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NUCLEOPHILIC SUBSTITUTION REACTION OF 1-METHOXY-6-NITRO-INDOLE<sup>1</sup>

Koji Yamada, Toshiya Kawasaki, Tomomi Fujita, and Masanori Somei\*

Faculty of Pharmaceutical Sciences, Kanazawa University,  
13-1 Takara-machi, Kanazawa 920-0934, Japan

*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.<sup>2</sup> They undergo nucleophilic substitution reactions and provide various kinds of products depending on the structures of substrates, nucleophiles, and reaction conditions.<sup>3</sup> 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,<sup>4</sup> **1** was prepared by the following sequence of reactions as shown in Scheme 1: 1) nitration of indoline<sup>5</sup> (**2**) with H<sub>2</sub>SO<sub>4</sub> and NaNO<sub>3</sub> giving 6-nitroindoline (**3**) in 92% yield, 2) oxidation of **3** with NaWO<sub>4</sub>·2H<sub>2</sub>O and 30% H<sub>2</sub>O<sub>2</sub> affording 1-hydroxy-6-nitroindole<sup>4</sup> (**4**) in 79% yield, and 3) methylation of **4** with Me<sub>2</sub>SO<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub> or CH<sub>2</sub>N<sub>2</sub> providing **1** in 100 and 96% yields, respectively.

The reaction of **1** with NaOMe in refluxing DMF afforded 6-nitroindole<sup>6</sup> (**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<sub>2</sub>O 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<sup>t</sup>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**



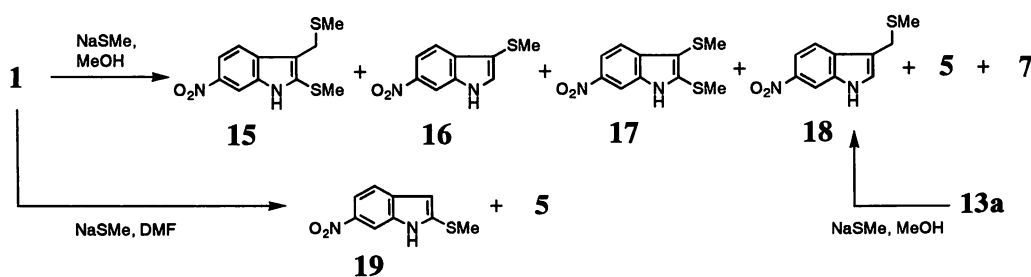
and **7** in the respective yields of 20 and 5%.

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<sup>7</sup> with diethyl malonate using tri-*n*-butylphosphine<sup>7</sup> as a catalyst. Reduction of **11** to the corresponding 2,3-dihydroindole (**12a**) with triethylsilane<sup>8</sup> and trifluoroacetic acid proceeded in 82% yield. Nitration of **12a** with NaNO<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub> 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<sup>9</sup> afforded **9** in 56% yield. All spectral data were identical with those of **9** obtained from **1**. The second synthetic trial used 6-nitrogramine<sup>10</sup> (**13a**) as a substrate, which was available either from **10** by nitration<sup>10a</sup> or from **5** by Mannich reaction.<sup>10b</sup> The reaction of **13a** with diethyl malonate and tri-*n*-butylphosphine<sup>7</sup> afforded **9** in 67% yield. It is interesting to note that when the reaction of **5** with HCHO-Me<sub>2</sub>NH 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<sub>N</sub>2'* 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-6-nitroindole (**16**), 2,3-dimethylthio-6-nitroindole (**17**), 3-methylthio-6-nitroindole (**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 methanesulfonyl 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  $^1\text{H-NMR}$  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 ( $\text{SiO}_2$ , 100-200 mesh, from Kanto Chemical Co. Inc.) or activated alumina ( $\text{Al}_2\text{O}_3$ , 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<sub>254</sub> (Type 60) ( $\text{SiO}_2$ ).

