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The Chemistry of Indoles. XXIV.[1] Syntheses of 3-Indoleacetic Acid and 3-Indoleacetonitrile Having a Halogeno Group and a Carbon Functional Group at the 4-Position

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Various 4-halogeno-3-indoleacetic acids and -3-indoleacetonitriles were synthesized for the first time by means of the Sandmeyer or Schiemann reaction, demonstrating the versatility of 4-indolediazonium salts in 4-substituted indole chemistry. A practical synthetic method for 4-halogenoindoles was developed by regio-selective thallation-halogenation, and the products were also led to 4-halogeno-3-indoleacetic acids. The first synthesis of 4-formyl-3-indoleacetonitrile is also reported.

Keywords——4-halogenoindole; 4-halogeno-3-indoleacetic acid; 4-halogeno-3-indoleacetonitrile; 4-formyl-3-indoleacetonitrile; Schiemann reaction; Sandmeyer reaction; thallation-halogenation; 4-halogeno-3-methoxycarbonylindole; 4-halogeno-3-indolecarbaldehyde; auxin

3-Indoleacetic acid (IAA) and 3-indoleacetonitrile (IAN) are well known as plant growth regulators.[2] In 1951, Hansch and Godfrey[3] prepared 4-chloro-3-indoleacetic acid (**1a**) and observed its auxin activity. In 1968, Marumo *et al.*[4] proved that **1a** was a natural auxin by isolating it from immature green pea seeds. Since then, much attention has been focused on the preparation of various IAA having a halogeno group in the benzene part of the indole nucleus, and **1a** was found to have the strongest auxin activity among them.[5] This finding suggests that substituents at the 4-position of IAA play an important role in enhancing the auxin activity. Therefore, 4-substituted IAAs and IANs should be useful compounds for studying the action and metabolism of auxin and also for investigating structure–activity correlations.[6] However, these compounds are not readily accessible as yet due to the lack of a facile synthetic method for 4-substituted indoles.

In this paper, we wish to report a convenient synthesis of 4-halogenoindoles (**22a—d**) by regio-selective thallation-halogenation[7] and *via* 4-indolediazonium salt.[8] We also describe the first syntheses of 4-halogeno-IANs (**25b—d**) and -IAAs (**1b—d**), as well as 4-formyl-IAN (**31**) which is a key synthetic intermediate for IAAs having various carbon side chains.

Preparation of 4-Halogeno-3-indoleacetic Acids *via* 4-Indolediazonium Salt

Our synthetic strategy for 4-halogeno-IAAs is based on the following criteria: 1) a common synthetic method applicable to all halogens should be used; 2) reduction of compounds containing halogen should be avoided in order to prevent the loss of halogens; 3) introduction of halogens into the 4-position should be carried out at a late stage in the synthesis, making it possible to obtain isotope-labelled IAA. Taking these criteria into consideration, we chose the synthetic method *via* 4-indolediazonium salts.[8]

First, 4-nitroindole (**3**) was prepared from 2,6-dinitrotoluene (**2**) in three steps in 66.6% overall yield as described before.[8] Mannich reaction of **3** by treatment with formalin (HCHO) and *N*,*N*-dimethylamine (Me_2NH) in acetic acid (AcOH) gave 3-dimethylaminomethyl-4-nitroindole (**4**) in 82.5% yield (Chart 1). In the next step, treatment of **4** with potassium

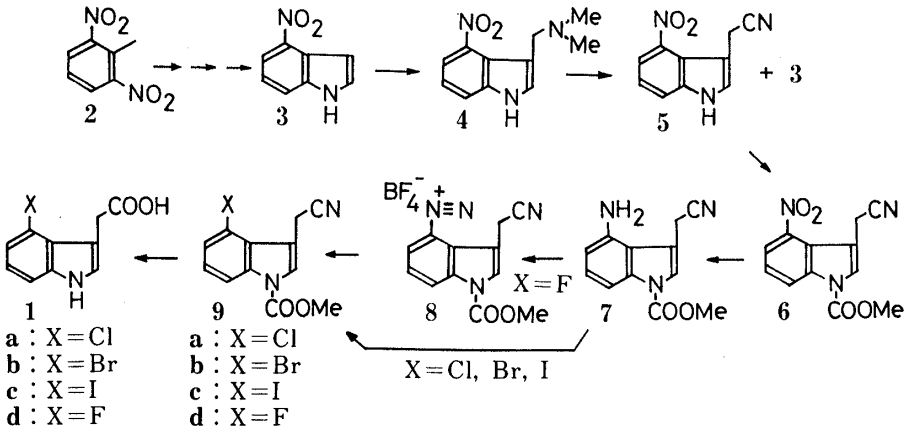
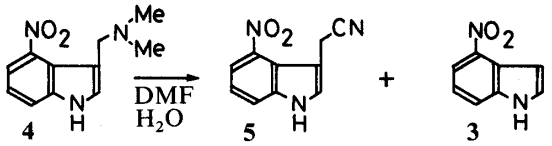


Chart 1

TABLE I. Preparation of 3-Cyanomethyl-4-nitroindole



Entry	KCN (mol eq to **4**)	Refluxing time (h)	Yield (%) of	
			5	**3**
1	9.8	2.0	50.7	24.6
2	10.0	3.5	33.4	22.5
3	32.6	1.5	55.9	9.9
4	50.9	2.25	14.7	7.6

cyanide (KCN) in refluxing *N*,*N*-dimethylformamide (DMF) and water (H_2O) was found to afford 4-nitro-IAN[9] (**5**) and **3**. The yields changed significantly depending on the reaction conditions, and the results are summarized in Table I. These results suggest that the use of a large amount of base and a long reaction time promotes retrograde Mannich reaction to give **3**. Finally, under the reaction conditions described in entry **3**, the desired compound (**5**) was obtained in 55.9% yield together with a 9.9% yield of **3**.

