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NUCLEOPHILIC SUBSTITUTION REACTION IN INDOLE CHEMISTRY: 1-METHOXY-6-NITROINDOLE-3-CARBALDEHYDE AS A VERSATILE BUILDING BLOCK FOR 2,3,6-TRISUBSTITUTED INDOLES[1,#]

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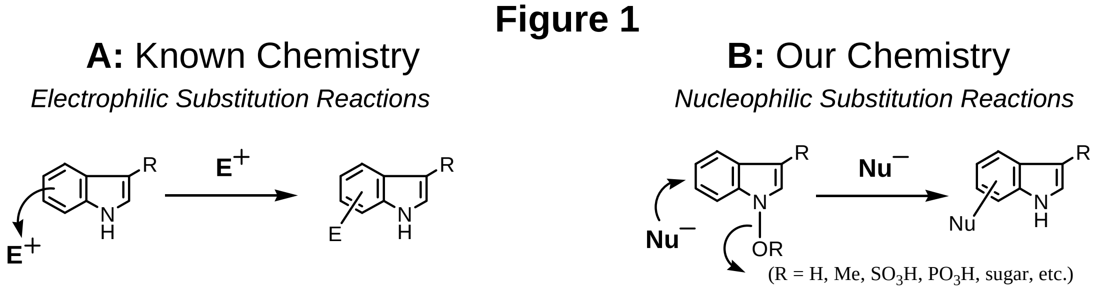
Abstract – 1-Methoxy-6-nitroindole-3-carbaldehyde is proved to be a versatile electrophile and reacts regioselectively at the 2-position with various types of nucleophiles providing 2,3,6-trisubstituted indole derivatives. The reaction is applicable for the preparation of a novel pyrimido[1,2-*a*]indole derivative.

Indole is one of the electron rich hetero-aromatics. In the indole chemistry, therefore, electrophilic substitution reaction has been well studied[2] (as shown in general formula in Figure 1, **A**) and been applied to explain the biosyntheses of various types of indole alkaloids.[2]

Figure 1



Dedicated to the 75th birthday of Dr. Keiichiro Fukumoto

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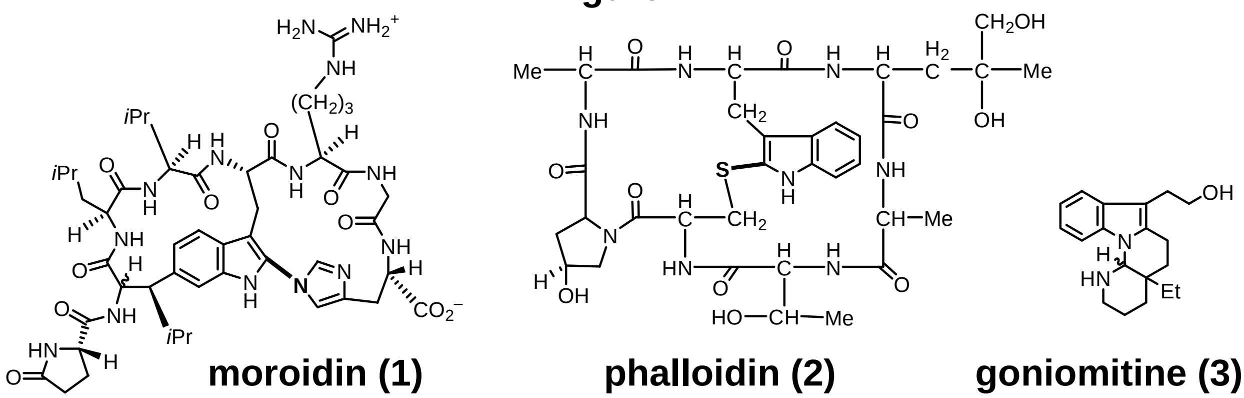
It is evident, however, that some of natural products are difficult to produce by the electrophilic substitution reaction. Some examples are moroidin (**1**, Figure 2),[3a] phalloidin (**2**),[3b] goniomitine (**3**),[3c] and so on.[3d] They have either a C—N, a C—S, or a C—C bond at the 2 position of indole nucleus. Their syntheses require N^+, S^+, and C^+ synthons, respectively. Except for S^+ and C^+, the N^+ synthon is rarely available chemical species. If by chance a nucleophilic substitution reaction could be applied, their syntheses would become easy because the readily available N^- synthon would be employed. In the cases of **2** and **3**, the required S^- and C^- synthons have ample synthetic equivalents as well. Based on these ideas, we have thus far developed the unprecedented[2,4] nucleophilic substitution reaction[5] (as shown in general formula in Figure 1, **B**) simply by introducing a hydroxy or its modified group onto the nitrogen, N(1),[5] of indole substrates.

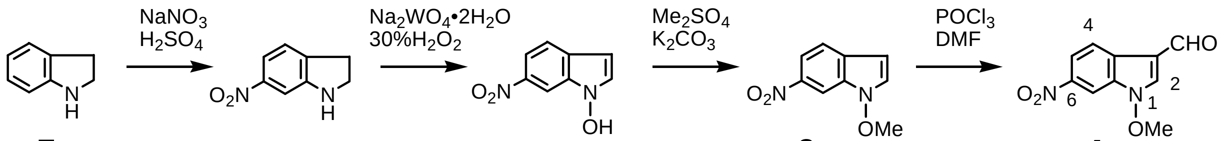
Figure 2



moroidin (1) **phalloidin (2)** **goniomitine (3)**

In this paper, we wish to report that 1-methoxy-6-nitroindole-3-carbaldehyde (**4**) is an excellent substrate for achieving nucleophilic substitution reactions with variety of nucleophiles. Consequently, various types of 2,3,6-trisubstituted indole derivatives become readily available, providing useful building blocks for the syntheses of **1**, **2**, and **3**. Preparation of a novel pyrimido[1,2-*a*]indole derivative is also reported.