**1-Hydroxy-6-nitroindole (4) from 6-Nitroindoline (3)** — 30% Aq.  $\text{H}_2\text{O}_2$  (0.58 mL, 5.7 mmol) was added to a solution of **3** (101.3 mg, 0.57 mmol) and  $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$  (18.8 mg, 0.06 mmol) in MeOH (10 mL) and  $\text{H}_2\text{O}$  (1.0 mL) at  $0^\circ\text{C}$  with stirring. Stirring was continued at rt for 7 h and then the whole was extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $\text{SiO}_2$  with  $\text{CH}_2\text{Cl}_2$ -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  $153\text{--}155^\circ\text{C}$  (decomp, orange needles recrystallized from  $\text{CHCl}_3$ ). IR (KBr): 3240, 1617, 1586, 1514, 1332, 1095  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ :  $\text{CD}_3\text{OD}$ , 95:5, v/v)  $\delta$ : 6.43 (1H, d,  $J=3.3$  Hz,  $\text{C}_3\text{-H}$ ), 7.51 (1H, d,  $J=3.3$  Hz,  $\text{C}_2\text{-H}$ ), 7.61 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 7.95 (1H, dd,  $J=8.8$  and 2.1 Hz,  $\text{C}_5\text{-H}$ ), 8.42 (1H, d,  $J=2.1$  Hz,  $\text{C}_7\text{-H}$ ). MS  $m/z$ : 178 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_8\text{H}_6\text{N}_2\text{O}_3$ : 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),  $\text{K}_2\text{CO}_3$  (6.472 g, 46.8 mmol) and  $\text{Me}_2\text{SO}_4$  (4.45 mL, 46.9 mmol) in MeOH (25 mL) was stirred at rt for 1 h. After addition of  $\text{H}_2\text{O}$ , the whole was extracted with AcOEt. The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3$ -hexane (1:1, v/v) to give **1** (1.79 g, 100%). **1**: mp  $90\text{--}91^\circ\text{C}$  (yellow needles recrystallized from MeOH). IR (KBr): 1613, 1584, 1508, 1339, 1100, 955, 756, 720  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.17 (3H, s,  $\text{CH}_3$ ), 6.45 (1H, dd,  $J=3.4$ , 0.8 Hz,  $\text{C}_3\text{-H}$ ), 7.52 (1H, d,  $J=3.4$  Hz,  $\text{C}_2\text{-H}$ ), 7.60 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 7.98 (1H, dd,  $J=8.8$  and 2.2 Hz,  $\text{C}_5\text{-H}$ ), 8.38 (1H, br