Treatment of **5** with sodium hydride in abs. DMF, then with methyl chloroformate, afforded 1-methoxycarbonyl-4-nitro-IAN (**6**) in 86.2% yield. Subsequent reduction of **6** with aq. titanium (III) chloride[10] ($TiCl_3$) produced 4-amino-1-methoxycarbonyl-IAN (**7**) in 77.6% yield. Diazotization of **7** with sodium nitrite ($NaNO_2$) and hydrochloric acid (HCl), followed by pyrolysis in the presence of cuprous chloride (CuCl), cuprous bromide (CuBr), or potassium iodide (KI) gave 4-chloro- (**9a**), 4-bromo- (**9b**), or 4-iodo-1-methoxycarbonyl-IAN (**9c**) in 61.3%, 82.1%, or 88.9% yield, respectively. In order to obtain the fluoro compound, **7** was converted to 3-cyanomethyl-1-methoxycarbonyl-4-indole diazonium tetrafluoroborate (**8**) in 68.1% yield by the treatment of an aqueous solution containing the corresponding 4-indolediazonium chloride with aq. sodium tetrafluoroborate. Pyrolysis of **8** over silica gel resulted in the formation of 4-fluoro-1-methoxycarbonyl-IAN (**9d**) in 40.2% yield. Hydrolysis of **9a**—**d** with 20% aq. sodium hydroxide (NaOH) produced the corresponding 4-halogeno-IAAs (**1a-d**) in 78.1%, 93.9%, 66.5%, and 53.6% yields, respectively.

Reduction of 4-nitro-IAN (**5**) with aq. $TiCl_3$ gave 4-amino-IAN (**10**) and 4-amino-7-

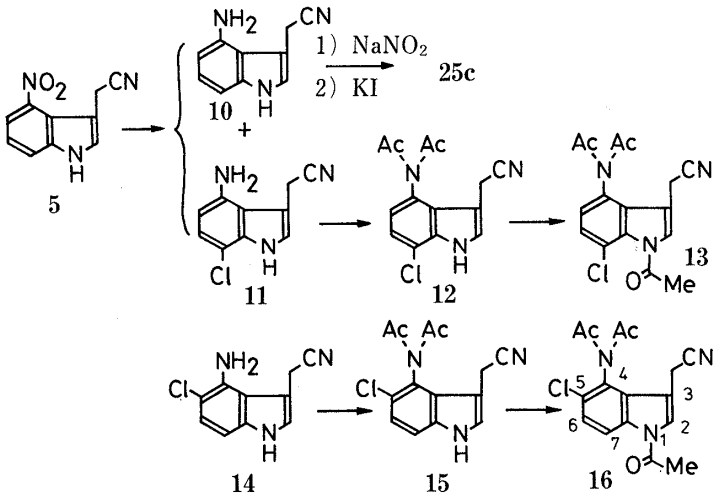


Chart 2

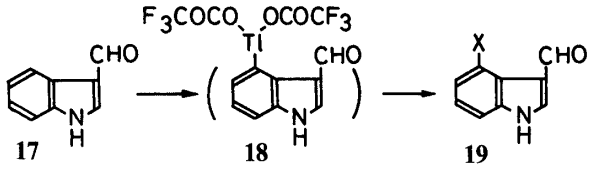
chloro-IAN (**11**) in 43.7% and 27.4% yields, respectively. Diazotization of **10** with $NaNO_2$ and HCl, followed by treatment with aq. KI afforded **25c** in 29.7% yield (Chart 2) and a significant amount of polymer formation was observed. A comparison of the Sandmeyer reactions of **7** and **10** clearly demonstrated that the presence of an electron-withdrawing substituent at the 1 position was necessary for obtaining good results in the diazotization reaction.

The structure of **11** was established by the following results. First, **11** was reacted with refluxing acetic anhydride for 3 h to give 7-chloro-4-(*N*,*N*-diacetylamino)-IAN (**12**) in 97.3% yield. Further treatment of **12** with refluxing acetic anhydride for 24 h afforded 1-acetyl-7-chloro-4-(*N*,*N*-diacetylamino)-IAN (**13**) in 89.5% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of these compounds (**12** and **13**), the two aromatic protons appeared clearly as two sets of doublets with a coupling constant of 8 Hz, indicating that these protons were placed in an *ortho* relationship. Therefore, two structures, **11** and **14**, are possible for compound **11**. If the structure **14** is correct, compounds **12** and **13** should have the structures **15** and **16**, respectively (Chart 2). In the ^{1}H-NMR spectra, the signal of the C-7 proton of **16** should appear at lower magnetic field by about 1 ppm than that of **15** because of the well-known deshielding effect of the 1-carbonyl group.[11] In fact, the observed deshielding effect was only 0.15 ppm. Based on these results, the structures **14**—**16** were eliminated. It is interesting that chloride was introduced into the aromatic nucleus during the $TiCl_3$ reduction of the nitro compound.[12]

A Practical Synthesis of 4-Halogenoindoles and Their Conversion to 4-Halogeno-3-indoleacetic Acid

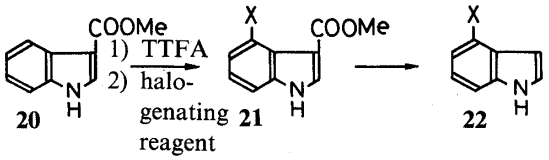
Regio-selective thallation-halogenation[7] was successfully applied to the synthesis of 4-halogenoindoles. Thus, indole-3-carbaldehyde (**17**) was thallated with 1.5 mol eq of thallium (III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA)[13] at room temperature. Without isolation of (3-formylindol-4-yl)thallium (III) bis-trifluoroacetate (**18**), the residue obtained after evaporation of TFA was treated with CuCl in DMF to afford **19a** in 16.7% yield. However, when cupric chloride ($CuCl_2$) was used instead of CuCl, the yield of **19a** was found to increase to 48.2%. Similarly, cupric bromide ($CuBr_2$) was found to be superior to CuBr[14] for the preparation of bromoderivatives (**19b**), and the results are summarized in Table II. 4-Iodo-3-indolecarbaldehyde (**19c**) was prepared by the action of molecular iodine and cuprous iodide (CuI); this result was reported in our previous paper.[7] Although all attempts to obtain 4-fluoro-3-indolecarbaldehyde, involving Taylor's method,[15] ended in failure, further efforts are in progress.