Scheme 1



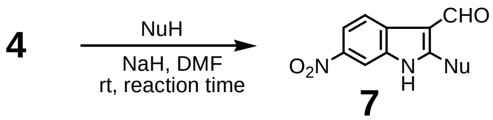
5 **6** **4**

According to our synthetic method,[6] we prepared 1-methoxy-6-nitroindole (**6**) from indoline (**5**) in 70% overall yield in 3 steps as shown in Scheme 1. Subsequent Vilsmeier-Haack reaction of **6** with $POCl_3$ and *N*,*N*-dimethylformamide (DMF) provided 1-methoxy-6-nitroindole-3-carbaldehyde (**4**) in 94% yield. Thus, **4** is now readily available from **5** in 4 steps in 66% overall yield.

With **4** in hand, we examined its nucleophilic substitution reaction with nitrogen-centered nucleophiles.

Using NaH as a base in DMF, piperidine was allowed to react with **4** at room temperature culminating in the formation of **7a** in 92% yield (Table 1).

Table 1



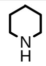
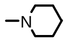
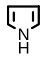
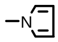
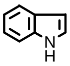
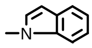
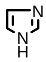
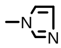
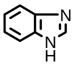
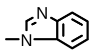
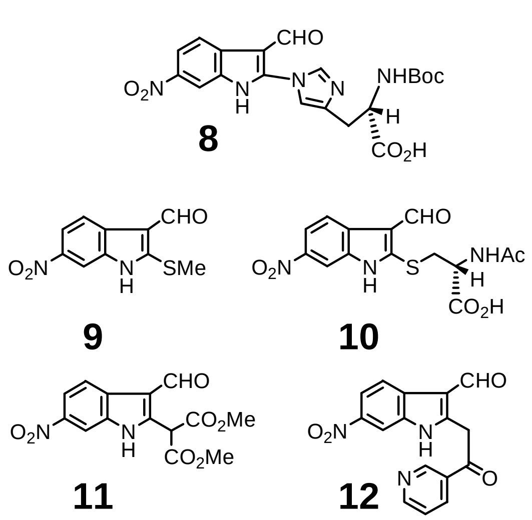
NuH	Reaction Time (h)	Compound 7	Nu	Yield (%)
	2.5	**a**		92
	3.5	**b**		98
	2.0	**c**		96
	1.5	**d**		97
	3.5	**e**		87

Figure 3



Under similar reaction conditions, pyrrole and indole provided **7b** and **7c** in 98 and 96% yields, respectively. Imidazole and benzimidazole also reacted with **4** providing **7d** and **7e** in the respective yields of 97 and 87%. Based on these successful results, we attempted the synthesis of **8**, a core structure of **1**. As expected, the reaction of N_α-Boc-L-histidine with **4** in DMF by the action of NaH as a base resulted in the formation of the desired N_α-Boc(3-formyl-6-nitroindol-2-yl)-L-histidine (**8**) in 94% yield.

We next examined NaSMe as a representative of sulfur-centered nucleophile. It reacted smoothly with **4** in DMF to afford **9** in 98% yield. In the next model experiment directed toward the phalloidin synthesis, *N*-acetyl-L-cysteine reacted successfully with **4** producing the expected *N*-acetyl-*S*-(3-formyl-6-nitroindol-2-yl)-L-cysteine (**10**) in 73% yield by the action of NaH in DMF.

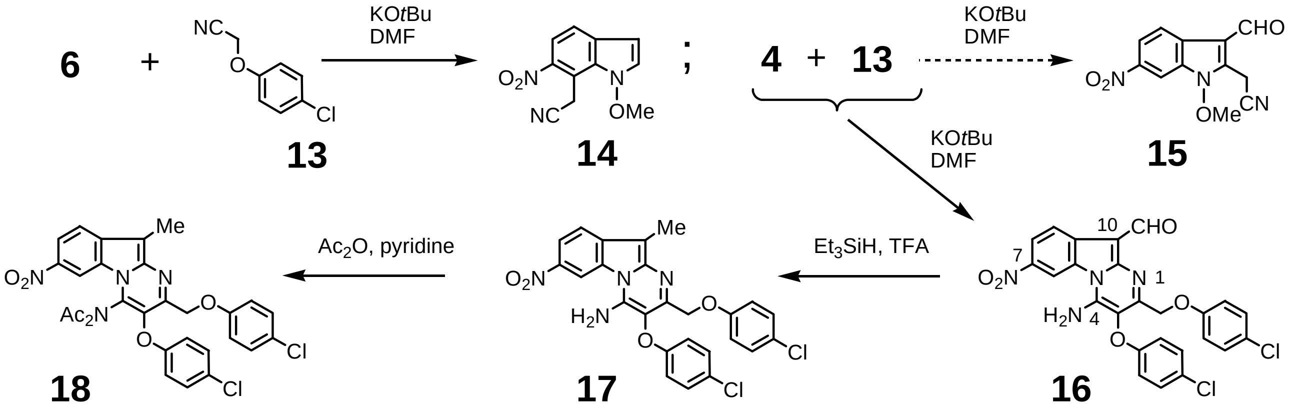
As for a carbon nucleophile, we chose dimethyl malonate at first. In the presence of KO*t*Bu in DMF at room temperature, it reacted with **4** to give **11** in 92% yield. Next, in order to prepare a suitable synthetic intermediate for **3**, 3-acetylpyridine was allowed to react with **4** by the action of KH in THF. The desired **12** was successfully isolated in 92% yield.

