1321, 1298, 1053 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, CH_3), 3.91 (2H, s, CH_2), 7.44 (1H, d, *J*=2.5 Hz, collapsed to s on addition of D_2O, C_2-H), 7.79 (1H, d, *J*=8.8 Hz, C_4-H), 8.05 (1H, dd, *J*=8.8, 2.2 Hz, C_5-H), 8.35 (1H, d, *J*=2.2 Hz, C_7-H), 8.47 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 222 (M^+). *Anal*. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.62; H, 4.45; N, 12.22.

2-Methylthio-6-nitroindole (19) and 5 from 1 — A solution of **1** (204.1 mg, 1.06 mmol) and $NaSCH_3$ (15 % in water, 2 mL, 4.29 mmol) in DMF (5 mL) was refluxed for 1 h with stirring. After addition of H_2O, the whole was made acidic with 2N HCl, and extracted with AcOEt. 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 AcOEt–hexane (1:5, v/v) to give **19** (29.7 mg, 13%) and **5** (93.7 mg, 54%) in the order of elution. **19**: mp 132—133°C (orange needles recrystallized from $CHCl_3$–hexane). IR (KBr): 1608, 1585, 1504, 1456, 1301 (br), 1065 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (3H, s, CH_3), 6.52 (1H, dd, *J*=2.2, 1.0 Hz, collapsed to d, *J*=1.0 Hz on addition of D_2O, C_3-H), 7.52 (1H, d, *J*=8.8 Hz, C_4-H), 8.01 (1H, dd, *J*=8.8, 2.0 Hz, C_5-H), 8.24 (1H, dd, *J*=2.0, 1.0 Hz, C_7-H), 8.43 (1H, br s, NH, disappeared on addition of D_2O). MS *m/z*: 208 (M^+). *Anal*. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.76; H, 3.83; N, 13.45.

3-Methylthiomethyl-6-nitroindole (18) from 13a — A solution of **13a**[10] (50.5 mg, 0.23 mmol) in $NaSCH_3$ (15% in water, 1 mL, 2.14 mmol) and MeOH (5 mL) was refluxed for 8 h with stirring. After addition of H_2O, the whole was made acidic with 2N HCl, and extracted with AcOEt. 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 $CHCl_3$–hexane (2:1, v/v) to give **18** (47.9 mg, 94%).

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