TABLE II. Preparation of 4-Halogeno-3-indolecarbaldehydes



	X	Halogenating reagent (mol eq to **17**)	Yield (%) of **19**
a	Cl	CuCl (3.2)	16.7
	Cl	$CuCl_2$ (4.4)	48.2
b	Br	CuBr (3.3)	50.2
	Br	$CuBr_2$ (3.0)	58.3
c	I	I_2 (3.1) and CuI (2.0)	94.0[7]

TABLE III. Preparation of 4-Halogenoindoles



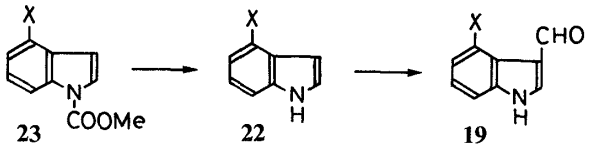
	X	Halogenating reagent (mol eq to **20**)	Yield (%) of **21**	Yield (%) of **22**
a	Cl	Anhydrous $CuCl_2$ (4.0)	65.9	61.7
b	Br	$CuBr_2$ (4.0)	58.9	60.5
c	I	KI (10.5) in H_2O	64.9	89.3

When the above thallation-halogenation procedure was applied to 3-methoxycarbonylindole (**20**), 4-halogeno-3-methoxycarbonylindoles (**21a—c**) were successfully obtained in good yields; the results are summarized in Table III. In order to obtain 4-halogenoindoles, deformylation of **19a—c** was examined with acids and bases, but we have not yet been able to obtain the desired compounds. However, hydrolysis of **21a—c** with 20% aq. sodium hydroxide (NaOH) in methanol (MeOH) was found to afford the corresponding 4-halogenoindoles (**22a—c**) in good yields, as shown in Table III.

The structures of **22a—c** were established unequivocally by the following alternative synthesis. Thus, according to our method,[8] 4-halogeno-1-methoxycarbonylindoles (**23a—d**) were prepared *via* 1-methoxycarbonylindole-4-diazonium salt. Hydrolysis of these compounds with 20% aq. NaOH in MeOH produced the corresponding 4-halogenoindoles (**22a—d**). Subsequent Vilsmeyer–Haack reaction of **22a—c** afforded 4-halogeno-3-indolecarbaldehydes (**19a—c**) in good yields as shown in Table IV. These compounds, **19a—c** and **22a—c**, were identical with those prepared by the thallation-halogenation method.

Since, 4-halogenoindoles (**22a—d**) were now readily available, we next tried the synthesis of 4-halogeno-IANs and -IAAs by the conventional method. Thus, the Mannich reaction of **22a—d** with HCHO and Me_2NH in AcOH gave the corresponding gramine derivatives (**24a—d**) in good yields, as shown in Table V. Treatment of **24a—d** with KCN in refluxing DMF and H_2O gave the desired 4-halogeno-IANs (**25a—d**) in excellent yields. Alkaline hydrolysis of **25a—d** with 20% aq. NaOH produced excellent yields of 4-halogeno-IAAs (**1a—d**), which were identical with the samples prepared from **9a—d**.

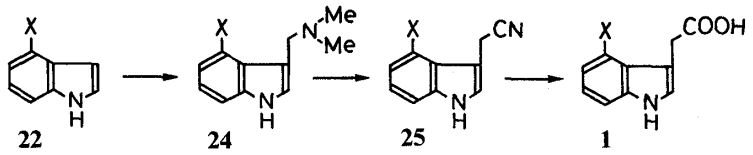
TABLE IV. Preparation of 4-Halogenoindoles and 4-Halogeno-3-indolecarbaldehydes



	X	Yield (%) of 22	Yield (%) of 19
a	Cl	79.0[8]	65.8
b	Br	88.5	67.1
c	I	92.7[8]	99.6[7]
d	F	94.2	—

Preparation of these compounds was reported in our previous papers.[7,8]

TABLE V. Preparation of 4-Halogeno-3-indoleacetic Acids



	X	Yield (%) of 24	Yield (%) of 25	Yield (%) of 1
a	Cl	59.9[8]	87.4[a]	48.9[a]
b	Br	96.3	89.1	77.7
c	I	70.9	93.6	99.0
d	F	81.6	81.8	88.6

a) These compounds were prepared according to the procedure reported by Hansch and Godfrey: See reference 3.

Preparation of 4-Formyl-3-indoleacetonitrile

Next, we attempted to prepare 4-formyl-3-indoleacetonitrile (**31**) which would be an important synthetic intermediate for IAN and IAA having carbon side chains at the 4-position. Mannich reaction of 4-indolecarbaldehyde[16] (**26**) with HCHO and Me_2NH in AcOH gave a 77.6% yield of 3-dimethylaminomethyl-4-indolecarbaldehyde (**27**). Subsequent treatment of **27** with KCN in refluxing DMF and H_2O did not provide **31**. To our suprise, the corresponding quaternary salt, prepared by the reaction of **27** with methyl iodide, also did not produce **31** under similar reaction conditions. Therefore, the following route was developed (Chart 3). First, 4-indolecarbaldehyde (**26**) was transformed to 4-(1,3-dithiolan-2-yl)indole (**28**) in 83.1% yield by reaction with ethanedithiol in the presence of boron trifluoride etherate. Mannich reaction of **28** with HCHO and Me_2NH in AcOH afforded the corresponding gramine (**29**) in 94.2% yield. Treatment of **29** with KCN in refluxing DMF and H_2O produced 4-(1,3-dithiolan-2-yl)-IAN (**30**) in 84.5% yield. Deprotection of **30** was successfully carried out by treatment with mercuric chloride and calcium carbonate in acetonitrile to afford the desired 4-formyl-IAN (**31**) in 66.9% yield.

In conclusion, 3-indoleacetic acids and 3-indoleacetonitriles having various substituents at the 4-position were synthesized. Some of these compounds exhibited interesting biological activity, and the results will be reported elsewhere in due course.

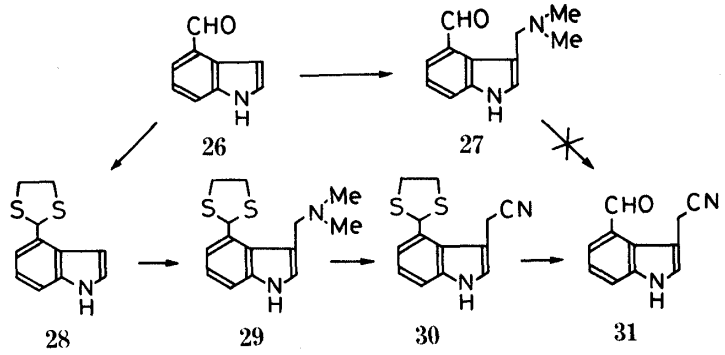


Chart 3

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H-NMR spectra with a JEOL JNM-PMX60 spectrometer, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 spectrometer. Commercial aq. titanium (III) chloride ($TiCl_3$, 16%, $d=1.5$, from Kanto Chemical Co., Inc.) was used. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (Type 60) (SiO_2) or Merck Aluminium Oxid GF_{254} (Al_2O_3, Type 60/E). 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.