On the other hand, we examined the reaction of **6** with *p*-chlorophenoxyacetonitrile (**13**) in the presence of KO*t*Bu in DMF at 0 °C and isolated vicarious[7] product **14** in 67% yield (Scheme 2). It should be noted that, under similar reaction conditions, attempts to convert **4** to **15** by the reaction with **13** resulted in the formation of a novel 4-amino-3-*p*-chlorophenoxy-2-*p*-chlorophenoxymethyl-7-nitropyrimido[1,2-*a*]indole-10-carbaldehyde (**16**) in 71% yield.

The structure of pyrimido[1,2-*a*]indole skeleton was determined as follows. First, **16** was converted to

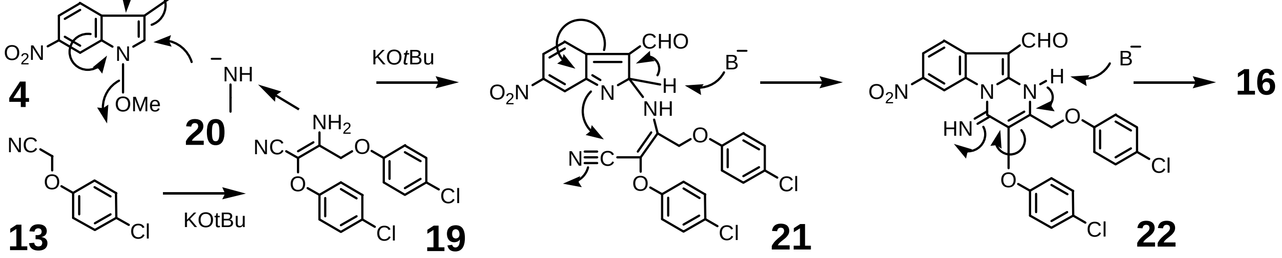
10-methyl compound **17** in 93% yield by the treatment with Et_3SiH in refluxing TFA. Subsequent reaction of **17** with Ac_2O-pyridine at room temperature afforded 89% yield of **18**. The structure of **18** was determined by X-ray single crystallographic analysis and the results are shown in ORTEP drawing in Figure 4.

Scheme 2



To clear the reaction mechanism for the formation of **16**, **13** was treated with KO*t*Bu in DMF at 0°C in the absence of **4** resulting in the formation of a 41% yield of 3-amino-2-butenonitrile **19** together with the recovery of **13**. Therefore, we can propose the following possible mechanism as shown in Scheme 3. By the reaction of KO*t*Bu and **13**, rapid formation of **19** occurs and it is converted to the corresponding N anion species **20**. Subsequent nucleophilic attack at the 2-position of **4** together with the liberation of the methoxy group produces an intermediate **21**. Then KO*t*Bu abstracts the proton at the 2-position of **21**. The resultant anion of indole nitrogen attacks the cyano group on the side chain to afford **22**. Subsequent prototropy of the imine group completes the formation of **16**.

Scheme 3



In conclusion, we have demonstrated that **4** is an excellent electrophile and it reacts regioselectively at the 2-position with nitrogen, sulfur, and carbon centered nucleophiles. Since the 6-nitro group can be transformed into variety of functional groups, this methodology could be applied to the synthesis of various types of 2,3,6-trisubstituted indole derivatives and natural products. The formation of **16** suggests that if we treat **4** with nucleophiles having 3-amino-2-butenonitrile like synthon, the construction of new heterocycles would become possible.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Shimadzu IR-420 and proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-SX102A or JEOL JMS-AX5 instruments. Optical rotations were determined on a Horiba SEPA-300 spectrometer. Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

1-Methoxy-6-nitroindole-3-carbaldehyde (**4**) **from 1-Methoxy-6-nitroindole**[6] **(6)** — A mixture of $POCl_3$ (0.97 mL, 10.6 mmol) and anhydrous DMF (5.84 mL, 75.1 mmol) was stirred at rt for 15 min. To the resulting mixture, a solution of **6** (1.00 g, 5.23 mmol) in anhydrous DMF (15 mL) was added and the mixture was stirred at rt for 7 h. After addition of H_2O, the whole was made alkaline with saturated aqueous $NaHCO_3$ 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 EtOAc–hexane (1:2, v/v) to give **4** (1.08 g, 94 %). **4**: mp 180—182°C (yellow prisms, recrystallized from $CHCl_3$–Hexane). IR (KBr): 1664, 1653, 1508, 1342 cm^{-1}. ^{1}H-NMR ($CDCl_3$) 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 $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.32; H, 3.61; N, 12.54.