d,  $J=2.2$  Hz, C<sub>7</sub>-H). MS  $m/z$ : 192 (M<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: 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<sub>2</sub>N<sub>2</sub> 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 disappearance of **4** monitoring with TLC, the solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>–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<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on Al<sub>2</sub>O<sub>3</sub> 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<sub>2</sub> with AcOEt–hexane (1:5, v/v) to give **5**<sup>6</sup> (52.5 mg, 57%). The latter was purified by P-TLC on SiO<sub>2</sub>, developed three times with AcOEt–hexane (1:5, v/v). Extraction of the band having an R<sub>f</sub> value of 0.47–0.32 with CHCl<sub>3</sub>–MeOH (95:5, v/v) gave **6** (24.6 mg, 22%). Extraction of the band having an R<sub>f</sub> value of 0.32–0.21 with CHCl<sub>3</sub>–MeOH (95:5, v/v) gave **7** (6.3 mg, 6%). **6**: mp 158–160 °C (yellow prisms recrystallized from CHCl<sub>3</sub>). IR (KBr): 3338, 1548, 1292 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 4.01 (3H, s, CH<sub>3</sub>), 5.72 (1H, dd,  $J=2.2, 0.7$  Hz, C<sub>3</sub>-H), 7.41 (1H, d,  $J=8.7$  Hz, C<sub>4</sub>-H), 8.00 (1H, dd,  $J=8.7, 2.0$  Hz, C<sub>5</sub>-H), 8.11 (1H, br s, NH), 8.14 (1H, d,  $J=2.0$  Hz, C<sub>7</sub>-H). MS  $m/z$ : 192 (M<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>·1/4H<sub>2</sub>O: 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<sub>3</sub>–hexane). IR (film): 1556, 1508, 1331, 1300, 1097, 1061 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.29 (3H, s, CH<sub>3</sub>), 6.99 (1H, d,  $J=2.7$  Hz, collapsed to s on addition of D<sub>2</sub>O, C<sub>2</sub>-H), 7.70 (1H, d,  $J=8.8$  Hz, C<sub>4</sub>-H), 7.94 (1H, br s, NH, disappeared on addition of D<sub>2</sub>O), 7.98 (1H, dd,  $J=8.8, 2.1$  Hz, C<sub>5</sub>-H), 8.27 (1H, d,  $J=2.1$  Hz, C<sub>7</sub>-H). Anal. Calcd for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: 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<sub>2</sub>O (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<sub>3</sub>–MeOH (95:5, v/v). The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>–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<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ: 6.84 (1H, d,  $J=3.2$  Hz, C<sub>3</sub>-H), 7.90 (1H, d,  $J=3.2$  Hz, C<sub>2</sub>-H), 8.06 (1H, d,  $J=8.5$  Hz, C<sub>4</sub>- or C<sub>5</sub>-H), 8.09 (1H, d,  $J=8.5$  Hz, C<sub>4</sub>- or C<sub>5</sub>-H), 12.76 (1H, br s, NH, disappeared on addition of D<sub>2</sub>O). Anal. Calcd for C<sub>9</sub>H<sub>5</sub>N<sub>3</sub>O<sub>2</sub>: 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<sub>2</sub>O under ice cooling, the whole was made acidic with 2N HCl, and extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a residue, which was purified by P-TLC on SiO<sub>2</sub> developed twice with AcOEt-hexane (1:4, v/v). Extraction of the band having an R<sub>f</sub> value of 0.75–0.59 with CHCl<sub>3</sub>-MeOH (95:5, v/v) gave **5** (8.4 mg, 20%). Extraction of the band having an R<sub>f</sub> value of 0.53–0.31 with CHCl<sub>3</sub>-MeOH (95:5, v/v) gave a mixture (39.8 mg) of **7** and **9**. The mixture was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub> 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<sub>3</sub>-hexane). IR (KBr): 3350, 1718 (br), 1504, 1342, 1329, 1309, 1055 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.21 (6H, t, *J*=7.3 Hz, CH<sub>3</sub>CH<sub>2</sub>), 3.40 (2H, d, *J*=7.6 Hz, CH<sub>2</sub>CH), 3.72 (1H, t, *J*=7.6 Hz, CH<sub>2</sub>CH), 4.11–4.21 (4H, m, CH<sub>3</sub>CH<sub>2</sub>), 7.37 (1H, d, *J*=2.5 Hz, C<sub>2</sub>-H), 7.67 (1H, d, *J*=8.8 Hz, C<sub>4</sub>-H), 8.03 (1H, dd, *J*=8.8, 2.0 Hz, C<sub>5</sub>-H), 8.32 (1H, d, *J*=2.0 Hz, C<sub>7</sub>-H), 8.53 (1H, br s, NH, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 334 (M<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>·1/4H<sub>2</sub>O: 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<sup>7</sup> (0.44 mL, 1.79 mmol) in MeCN (50 mL) was refluxed for 1 day with stirring. After evaporation of the solvent, H<sub>2</sub>O and CHCl<sub>3</sub> 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<sub>3</sub>-MeOH (95:5, v/v). The combined extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> 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<sub>3</sub>-hexane). IR (film): 3352, 1747, 1716, 1344, 1298, 744 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.20 (6H, t, *J*=7.1 Hz, CH<sub>3</sub>CH<sub>2</sub>), 3.39 (2H, d, *J*=7.6 Hz, CH<sub>2</sub>CH), 3.76 (1H, t, *J*=7.6 Hz, CH<sub>2</sub>CH), 4.11–4.21 (4H, m, CH<sub>3</sub>CH<sub>2</sub>), 7.05 (1H, d, *J*=2.2 Hz, C<sub>2</sub>-H), 7.13 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz, C<sub>5</sub> or C<sub>6</sub>-H), 7.19 (1H, ddd, *J*=8.1, 7.1, 1.0 Hz, C<sub>5</sub> or C<sub>6</sub>-H), 7.34 (1H, dt, *J*=8.1, 1.0 Hz, C<sub>4</sub> or C<sub>7</sub>-H), 7.61 (1H, dt, *J*=8.1, 1.0 Hz, C<sub>4</sub> or C<sub>7</sub>-H), 7.98 (1H, br s, NH). MS *m/z*: 289 (M<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>: 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<sub>3</sub>SiH (1.14 mL, 7.14 mmol) in TFA (8 mL) was refluxed for 3 day with stirring. After evaporation of the solvent, H<sub>2</sub>O and CHCl<sub>3</sub> were added and the whole was made alkaline with 2N NaOH. After separating organic layer, the water layer was extracted with CHCl<sub>3</sub>-MeOH (95:5, v/v). The combined extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> 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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27 (3H, t, *J*=6.8 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.28 (3H, t, *J*=6.8 Hz, CH<sub>3</sub>CH<sub>2</sub>), 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<sub>3</sub>CH<sub>2</sub>), 6.64 (1H, d, *J*=7.6 Hz, C<sub>4</sub> or C<sub>7</sub>-H), 6.73 (1H, dt, *J*=1.0, 7.6 Hz,