3-Dimethylamino-4-nitroindole (4) from 4-Nitroindole (3)——A solution of **3** (1.739 g) in AcOH (30.0 ml) was added to a mixture of 50% aq. Me_2NH (1.162 g), 37% formalin (957.7 mg), and AcOH (4.0 ml). After being stirred for 12 h at room temperature, the whole was made alkaline by adding 20% aq. NaOH, then extracted with CH_2Cl_2–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 subjected to column chromatography on SiO_2 with CH_2Cl_2–MeOH (98 : 2, v/v) as an eluent to give **4** (1.941 g, 82.5%). Recrystallization from MeOH afforded yellow prisms. mp 119.0—120.0 °C (lit.[9] mp 120—123 °C). IR (KBr): 1327, 1516 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (6H, s), 3.70 (2H, s), 7.01 (1H, t, $J=8.0$ Hz), 7.22 (1H, br s), 7.50 (1H, dd, $J=8.0$, 1.0 Hz), 7.67 (1H, dd, $J=8.0$, 1.0 Hz). MS *m/e*: 219 (M^+). *Anal.* Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.39; H, 5.78; N, 19.00.

4-Nitro-3-indoleacetonitrile (5) and 4-Nitroindole (3) from 3-Dimethylaminomethyl-4-nitroindole (4)——Entry **1**: A solution of **4** (336.6 mg) in DMF (10.0 ml) was added to a solution of KCN (1.015 g) in H_2O (10.0 ml) and the mixture was refluxed for 2 h with stirring. After addition of H_2O, the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v), washed with brine, and dried over Na_2SO_4. The solvent was evaporated off under reduced pressure to leave a crystalline solid, which was subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent. From the early part of the eluate, 61.3 mg (24.6%) of **3** was obtained. From the later part, 156.6 mg (50.7%) of **5** was obtained. Recrystallization of **5** from CH_2Cl_2–MeOH afforded yellow needles. mp 202.5—203.5 °C (lit.[9] mp 199—200 °C). IR (KBr): 3380, 2245, 1517, 1321 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 4.20 (2H, s), 7.06 (1H, t, $J=8.0$ Hz), 7.63 (1H, dd, $J=$ 8.0, 1.0 Hz), 7.66 (1H, br s), 7.94 (1H, dd, $J=8.0$, 1.0 Hz). MS *m/e*: 201 (M^+). *Anal.* Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.76; N, 20.89. Found: C, 59.56; H, 3.51; N, 20.73.

Entry **3**: In this case, 102.7 mg of **4**, 3 ml of DMF, 1.027 g of KCN, and 3.0 ml of H_2O were used and the whole was refluxed for 1.5 h. After work-up and subsequent column chromatography as described in entry 1, 7.5 mg (9.9%) of **3** and 52.7 mg (55.9%) of **5** were obtained.

1-Methoxycarbonyl-4-nitro-3-indoleacetonitrile (6) from 4-Nitro-3-indoleacetonitrile (5)——A solution of **5** (236.0 mg) in abs. DMF (3.0 ml) was added to 50% NaH (196.2 mg, washed twice with benzene). The mixture was stirred for 15 min at room temperature, then a solution of methyl chloroformate (311.6 mg) in benzene (1.0 ml) was added as a single portion. The mixture was stirred for 10 h at room temperature and cooled in an ice bath, then H_2O was added. The whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v), washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product, which was purified by column chromatography on SiO_2 with CH_2Cl_2 as an eluent to give **6** (262.0 mg, 86.2%). mp 179.0—180.0 °C (pale yellow prisms from CH_2Cl_2–MeOH). IR (KBr): 3420, 2260, 1741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (2H, d, $J=1.2$ Hz), 4.01 (3H, s), 7.28 (1H, t, $J=8.0$ Hz), 7.79 (1H, t, $J=1.2$ Hz), 7.87 (1H, dd, $J=8.0$, 1.0 Hz), 8.45 (1H, dd, $J=8.0$, 1.0 Hz). MS *m/e*: 259 (M^+). *Anal.* Calcd for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.82; H, 3.40; N, 16.50.

4-Amino-1-methoxycarbonyl-3-indoleacetonitrile (7) from 1-Methoxycarbonyl-4-nitro-3-indoleacetonitrile (6)—— Aqueous $TiCl_3$ (5.0 ml, 20.6 mol eq) was added as a single portion to a solution of **6** (97.6 mg) in tetrahydrofuran (THF 10.0 ml) and stirring was continued for 20 min at room temperature. The whole was made alkaline by adding 40% aq. NaOH, then extracted with CH_2Cl_2–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 purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (99:1, v/v) as a developing solvent to give **7** (67.0 mg, 77.6%). mp 176.0—177.0 °C (pale yellow prisms from CH_2Cl_2–MeOH). IR (KBr): 3440, 3365, 2240, 1732 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.93 (2H, d, J=1.2 Hz), 3.94 (3H, s), 6.45 (1H, dd, J=8.0, 1.0 Hz), 6.99 (1H, t, J=8.0 Hz), 7.33 (1H, t, J=1.2 Hz), 7.53 (1H, dd, J=8.0, 1.0 Hz). MS *m/e*: 229 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.89; H, 4.68; N, 18.56.