6-Nitro-2-(piperidin-1-yl)indole-3-carbaldehyde (**7a**) **from 4 — General Procedure:** A solution of piperidine (82.4 mg, 0.96 mmol) in anhydrous DMF (1 mL) was added to NaH (60% suspension in paraffin oil, 48.4 mg, 1.21 mmol) under ice cooling. The mixture was stirred at 0 °C for 30 min and then a solution of **4** (51.3 mg, 0.23 mmol) in anhydrous DMF (2 mL) was added. The reaction mixture was stirred at rt for 2.5 h. After addition of H_2O, the whole was made acidic with saturated aqueous NH_4Cl, 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 (98:2, v/v) to give **7a** (58.2 mg, 92%). **7a**: mp >300 °C (yellow powder, recrystallized from acetone). IR (KBr): 1606, 1577, 1500, 1487, 1387, 1300 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 90 °C) δ: 1.68—1.75 (6H, m), 3.63—3.69 (4H, m), 7.91 (1H, dd, *J*=8.5, 2.1 Hz), 7.95 (1H, d, *J*=2.1 Hz), 8.00 (1H, d, *J*=8.5 Hz), 10.00 (1H, s), 11.25 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 273 (M^+). *Anal*. Calcd for $C_{14}H_{15}N_3O_3 \cdot 1/4H_2O$: C, 60.53; H, 5.66; N, 15.13. Found: C, 60.56; H, 5.56; N, 15.01.

6-Nitro-2-(pyrrol-1-yl)indole-3-carbaldehyde (**7b**) **from 4** — In the general procedure, pyrrole (63.1 mg, 0.94 mmol), NaH (28.7 mg, 0.72 mmol), and **4** (50.0 mg, 0.23 mmol) were used. The reaction time was 3.5 h. After the work-up and column-chromatography with $CHCl_3$–MeOH (98:2, v/v), **7b** (56.6 mg, 98%) was obtained. **7b**: mp >300 °C (yellow powder, recrystallized from acetone). IR (KBr): 1630, 1620, 1566, 1510, 1487, 1336 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.50 (2H, t, *J*=2.2 Hz), 7.55 (2H, t, *J*=2.2 Hz), 8.14 (1H, dd, *J*=8.8, 2.1 Hz), 8.26 (1H, d, *J*=2.1 Hz), 8.31 (1H, d, *J*=8.8 Hz), 10.06 (1H, s), 13.23 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 255 (M^+). *Anal*. Calcd for $C_{13}H_9N_3O_3 \cdot 1/4H_2O$: C, 60.12; H, 3.49; N, 16.18. Found: C, 60.15; H, 3.63; N, 15.91.

2-(Indol-1-yl)-6-nitroindole-3-carbaldehyde (7c) from 4 — In the general procedure, indole (86.1 mg, 0.74 mmol), NaH (43.0 mg, 1.10 mmol), and **4** (51.6 mg, 0.24 mmol) were used. The reaction time was 2 h. After the work-up and column-chromatography with $CHCl_3$, **7c** (68.7 mg, 96%) was obtained. **7c**: mp 291—293 °C (yellow powder, recrystallized from EtOAc). IR (KBr): 1630, 1618, 1558, 1508, 1483, 1383, 1327 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.93 (1H, d, *J*=3.4 Hz), 7.28 (1H, t, *J*=7.8 Hz), 7.35 (1H, t, *J*=7.8 Hz), 7.70 (1H, d, *J*=7.8 Hz), 7.76 (1H, d, *J*=7.8 Hz), 7.97 (1H, d, *J*=3.4 Hz), 8.20 (1H, dd, *J*=8.9, 2.5 Hz), 8.35 (1H, d, *J*=2.5 Hz), 8.36 (1H, d, *J*=8.9 Hz), 9.92 (1H, s), 13.49 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 305 (M^+). *Anal*. Calcd for $C_{17}H_{11}N_3O_3 \cdot 1/4H_2O$: C, 65.91; H, 3.74; N, 13.56. Found: C, 66.11; H, 3.76; N, 13.29.

2-(Imidazol-1-yl)-6-nitroindole-3-carbaldehyde (7d) from 4 — In the general procedure, imidazole (53.2 mg, 0.77 mmol), NaH (39.8 mg, 1.00 mmol), and **4** (51.5 mg, 0.23 mmol) were used. The reaction time was 1.5 h. After the work-up and column-chromatography with $CHCl_3$–MeOH (98:2, v/v), **7d** (54.9 mg, 97%) was obtained. **7d**: mp 268—272 °C (yellow powder, recrystallized from acetone). IR (KBr): 1660, 1510, 1331 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.30 (1H, s), 7.94 (1H, s), 8.17 (1H, dd, *J*=8.8, 2.2 Hz), 8.34 (1H, d, *J*=2.2 Hz), 8.35 (1H, d, *J*=8.8 Hz), 8.48 (1H, br s), 9.99 (1H, s). MS *m/z*: 256 (M^+). *Anal*. Calcd for $C_{12}H_8N_4O_3 \cdot 1/4H_2O$: C, 55.28; H, 3.29; N, 21.49. Found: C, 55.53; H, 3.20; N, 21.31.

2-(Benzimidazol-1-yl)-6-nitroindole-3-carbaldehyde (7e) from 4 — In the general procedure, benzimidazole (86.1 mg, 0.71 mmol), NaH (28.3 mg, 0.71 mmol), and **4** (50.0 mg, 0.23 mmol) were used. The reaction time was 3.5 h. After the work-up and column-chromatography with EtOAc, **7e** (60.4 mg, 87%) was obtained. **7e**: mp >300 °C (yellow powder, recrystallized from MeOH). IR (KBr): 1672, 1502, 1338, 1203 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.41—7.48 (2H, m), 7.75 (1H, dd, *J*=7.3, 1.6 Hz), 7.87 (1H, dd, *J*=7.3, 1.6 Hz), 8.21 (1H, dd, *J*=8.8, 2.0 Hz), 8.40 (1H, d, *J*=8.8 Hz), 8.41 (1H, d, *J*=2.0 Hz), 8.87 (1H, s), 9.93 (1H, s), 13.65 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 306 (M^+). *Anal*. Calcd for $C_{16}H_{10}N_4O_3 \cdot 1/2H_2O$: C, 60.95; H, 3.56; N, 17.77. Found: C, 61.02; H, 3.37; N, 17.49.