C<sub>5</sub> or C<sub>6</sub>-H), 7.04 (1H, dt,  $J=1.0, 7.6$  Hz, C<sub>5</sub> or C<sub>6</sub>-H), 7.14 (1H, d,  $J=7.6$  Hz, C<sub>4</sub> or C<sub>7</sub>-H). HR-MS  $m/z$ : Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>: 291.1470. Found: 291.1473.

**Diethyl 2-(2,3-Dihydro-6-nitroindol-3-yl)methylmalonate (12b) from 12a** — NaNO<sub>3</sub> (18.2 mg, 0.21 mmol) was added to a solution of **12a** (51.3 mg, 0.18 mmol) in conc. H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>–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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28 (3H, t,  $J=7.1$  Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.29 (3H, t,  $J=7.1$  Hz, CH<sub>3</sub>CH<sub>2</sub>), 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<sub>2</sub>O), 4.17–4.27 (4H, m, CH<sub>3</sub>CH<sub>2</sub>), 7.21 (1H, d,  $J=8.1$  Hz, C<sub>4</sub>-H), 7.37 (1H, d,  $J=2.0$  Hz, C<sub>7</sub>-H), 7.59 (1H, dd,  $J=8.1, 2.0$  Hz, C<sub>5</sub>-H). HR-MS  $m/z$ : Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: 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<sub>2</sub> 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**<sup>10</sup> (54.0 mg, 0.25 mmol), diethyl malonate (0.056 mL, 0.37 mmol) and tri-*n*-butylphosphine<sup>7</sup> (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<sup>7</sup> (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<sub>2</sub> with AcOEt–hexane (2:1, v/v) to give **9** (55.2 mg, 67%).

**1-(*N,N*-Dimethylamino methyl)-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<sub>2</sub>NH (50% in water, 286.0 mg, 3.34 mmol) in MeOH (2 mL). The mixture was stirred at rt for 6 h. After addition of H<sub>2</sub>O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO<sub>2</sub> 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<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.32 (6H, s, NMe<sub>2</sub>), 4.82 (2H, s, CH<sub>2</sub>), 6.62 (1H, d,  $J=3.2$  Hz, C<sub>3</sub>-H), 7.43 (1H, d,  $J=3.2$  Hz, C<sub>2</sub>-H), 7.65 (1H, d,  $J=8.8$  Hz, C<sub>4</sub>-H), 8.02 (1H, dd,  $J=8.8, 2.2$  Hz, C<sub>5</sub>-H), 8.44 (1H, d,  $J=2.2$  Hz, C<sub>7</sub>-H). *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: 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<sub>3</sub> (15 % in water, 2 mL, 4.29 mmol) in MeOH (5 mL) was refluxed for 1 h with stirring. After addition of H<sub>2</sub>O, the whole was made acidic with 2N HCl and extracted with AcOEt. The

extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $\text{SiO}_2$  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  $\text{CHCl}_3$ ). IR (KBr): 3284, 1614, 1498, 1456, 1425, 1288 (br), 1061  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.07 (3H, s,  $\text{CH}_3$ ), 2.52 (3H, s,  $\text{CH}_3$ ), 4.00 (2H, s,  $\text{CH}_2$ ), 7.75 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 8.04 (1H, dd,  $J=8.8, 2.2$  Hz,  $\text{C}_5\text{-H}$ ), 8.27 (1H, d,  $J=2.2$  Hz,  $\text{C}_7\text{-H}$ ), 8.44 (1H, br s, NH, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 268 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$ : 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  $\text{CHCl}_3$ ). IR (KBr): 3325, 1612, 1587, 1504, 1325, 1300, 1275, 1065  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.40 (3H, s,  $\text{CH}_3$ ), 7.58 (1H, d,  $J=2.4$  Hz, collapsed to s on addition of  $\text{D}_2\text{O}$ ,  $\text{C}_2\text{-H}$ ), 7.82 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 8.11 (1H, dd,  $J=8.8, 2.0$  Hz,  $\text{C}_5\text{-H}$ ), 8.37 (1H, d,  $J=2.0$  Hz,  $\text{C}_7\text{-H}$ ), 8.63 (1H, br s, NH, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 208 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$ : 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  $\text{CHCl}_3$ ). IR (KBr): 3302, 1606, 1583, 1495, 1435, 1288 (br), 1065  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.36 (3H, s,  $\text{CH}_3$ ), 2.65 (3H, s,  $\text{CH}_3$ ), 7.73 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 8.09 (1H, dd,  $J=8.8, 2.0$  Hz,  $\text{C}_5\text{-H}$ ), 8.27 (1H, d,  $J=2.0$  Hz,  $\text{C}_7\text{-H}$ ), 8.58 (1H, br s, NH, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 254 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S}_2$ : 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  $\text{CHCl}_3$ –hexane). IR (KBr): 1619, 1587, 1504, 1321, 1298, 1053  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.05 (3H, s,  $\text{CH}_3$ ), 3.91 (2H, s,  $\text{CH}_2$ ), 7.44 (1H, d,  $J=2.5$  Hz, collapsed to s on addition of  $\text{D}_2\text{O}$ ,  $\text{C}_2\text{-H}$ ), 7.79 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 8.05 (1H, dd,  $J=8.8, 2.2$  Hz,  $\text{C}_5\text{-H}$ ), 8.35 (1H, d,  $J=2.2$  Hz,  $\text{C}_7\text{-H}$ ), 8.47 (1H, br s, NH, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 222 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ : 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  $\text{NaSCH}_3$  (15% in water, 2 mL, 4.29 mmol) in DMF (5 mL) was refluxed for 1 h with stirring. After addition of  $\text{H}_2\text{O}$ , the whole was made acidic with 2N HCl, and extracted with AcOEt. The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $\text{SiO}_2$  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  $\text{CHCl}_3$ –hexane). IR (KBr): 1608, 1585, 1504, 1456, 1301 (br), 1065  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.61 (3H, s,  $\text{CH}_3$ ), 6.52 (1H, dd,  $J=2.2, 1.0$  Hz, collapsed to d,  $J=1.0$  Hz on addition of  $\text{D}_2\text{O}$ ,  $\text{C}_3\text{-H}$ ), 7.52 (1H, d,  $J=8.8$  Hz,  $\text{C}_4\text{-H}$ ), 8.01 (1H, dd,  $J=8.8, 2.0$  Hz,  $\text{C}_5\text{-H}$ ), 8.24 (1H, dd,  $J=2.0, 1.0$  Hz,  $\text{C}_7\text{-H}$ ), 8.43 (1H, br s, NH, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 208 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$ : 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**<sup>10</sup> (50.5 mg, 0.23 mmol) in  $\text{NaSCH}_3$  (15% in water, 1 mL, 2.14 mmol) and MeOH (5 mL) was refluxed for 8 h with stirring. After addition of  $\text{H}_2\text{O}$ , the whole was made acidic with 2N HCl, and extracted with AcOEt. The extract was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3$ –hexane (2:1, v/v) to give **18** (47.9 mg, 94%).

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