4-Halogeno-1-methoxycarbonyl-3-indoleacetonitrile (9a—c) from 4-Amino-1-methoxycarbonyl-3-indoleacetonitrile (7)——General Procedure for Aqueous Solution Containing 3-Cyanomethyl-1-methoxycarbonyl-4-indolediazonium Halide: A solution of $NaNO_2$ in H_2O (1.0 ml) was added dropwise to an ice-cooled solution of **7** in H_2O (1.0 ml), THF (1.0 ml), and 2 N HCl (or 4.7% aq. HBr) with stirring, while the reaction temperature was kept below 5 °C. Stirring was continued for 15 min, then ice-cooled H_2O (5.0 ml) was added. The whole was extracted with ice-cooled CH_2Cl_2 (10.0 ml) and the aqueous layer containing the diazonium salt was separated.

i) 4-Chloro-1-methoxycarbonyl-3-indoleacetonitrile (**9a**): In the general procedure, 41.5 mg of $NaNO_2$, 59.6 mg of **7**, and 1.0 ml of 2 N HCl were used. The separated aqueous layer, obtained after work-up as described above, was added to a cold solution of CuCl (1.387 g) in concd. HCl (4.0 ml). After being stirred for 0.5 h at room temperature, the whole was heated on a water bath (95 °C) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2–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 subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent to give **9a** (39.6 mg, 61.3%). mp 164.0—165.0 °C (colorless prisms from CH_2Cl_2–MeOH). IR (KBr): 2235, 1733, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s), 4.01 (2H, d, J=1.2 Hz), 7.09 (1H, d, J=4.0 Hz), 7.11 (1H, d, J=6.0 Hz), 7.56 (1H, t, J=1.2 Hz), 7.98 (1H, dd, J=6.0, 4.0 Hz). MS *m/e*: 250 and 248 (M^+). *Anal.* Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.96; H, 3.51; N, 11.47.

ii) 4-Bromo-1-methoxycarbonyl-3-indoleacetonitrile (**9b**): In the general procedure, 34.8 mg of $NaNO_2$, 50.4 mg, of **7**, and 1.653 g of 4.7% aq. HBr were used. The separated aqueous layer, obtained after work-up as described above, was added to a cold solution of CuBr (674.3 mg) in concd. HBr (2.0 ml). After being stirred for 20 min at room temperature, the whole was heated on a water bath (95 °C) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2–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 subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **9b** (52.9 mg, 82.1%). mp 159.5—161.0 °C (colorless prisms from MeOH). IR (KBr): 2240, 1735, 1604, 1558 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.95 (3H, s), 4.05 (2H, d, J=1.2 Hz), 7.02 (1H, t, J=8.0 Hz), 7.26 (1H, dd, J=8.0, 1.0 Hz), 7.58 (1H, t, J=1.2 Hz), 8.03 (1H, dd, J=8.0, 1.0 Hz). MS *m/e*: 294 and 292 (M^+). *Anal.* Calcd for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.10; N, 9.56. Found: C, 49.00; H, 3.12; N, 9.56.

iii) 4-Iodo-1-methoxycarbonyl-3-indoleacetonitrile (**9c**): In the general procedure, 36.8 mg of $NaNO_2$, 52.9 mg of **7**, and 1.0 ml of 2 N HCl were used. The separated aqueous solution, obtained after work-up as described above, was added to a cold solution of KI (1.087 g) in H_2O (2.0 ml). After being stirred for 1 h at room temperature, the whole was heated on a water bath (95 °C) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under a reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (3:1, v/v) as a developing solvent to give **9c** (69.8 mg, 88.9%). mp 171.0—172.0 °C (colorless needles from CH_2Cl_2–MeOH). IR (KBr): 2240, 1740, 1603 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (3H, s), 4.08 (2H, d, J=1.2 Hz), 6.86 (1H, t, J=8.0 Hz), 7.55 (1H, dd, J=8.0, 1.0 Hz), 7.61 (1H, t, J=1.2 Hz), 8.08 (1H, dd, J=8.0, 1.0 Hz). MS *m/e*: 341 (M^+). *Anal.* Calcd for $C_{12}H_9IN_2O_2$: C, 42.37; H, 2.67; N, 8.24. Found: C, 42.51; H, 2.52; N, 8.54.

3-Cyanomethyl-1-methoxycarbonyl-4-indolediazonium Tetrafluoroborate (8) from 4-Amino-1-methoxycarbonyl-3-indoleacetonitrile (7)——A solution of $NaNO_2$ (129.8 mg) in H_2O (6.0 ml) was added dropwise to an ice-cooled solution of **7** (187.9 mg) in H_2O (6.0 ml), 2 N HCl (4.65 ml), and THF (2.0 ml) with stirring, while the reaction temperature was kept below 5 °C. After being stirred for 20 min at room temperature, the whole was extracted with ice-cooled CH_2Cl_2 (5.0 ml). Saturated aq. $NaBF_4$ (1.0 ml) was added to the separated aqueous layer and stirring was continued for 30 min at room temperature. Precipitates were collected by filtration, washed with CH_2Cl_2, and dried over P_2O_5 to give **8** (183.3 mg, 68.1%). mp 121.5—123.0 °C (dec., yellow powder). IR (KBr): 2240, 2210, 1770—1713 (br). ^{1}H-NMR (DMSO-d_6) δ: 3.90 (3H, s), 4.02 (2H, s), 7.03—7.80 (3H, m), 8.02 (1H, dd, J=8.0, 6.0 Hz). In the MS, no M^+ peak was observed and the base peak was 232 (*m/e*), which corresponds to 4-fluoro-1-methoxycarbonyl-3-indoleacetonitrile (**9d**). This diazonium salt was used for the following pyrolysis without further purification.

4-Fluoro-1-methoxycarbonyl-3-indoleacetonitrile (9d) from 3-Cyanomethyl-1-methoxycarbonyl-4-indolediazonium Tetrafluoroborate (8)——The diazonium salt **8** (65.8 mg) was mixed with SiO_2 (1.0 g, 100—200 mesh, from Kanto Chemical Co., Inc.) and the whole was heated for 5 min at 187 °C with stirring in a round-bottomed flask fitted with a condenser. The tarry matter adhering to the condenser was washed into the flask with CH_2Cl_2. The whole was made alkaline by adding sat. aq. $NaHCO_3$. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–hexane (4:1, v/v) as a developing solvent to give **9d** (18.7 mg, 40.2%). mp 129.0—130.5 °C (colorless needles from CH_2Cl_2–MeOH). IR (KBr): 2240, 1730, 1627, 1572 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (2H, d, J=1.2 Hz), 3.97 (3H, s), 6.79 (1H, ddd, J=10.0, 7.5,

1.0 Hz), 7.15 (1H, dt, J=7.5, 7.5, 5.5 Hz), 7.47 (1H, t, J=1.2 Hz), 7.82 (1H, dd, J=7.5, 1.0 Hz). High-resolution MS *m/e*: Calcd for $C_{12}H_9FN_2O_2$: 232.0646. Found: 232.0628.