N_α-Boc-1-(3-formyl-6-nitroindol-2-yl)-L-histidine (8) from 4 — In the general procedure, N_α-Boc-L-histidine (208.7 mg, 0.82 mmol), NaH (58.0 mg, 1.21 mmol), and **4** (58.0 mg, 0.26 mmol) were used. The reaction time was 2 h. After the work-up and column-chromatography successively with $CHCl_3$–MeOH–AcOH (46:10:1, v/v) and $CHCl_3$–MeOH (6:4, v/v), **8** (110.3 mg, 94%) was obtained. **8**:

mp 125—136 °C (decomp., yellow fine needles, recrystallized from EtOAc). IR (KBr): 1655, 1518, 1340 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (9H, s), 2.93 (1H, dd, *J*=14.7, 8.8 Hz), 3.00 (1H, dd, *J*=14.7, 4.8 Hz), 4.27 (1H, td, *J*= 8.8, 4.8 Hz, collapsed to dd, *J*=8.8, 4.8 Hz on addition of D_2O), 7.05 (1H, d, *J*=8.8 Hz, disappeared on addition of D_2O), 7.64 (1H, s), 8.13 (1H, dd, *J*=8.8, 2.0 Hz), 8.30 (1H, d, *J*=8.8 Hz), 8.30 (1H, d, *J*=2.0 Hz), 8.39 (1H, br s), 9.98 (1H, s). FAB-MS *m/z*: 444 (M^++1). *Anal*. Calcd for $C_{20}H_{21}N_5O_7$·1/2H_2O: C, 53.10; H, 4.90; N, 15.48. Found: C, 53.11; H, 4.75; N, 15.41. $[\alpha]_D^{23}$ +24.26° (c=0.101, MeOH).

2-Methylthio-6-nitroindole-3-carbaldehyde (9) from 4 — A solution of **4** (51.4 mg, 0.23 mmol) and $NaSCH_3$ (15% in water, 1 mL, 2.14 mmol) in DMF (2 mL) was refluxed for 1 h with stirring. After addition of H_2O, the whole was made acidic with 6% HCl. The resulted precipitates (**9**, 54.2 mg, 98%) were collected by filtration and washed with EtOAc. **9**: mp >300 °C (yellow powder, recrystallized from acetone). IR (KBr): 1626, 1608, 1500, 1311, 1298 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.76 (3H, s), 8.07 (1H, dd, *J*=8.6, 2.0 Hz), 8.11 (1H, d, *J*=8.6 Hz), 8.25 (1H, d, *J*=2.0 Hz), 10.10 (1H, s). *Anal*. Calcd for $C_{10}H_8N_2O_3S$·1/4H_2O: C, 49.89; H, 3.56; N, 11.64. Found: C, 49.70; H, 3.29; N, 11.59.

***N*-Acetyl-*S*-(3-formyl-6-nitroindol-2-yl)-L-cysteine (10) from 4** — A solution of *N*-acetyl-L-cysteine (150.8 mg, 0.92 mmol) in anhydrous THF (3 mL) was added to a suspension of NaH (60% suspension in paraffin oil, 74.5 mg, 1.68 mmol) in anhydrous THF (2 mL) under ice cooling with stirring. Stirring was continued at rt for 10 min. After evaporation of the solvent, the residue was dissolved in DMF (3 mL). Then a solution of **4** (58.0 mg, 0.26 mmol) in anhydrous DMF (2 mL) was added and the reaction mixture was stirred at rt for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl, 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 (90:7:3, v/v) to give **10** (117.6 mg, 73%). **10**: mp 212—214 °C (decomp., yellow prisms, recrystallized from MeOH). IR (KBr): 1722, 1630, 1610, 1518, 1335 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.74 (3H, s), 3.55 (1H, dd, *J*=13.7, 8.3 Hz), 3.67 (1H, dd, *J*=13.7, 4.9 Hz), 4.47 (1H, td, *J*=8.3, 4.9 Hz, collapsed to dd, *J*=8.3, 4.9 Hz on addition of D_2O), 8.09 (1H, dd, *J*=8.8, 2.2 Hz), 8.18 (1H, d, *J*=8.8 Hz), 8.25 (1H, d, *J*=2.2 Hz), 8.42 (1H, br d, disappeared on addition of D_2O), 10.09 (1H, s) 12.97 (1H, br s, disappeared on addition of D_2O). *Anal*. Calcd for $C_{14}H_{13}N_3O_6S$: C, 47.86; H, 3.73; N, 11.96. Found: C, 47.75; H, 3.79; N, 11.71. $[\alpha]_D^{27}$ –29.60° (c=0.101, MeOH).

2-(3-Formyl-6-nitroindol-2-yl)malonic acid dimethyl ester（11）from 4 — A mixture of KO*t*Bu (52.2 mg, 0.47 mmol) and dimethyl malonate (61.5 mg, 0.47 mmol) in anhydrous DMF (2 mL) was stirred at rt for 10 min. To the resulting mixture, a solution of **4** (51.2 mg, 0.23 mmol) in anhydrous DMF (2 mL) was added with stirring. Stirring was continued at rt for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl under ice cooling 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 **11** (68.6 mg, 92%). **11**: mp >300 °C (yellow needles, recrystallized from acetone-hexane). IR (KBr): 1741, 1651, 1512, 1342 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.78 (6H, s), 6.13 (1H, s), 8.11 (1H, dd, *J*=8.8, 2.2 Hz), 8.30 (1H, d, *J*=8.8Hz), 8.43 (1H, d, *J*=2.2 Hz), 10.21 (1H, s), 12.91 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 320 (M^+). *Anal*. Calcd for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.29; H, 3.79; N, 8.63.