4-Halogeno-3-indoleacetic Acid (1a—d) from 4-Halogeno-1-methoxycarbonyl-3-indoleacetonitrile (9a—d)——General Procedure: A solution of 4-halogeno-1-methoxycarbonyl-3-indoleacetonitrile in MeOH and 40% aq. NaOH was refluxed for 2 h with stirring. The reaction mixture was cooled and made acidic by addition of concd. HCl. The whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v), then the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product.

i) 4-Fluoro-3-indoleacetic Acid (**1d**): In the general procedure, 39.4 mg of **9d**, 1.0 ml of MeOH, and 1.0 ml of 40% aq. NaOH were used. The crude product, obtained after work-up as described above, was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **1d** (17.6 mg, 53.6%). All spectral data were identical with those of the sample prepared by hydrolysis of **25d**.

ii) 4-Chloro-3-indoleacetic Acid (**1a**): In the general procedure, 37.5 mg of **9a**, 2.0 ml of MeOH, and 2.0 ml of 40% aq. NaOH were used. The crude product, obtained after work-up as described above, was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **1a** (24.7 mg, 78.1%). Recrystallization from CH_2Cl_2–MeOH afforded colorless prisms. mp 186.0—188.0 °C (lit.[17] mp 185—187 °C). IR (KBr): 3365, 3050, 1698, 1620 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.88 (2H, s), 6.80 (1H, d, J=3.6 Hz), 6.82 (1H, d, J=5.6 Hz), 7.00 (1H, br s), 7.12 (1H, dd, J=5.6, 3.6 Hz). MS *m/e*: 211 and 209 (M^+). All spectral data were identical with those of the sample prepared by hydrolysis of **25a**.

iii) 4-Bromo-3-indoleacetic Acid (**1b**): In the general procedure, 28.2 mg, of **9b**, 5.0 ml of MeOH, and 5.0 ml of 40% aq. NaOH were used. The crude product, obtained after work-up as described above, was purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as an eluent to give **1b** (22.9 mg, 93.9%). All spectral data were identical with those of the sample prepared by hydrolysis of 4-bromo-3-indoleacetonitrile (**25b**).

iv) 4-Iodo-3-indoleacetic Acid (**1c**): In the general procedure, 21.9 mg of **9c**, 3.0 ml of MeOH, and 3.0 ml of 40% aq. NaOH were used. The crude product, obtained after work-up as described above, was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **1c** (12.9 mg, 66.5%). All spectral data were identical with those of the sample prepared by hydrolysis of 4-iodoindole-3-acetonitrile (**25c**).

4-Amino-3-indoleacetonitrile (10) and 4-Amino-7-chloro-3-indoleacetonitrile (11) from 4-Nitro-3-indoleacetonitrile (5)——Aqueous $TiCl_3$ (8.5 ml, 6.5 mol eq) was added in a single portion to a solution of **5** (390.9 mg) in THF (20.0 ml), and stirring was continued for 7 min at room temperature. After the reaction mixture had cooled, it was made alkaline by adding 20% aq. NaOH, and 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 subjected to column chromatography on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as an eluent. From the early part of the eluate, **11** (109.6 mg, 27.4%) was obtained. mp 162.0—163.0 °C (dec., colorless prisms from MeOH). IR (KBr): 3180, 2260, 1615, 1509 cm^{-1}. ^{1}H-NMR (50% CD_3OD in $CDCl_3$) δ: 4.01 (2H, s), 6.28 (1H, d, J=8.0 Hz), 6.86 (1H, d, J=8.0 Hz), 7.03 (1H, br m). MS *m/e*: 207 and 205 (M^+). *Anal.* Calcd for $C_{10}H_8ClN_3$: C, 58.40; H, 3.92; N, 20.44. Found: C, 58.25, H, 3.96; N, 20.21. From the later part, **10** (145.2 mg, 43.7%) was obtained. Recrystallization from MeOH afforded colorless prisms. mp 137.0—138.0 °C (lit.[9] mp 135—136 °C). IR (KBr): 3230, 2255, 1612, 1586 cm^{-1}. ^{1}H-NMR (50% CD_3OD in $CDCl_3$) δ: 4.02 (2H, s), 6.31 (1H, dd, J=6.0, 2.4 Hz), 6.70—7.06 (3H, m). MS *m/e*: 171 (M^+). *Anal.* Calcd for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.24; H, 5.29; N, 24.30.

7-Chloro-4-(*N*,*N*-diacetylamino)-3-indoleacetonitrile (12) from 4-Amino-7-chloro-3-indoleacetonitrile (11)——A solution of **11** (11.0 mg) in Ac_2O (1.0 ml) was stirred for 1 h at room temperature, then refluxed for 3 h. The solvent was evaporated off under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (97 : 3, v/v) as a developing solvent to give **12** (15.4 mg, 97.3%). mp 170.5—171.5 °C (colorless prisms from MeOH). IR (KBr): 3320, 1719, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (6H, s), 3.58 (2H, s), 7.05 (1H, d, J= 2.5 Hz, collapsed to s on addition of D_2O), 6.76 (1H, d, J=8.0 Hz), 7.16 (1H, d, J=8.0 Hz), 8.65 (1H, br s, NH). MS *m/e*: 291 and 289 (M^+).

1-Acetyl-7-chloro-4-(*N*,*N*-diacetylamino)-3-indoleacetonitrile (13) from 7-Chloro-4-(*N*,*N*-diacetylamino)-3-indoleacetonitrile (12)——A solution of **12** (30.4 mg) in Ac_2O (3.0 ml) was refluxed for 24 h. The solvent was evaporated off under reduced pressure to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (98 : 2, v/v) as a developing solvent to give **13** (43.9 mg, 89.5%) as a colorless oil. IR (film): 1735, 1719 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (6H, s), 2.64 (3H, s), 3.51 (2H, d, J=1.0 Hz), 6.86 (1H, d, J=8.0 Hz), 7.31 (1H, d, J=8.0 Hz), 7.41 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.92; H, 4.25; N, 12.67. Found: C, 57.62; H, 4.09; N, 12.74.