3-[2-(3-Formyl-6-nitroindol-2-yl)acetyl]pyridine (**12**) **from 4** — 3-Acetylpyridine (69.6 mg, 0.57 mmol) was added to a suspension of KH (35% suspension in paraffin oil, 77.5 mg, 0.68 mmol) in anhydrous THF (4 mL), and the mixture was stirred at 0 °C for 10 min. To the resulting mixture, a solution of **4** (100.8 mg, 0.46 mmol) in anhydrous THF (5 mL) was added and the mixture was stirred at rt for 1 h. After addition of H_2O, the whole was extracted with EtOAc. The water layer was made neutral with 6% HCl, and extracted with EtOAc. The combined 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 EtOAc-MeOH (99:1,v/v) to give **12** (129.3 mg, 92%). **12**: mp >300 °C (orange amorphous solid, recrystallized from acetone-hexane). IR (KBr): 3114, 1701, 1639, 1585, 1504, 1468, 1338, 1298 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60°C) δ: 5.13 (2H, s), 7.61 (1H, dd, *J*=7.8, 4.9 Hz), 8.07 (1H, br d, *J*=8.8 Hz, collapsed to d on addition of D_2O), 8.26 (1H, d, *J*=8.8 Hz), 8.39 (1H, br s, collapsed to d on addition of D_2O), 8.42 (1H, br d, *J*=7.8 Hz, collapsed to ddd on addition of D_2O), 8.84 (1H, br d, *J*=4.9 Hz, collapsed to dd on addition of D_2O), 9.27 (1H, s), 10.16 (1H, s), 12.47 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 309 (M^+). *Anal*. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.59; N, 13.59. Found: C, 61.90; H, 3.56; N, 13.38.

7-Cyanomethyl-1-methoxy-6-nitroindole (**14**) **from 6** — KO*t*Bu (155.5 mg, 1.39 mmol) was added to a solution of **6** (52.8 mg, 0.28 mmol) and **13** (139.6 mg, 0.83 mmol) in DMF (1 mL) under ice cooling with stirring. Stirring was continued at 0°C for 5 min. After addition of H_2O, the whole was made acidic with 6% HCl, and extracted with EtOAc. 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 EtOAc–hexane (1:5, v/v) to give **14** (42.4 mg, 67%). **14**: mp 148—150 °C (yellow needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 2256, 1514, 1493, 1335, 1317 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.23 (3H, s), 4.55 (2H, s), 6.56 (1H, d, *J*=3.4 Hz), 7.58 (1H, d, *J*=3.4 Hz), 7.65 (1H, d, *J*=8.8 Hz), 7.29 (1H, d, *J*=8.8 Hz). *Anal*. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.11; H, 3.86; N, 18.04.

4-Amino-3-*p*-chlorophenoxy-2-*p*-chlorophenoxymethyl-7-nitropyrimido[1,2-*a*]indole-10-carbaldehyde (**16**) **from 4 and *p*-chlorophenoxyacetonitrile (13)** — A mixture of KO*t*Bu (156.3 mg, 1.39 mmol) and **13** (229.1 mg, 1.37 mmol) in anhydrous DMF (3 mL) was stirred at 0 °C for 30 min. To the resulting mixture, a solution of **4** (100.1 mg, 0.46 mmol) in anhydrous DMF (3 mL) was added with stirring. Stirring was continued at rt for 10 min. After addition of saturated aqueous NH_4Cl, the whole was 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 acetone–hexane (1:3, v/v) to give **16** (169.5 mg, 71%). **16**: mp 242—244 °C (yellow powder, recrystallized from acetone–hexane). IR (KBr): 1628, 1585, 1510, 1485, 1356, 1336 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 5.02 (2H, s), 6.84 (2H, d, *J*=9.0 Hz), 7.11 (2H, d, *J*=9.0 Hz), 7.26 (2H, d, *J*=9.0Hz), 7.34 (2H, d, *J*=9.0 Hz), 8.44 (1H, dd, *J*=8.8, 1.7 Hz), 8.49 (1H, d, *J*=8.8 Hz), 8.60 (2H, br s, disappeared on addition of D_2O), 9.33 (1H, br s), 10.32 (1H, s). *Anal*. Calcd for $C_{25}H_{16}Cl_2N_4O_5$: C, 57.38; H, 3.08; N, 10.71. Found: C, 57.13; H, 3.10; N, 10.56.