4-Halogeno-3-indolecarbaldehyde (19a—c) from 3-Indolecarbaldehyde (17) by the One-Pot Thallation-Halogenation Method——General Procedure: A 0.88 mol solution of TTFA in TFA (1.5 mol eq) was added to a solution of 3-indolecarbaldehyde (**17**) in TFA, and the mixture was stirred for 2 h at room temperature. After evaporation of the solvent under reduced pressure, a solution of halogenating reagent in DMF was added to the residue, and the whole was heated at 120 °C for 1 h with stirring. The reaction mixture was cooled and CH_2Cl_2–MeOH (99 : 5, v/v) was added. Insoluble precipitates were filtered off through celite. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave crystalline solid, which was purified by column chromatography on SiO_2 with ether–hexane (2 : 1, v/v) as an eluent.

i) 4-Chloro-3-indolecarbaldehyde (**19a**) by the Reaction with Cuprous Chloride (CuCl): In the general procedure, 339.7 mg of **17**, 2.0 ml of TFA, and 3.50 ml of 0.88 mol TTFA in TFA were used. Halogenation was carried out with 732.0 mg of CuCl and 10.0 ml of DMF. After work-up and subsequent column chromatography as described above, 70.0 mg (16.7%) of **19a** was obtained. mp 166.0—167.0 °C (colorless needles from MeOH–H_2O). IR (KBr): 3140, 1638 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 6.85—7.41 (3H, m), 7.92 (1H, s), 10.44 (1H, s). MS *m/e*: 181 and 179 (M^+). *Anal.* Calcd for $C_9H_6ClNO \cdot 1/4H_2O$: C, 58.71; H, 3.55; N, 7.60. Found: C, 58.99; H, 3.41; N, 7.61.

ii) 4-Chloro-3-indolecarbaldehyde (**19a**) by the Reaction with Cupric Chloride ($CuCl_2$): In the general procedure, 285.0 mg of **17**, 2.0 ml of TFA, 2.9 ml of 0.88 mol TTFA in TFA were used. Halogenation was carried out with 600 mg of anhydrous $CuCl_2$ and 10.0 ml of DMF. After work-up and subsequent column chromatography as described above, 170.4 mg (48.2%) of **19a** was obtained.

iii) 4-Bromo-3-indolecarbaldehyde (**19b**) by the Reaction with Cuprous Bromide (CuBr): In the general procedure, 102.3 mg of **17**, 1.0 ml of TFA, and 1.22 ml of 0.88 mol TTFA in TFA were used. Halogenation was carried out with 337.9 mg of CuBr and 7.0 ml of DMF. After work-up and subsequent column chromatography as described above, 79.3 mg (50.2%) of **19b** was obtained. mp 185.0—187.0 °C (colorless needles from MeOH–H_2O). IR (KBr): 3260, 1630 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 6.97 (1H, dd, J=9.0, 6.5 Hz), 7.33 (1H, d, J=6.5 Hz), 7.34 (1H, d, J=9.0 Hz), 7.96 (1H, br s), 10.63 (1H, s). MS *m/e*: 225 and 223 (M^+). *Anal.* Calcd for C_9H_6BrNO: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.09; H, 2.83; N, 6.16.

iv) 4-Bromo-3-indolecarbaldehyde (**19b**) by the Reaction with Cupric Bromide ($CuBr_2$): In the general procedure, 103.1 mg of **17**, 1.0 ml of TFA, and 1.22 ml of 0.88 mol TTFA in TFA were used. Halogenation was carried out with 478.0 mg of $CuBr_2$ and 5.0 ml of DMF. After work-up and subsequent column chromatography as described above, 92.8 mg (58.3%) of **19b** was obtained.

v) 4-Iodo-3-indolecarbaldehyde (**19c**): Preparation of **19c** by the thallation-halogenation method has already been reported in our previous paper.[7]

4-Halogeno-3-methoxycarbonylindole (21a—c) from 3-Methoxycarbonylindole (20) by the One-Pot Thallation-Halogenation Method——General Procedure: The same thallation-halogenation procedure was used as in the case of the preparation of 4-halogeno-3-indolecarbaldehyde (**19a—c**). Column chromatography was performed on SiO_2 with CH_2Cl_2–MeOH (99 : 1, v/v) as an eluent.

i) 4-Chloro-3-methoxycarbonylindole (**21a**): In the general procedure, 152.0 mg of **20**, 1.5 ml of TFA, and 1.5 ml of 0.88 mol TTFA in TFA were used for thallation. Halogenation was carried out with 467.0 mg of anhydrous $CuCl_2$ and 10.0 ml of DMF. After work-up and subsequent column chromatography as described above, 120.0 mg (65.9%) of **21a** was obtained. mp 134.0—136.0 °C (colorless prisms from MeOH). IR (KBr): 3230, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 6.81—7.33 (3H, m), 7.73 (1H, d, J=2.8 Hz), 9.34 (1H, br s). MS *m/e*: 211 and 209 (M^+). *Anal.* Calcd for $C_{10}H_8ClNO_2 \cdot 1/4H_2O$: C, 56.08; H, 4.00; N, 6.54. Found: C, 56.58; H, 3.72; N, 6.49.

ii) 4-Bromo-3-methoxycarbonylindole (**21b**): In the general procedure, 153.0 mg of **20**, 1.5 ml of TFA, and 1.5 ml of 0.88 mol TTFA in TFA were used for thallation. Halogenation was carried out with 779.8 mg of $CuBr_2$ and 5.0 ml of DMF. After work-up and subsequent column chromatography as described above, 130.7 mg (58.9%) of **21b** was obtained. mp 125.0—126.0 °C (colorless prisms from MeOH). IR (KBr): 3260, 1700 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.81 (3H, s), 6.90 (1H, dd, J=8.0, 7.2 Hz), 7.15—7.49 (2H, m), 7.75 (1H, br s). MS *m/e*: 255 and 253 (M^+). *Anal.* Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.26; H, 3.19; N, 5.35.

iii) 4-Iodo-3-methoxycarbonylindole (**21c**): In the general procedure, 150.0 mg of **20**, 1.0 ml of TFA, and 1.46 ml of 0.88 mol TTFA in TFA were used for thallation. Halogenation was carried out with a solution of KI (1.487 g) in H_2O (10.0 ml) at room temperature for 2 h with stirring. After work-up with extra washing of the filtrate with aq. sodium thiosulfate and subsequent column chromatography as described above, 167.5 mg (64.9%) of **21c** was obtained. mp 138.5—139.5 °C (colorless prisms from MeOH–H_2O). IR (KBr): 3310, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 6.75 (1H, dd, J=8.0, 7.2 Hz), 7.24 (1H, dd, J=8.0, 0.8 Hz), 7.56—7.76 (2H, m), 8.73 (1H, br s). High-resolution MS *m/e*: Calcd for $C_{10}H_8INO_2$: 300.9599. Found: 300.9592.