4-Amino-3-*p*-chlorophenoxy-2-*p*-chlorophenoxymethyl-10-methyl-7-nitropyrimido[1,2-*a*]indole (**17**) **from 16** — A mixture of **16** (113.1 mg, 0.22 mmol) and Et_3SiH (0.11 mL, 0.69 mmol) in TFA (5 mL) was refluxed for 30 min with stirring. After evaporation of the solvent, the resulting solid was column-chromatographed on SiO_2 with $CHCl_3$ to give **17** (102.9 mg, 93%). **17**: mp 240—241°C (decomp., brown fine needles, recrystallized from EtOAc). IR (KBr): 1523, 1489, 1483, 1468, 1308, 1284, 1275, 1232 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (3H, s), 5.06 (2H, s), 5.53 (2H, br s, disappeared on addition of D_2O), 6.71 (2H, d, *J*=9.0 Hz), 6.90 (2H, d, *J*=9.0 Hz), 7.16 (2H, d, *J*=9.0 Hz), 7.26 (2H, d, *J*=9.0 Hz), 7.81 (1H, d, *J*=9.0 Hz), 8.34 (1H, dd, *J*=9.0, 2.0 Hz), 8.97 (1H, d, *J*=2.0 Hz). *Anal*. Calcd for $C_{25}H_{18}Cl_2N_4O_4$: C, 58.95; H, 3.56; N, 11.00. Found: C, 58.88; H, 3.56; N, 10.90.

4-Diacetylamino-3-*p*-chlorophenoxy-2-*p*-chlorophenoxymethyl-10-methyl-7-nitropyrimido[1,2-*a*]-indole (**18**) **from 17** — Ac_2O (1 mL) was added to a solution of **17** (49.0 mg, 0.10 mmol) in pyridine (2 mL) and stirred at rt for 1 h. After evaporation of the solvent, the resulting solid was column-chromatographed on SiO_2 with $CHCl_3$–hexane (2:1, v/v) to give **18** (50.7 mg, 89%). **18**: mp 217—219 °C (decomp., orange prisms, recrystallized from EtOAc). IR (KBr): 1736, 1724, 1520, 1489, 1477, 1363, 1331, 1311, 1242, 1223, 1203 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (6H, s), 2.69 (3H, s), 5.07 (2H, s), 6.77 (2H, d, *J*=9.0 Hz), 6.86 (2H, d, *J*=9.0 Hz), 7.20 (2H, d, *J*=9.0 Hz), 7.23 (2H, d, *J*=9.0 Hz), 7.93 (1H, d, *J*=9.0 Hz), 8.32 (1H, dd, *J*=9.0, 2.0 Hz), 8.57 (1H, d, *J*=2.0 Hz). *Anal*. Calcd for $C_{29}H_{22}Cl_2N_4O_6$: C, 58.70; H, 3.74; N, 9.44. Found: C, 58.83; H, 3.69; N, 9.42.

(*E*)-3-Amino-2,4-di(*p*-chlorophenoxy)-2-butenonitrile (**19**) **from 13** — A mixture of KO*t*Bu (69.3 mg, 0.62 mmol) and **13** (102.3 mg, 0.61 mmol) in anhydrous DMF (2 mL) was stirred at 0 °C for 30 min. After addition of H_2O, the whole was made acidic with 6% HCl, and extracted with EtOAc. 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 (1:1, v/v) to give unreacted **14** (27.4 mg, 27%) and **19** (41.5 mg, 41%) in the order of elution. **19**: mp 101-101.5 °C (colorless fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 3473, 3361, 2197, 1645, 1489, 1485, 1205, 827 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.73 (2H, br s, disappeared on addition of D_2O), 4.86 (2H, s), 6.92—6.95 (4H, m), 7.29 (2H, d, *J*=9.0 Hz), 7.31 (2H, d, *J*=9.0 Hz). *Anal*. Calcd for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.14; H, 3.61; N, 8.33. Two protons attached to the amino group appeared as a singlet proving that they are equivalent and **19** is an *E* isomer. If **19** is a *Z* isomer, the two protons should be non-equivalent because of hydrogen bonding to phenoxy oxygen.

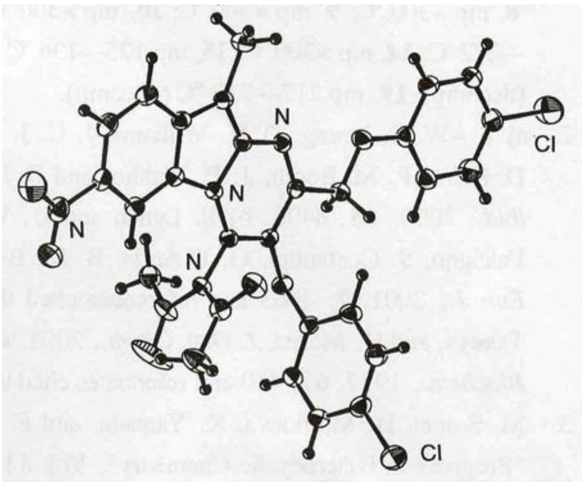
X-Ray Crystallographic Analysis of 18 — The reflection data were collected at rt on a Rigaku AFC-5R diffractometer with graphite monochromated Cu*Kα* radiation (*λ*=1.54178 Å). The structures were solved by direct methods using MITHRIL and refined by the full-matrix least squares. The non-hydrogen atoms were refined anisotropically. All calculations were performed using the teXsan crystallographic package.

Table 2. Positional Parameters and *B* (eq) for **18**

atom	*x*	*y*	*z*	*B* (eq)	atom	*x*	*y*	*z*	*B* (eq)
Cl (1)	0.72645(5)	–0.15397(8)	0.8776(1)	7.76(7)	C (21)	0.8912(1)	0.3008(2)	0.5782(3)	3.7(2)
Cl (2)	0.82339(6)	0.52886(7)	0.55544(9)	6.91(6)	C (22)	0.8712(2)	0.3804(2)	0.5987(3)	4.3(2)
O (1)	1.1842(1)	0.3255(2)	0.2748(2)	5.8(2)	C (23)	0.8484(1)	0.4286(2)	0.5278(3)	4.0(2)
O (2)	1.2627(1)	0.2980(2)	0.3376(3)	7.4(2)	C (24)	0.8444(2)	0.3983(2)	0.4351(3)	4.0(2)
O (3)	0.91157(9)	–0.0007(1)	0.6738(2)	4.0(1)	C (25)	0.8641(1)	0.3184(2)	0.4148(3)	3.4(2)
O (4)	0.90539(8)	0.1886(1)	0.4621(1)	3.1(1)	C (26)	1.0127(1)	0.3459(2)	0.4370(3)	3.6(2)
O (5)	1.0215(1)	0.3506(2)	0.5213(2)	4.8(1)	C (27)	1.0121(3)	0.4215(3)	0.3729(4)	5.9(3)
O (6)	0.9765(2)	0.2989(2)	0.2478(2)	9.8(2)	C (28)	0.9887(2)	0.2439(2)	0.3020(2)	4.2(2)
N (1)	1.0027(1)	0.0655(2)	0.6012(2)	2.8(1)	C (29)	0.9848(2)	0.1534(3)	0.2759(3)	4.4(2)
N (2)	1.0516(1)	0.1642(2)	0.4980(2)	2.8(1)	H (1)	1.109(1)	0.269(2)	0.368(2)	3.75(2)
N (3)	1.0037(1)	0.2633(2)	0.3977(2)	2.8(1)	H (2)	1.257(1)	0.196(2)	0.462(2)	3.87(2)
N (4)	1.2128(1)	0.2905(2)	0.3342(3)	4.6(2)	H (3)	1.218(1)	0.104(2)	0.575(2)	3.61(2)
C (1)	0.9566(1)	0.0956(2)	0.5687(2)	2.7(1)	H (4)	1.093(2)	–0.000(2)	0.707(3)	5.56(3)
C (2)	0.9556(1)	0.1633(2)	0.4996(2)	2.7(1)	H (5)	1.136(3)	–0.036(3)	0.637(3)	10.66(7)
C (3)	1.0027(1)	0.1960(2)	0.4654(2)	2.7(1)	H (6)	1.144(2)	0.040(3)	0.706(3)	7.32(5)
C (4)	1.1064(1)	0.1822(2)	0.4774(2)	2.8(1)	H (7)	0.882(1)	0.043(2)	0.552(2)	3.31(2)
C (5)	1.1300(1)	0.2352(2)	0.4091(2)	3.2(2)	H (8)	0.881(1)	0.111(2)	0.635(2)	3.90(2)
C (6)	1.1861(1)	0.2363(2)	0.4066(2)	3.4(1)	H (9)	0.910(1)	–0.105(2)	0.802(3)	4.46(2)
C (7)	1.2196(1)	0.1887(2)	0.4672(3)	4.0(2)	H (10)	0.840(1)	–0.166(2)	0.885(3)	4.63(2)
C (8)	1.1958(1)	0.1360(2)	0.5328(3)	3.7(2)	H (11)	0.734(1)	–0.037(2)	0.731(3)	5.18(2)
C (9)	1.1386(1)	0.1310(2)	0.5390(2)	3.0(1)	H (12)	0.803(1)	0.031(2)	0.647(2)	3.91(2)
C (10)	1.1037(1)	0.0802(2)	0.5955(2)	2.9(1)	H (13)	0.906(2)	0.261(2)	0.628(3)	5.49(3)
C (11)	1.0510(1)	0.0992(2)	0.5694(2)	2.7(1)	H (14)	0.874(2)	0.400(2)	0.659(3)	5.41(3)
C (12)	1.1201(2)	0.0156(3)	0.6685(3)	4.1(2)	H (15)	0.830(2)	0.434(3)	0.390(3)	6.35(4)
C (13)	0.9027(1)	0.0631(2)	0.6044(3)	3.1(1)	H (16)	0.859(1)	0.296(2)	0.354(2)	3.87(2)
C (14)	0.8659(1)	–0.0333(2)	0.7176(2)	3.2(1)	H (17)	0.974(2)	0.425(3)	0.344(4)	7.69(4)
C (15)	0.8759(1)	–0.0921(2)	0.7901(3)	4.1(2)	H (18)	1.020(3)	0.472(3)	0.410(4)	12.72(8)
C (16)	0.8332(2)	–0.1295(2)	0.8375(3)	4.3(2)	H (19)	1.034(3)	0.413(3)	0.322(4)	11.48(8)
C (17)	0.7807(1)	–0.1083(2)	0.8151(3)	4.3(2)	H (20)	1.013(2)	0.118(3)	0.305(3)	6.46(4)
C (18)	0.7703(2)	–0.0503(3)	0.7449(3)	4.8(2)	H (21)	0.986(2)	0.145(3)	0.214(3)	6.32(3)
C (19)	0.8131(1)	–0.0125(2)	0.6954(3)	3.8(2)	H (22)	0.948(2)	0.132(3)	0.290(3)	6.87(4)
C (20)	0.8872(1)	0.2705(2)	0.4864(2)	2.8(1)					

Crystal data for **18**; $C_{29}H_{22}Cl_2N_4O_6$, *FW*=593.42, orthorhombic; space group *P*bca (#61), *a*=24.344 (2), *b*=15.744 (2), *c*=13.955(2) Å, *V*=5349(2)$Å^3$, *Z*=8, *D*c=1.474g/cm^3, *R*=0.045, R_w=0.053 for 2906 observed reflections with *I*>3σ*I*).

Figure 4. ORTEP Drawing of **18** (R = 0.045)



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