4-Halogenoindoles (22a—c) from 4-Halogeno-3-methoxycarbonylindole (21a—c)——General Procedure: A solution of 4-halogeno-3-methoxycarbonylindole in MeOH and 40% aq. NaOH was refluxed for 1.5 h with stirring. After evaporation of the solvent, the residue was extracted with CH_2Cl_2–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 CH_2Cl_2–hexane (2 : 3, v/v) as a developing solvent.

i) 4-Chloroindole (**22a**): In the general procedure, 104.7 mg of **21a**, 6.0 ml of MeOH, and 6.0 ml of 40% aq. NaOH were used. After work-up and subsequent purification as described above, 45.8 mg (61.7%) of **22a** was obtained. This compound was identical with the sample prepared by hydrolysis of **23a**.[8]

ii) 4-Bromoindole (**22b**): In the general procedure, 42.0 mg of **21b**, 3.0 ml of MeOH, and 3.0 ml of 40% aq. NaOH were used. After work-up and subsequent purification as described above, 19.5 mg (60.5%) of **22b** was obtained. This compound was identical with the sample prepared by hydrolysis of **23b**.

iii) 4-Iodoindole (**22c**): In the general procedure, 88.5 mg of **21c**, 3.0 ml of MeOH, and 3.0 ml of 40% aq. NaOH were used. After work-up and subsequent purification as described above, 63.8 mg (89.3%) of **22c** was obtained. This

compound was identical with the sample prepared by hydrolysis of **23c**.[8]

4-Halogeno-3-indolecarbaldehyde (19a—b) from 4-Halogenoindole (22a—b)——General Procedure: Phosphorus oxychloride (0.1 ml) was added to ice-cooled absolute DMF (0.3 ml) with stirring. 4-Halogenoindole was added to the resulting viscous solution and stirring was continued for 1 h at room temperature. Then 20% aq. NaOH was added to the reaction mixture and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crude product. Purification was carried out by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent.

i) 4-Chloro-3-indolecarbaldehyde (**19a**): In the general procedure, 44.9 mg of **22a** was used. After work-up and subsequent purification as described above, 35.1 mg (65.8%) of **19a** was obtained. This compound was identical with the sample prepared from **17** by the thallation-halogenation method.

ii) 4-Bromo-3-indolecarbaldehyde (**19b**): In the general procedure, 33.5 mg of **22b** was used. After work-up and subsequent purification as described above, 25.7 mg (67.1%) of **19b** was obtained. This compound was identical with the sample prepared from **17** by the thallation-halogenation method.

iii) 4-Iodo-3-indolecarbaldehyde (**19c**): Preparation of **19c** under Vilsmeyer–Haack reaction conditions has already been reported in our previous paper.[7]

4-Fluoroindole (22d) from 4-Fluoro-1-methoxycarbonylindole (23d)——A solution of **23d** (262.6 mg) in MeOH (5.0 ml) and 40% aq. NaOH (5.0 ml) was refluxed for 0.5 h. After evaporation of the MeOH, H_2O was added and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to afford **22d** (173.8 mg, 94.2%). Recrystallization from MeOH–H_2O afforded colorless prisms. mp 28.0—29.0 °C (lit.[18] mp 29—30 °C). IR (KBr): 3380, 1633, 1577 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 6.43 (1H, dd, J=3.2, 0.8 Hz, collapsed to d, J=3.2 Hz on addition of D_2O), 6.53—7.13 (4H, m), 7.80 (1H, br s, NH). High-resolution MS *m/e*: Calcd for C_8H_6FN: 135.0484. Found: 135.0484.

4-Bromoindole (22b) from 4-Bromo-1-methoxycarbonylindole (23b)——A solution of **23b** (1.198 g) in MeOH (30 ml) and 40% aq. NaOH (30 ml) was refluxed for 1 h. After evaporation of the MeOH, H_2O was added and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, then evaporated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2–hexane (1 : 1, v/v) as an eluent to give **22b** (817.9 mg, 88.5%). Colorless oil[19] at room temperature (mp 15 °C, colorless prisms). IR (film): 3420, 1613, 1564 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 6.35 (1H, dd, J=3.2, 0.8 Hz, collapsed to d, J=3.2 Hz on addition of D_2O), 6.60—7.16 (4H, m), 7.73 (1H, br s, NH). MS *m/e*: 197 and 195 (M^+).

4-Chloro-(22a) and 4-Iodoindole (22c)——Preparation of these compounds from **23a** and **23c** was reported in our previous paper.[8]

Preparation of 3-Dimethylaminomethyl-4-halogenoindoles (24a—d) from 4-Halogenoindoles (22a—d)——General Procedure: A solution of 4-halogenoindole in AcOH was added to a mixture of 50% aq. Me_2NH, 37% formalin, and AcOH. After being stirred for 2 d at room temperature, the whole was made alkaline by adding 20% aq. NaOH, then extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product.

i) 3-Dimethylaminomethyl-4-fluoroindole (**24d**): In the general procedure, 142.1 mg of **22d**, 137.0 mg of 50% aq. Me_2NH, 108.1 mg of 37% formalin, and 3.0 ml of AcOH were used. The crude product, obtained after work-up as described above, was purified by p-TLC on Al_2O_3 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **24d** (165.1 mg, 81.7%). mp 136.0—137.0 °C (colorless prisms from MeOH). IR (KBr): 2750, 1633, 1581 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (6H, s), 3.69 (2H, s), 6.83 (1H, br s), 6.40—7.02 (3H, m), 9.05 (1H, br s, NH). High-resolution MS *m/e*: Calcd for $C_{11}H_{13}FN_2$: 192.1062. Found: 192.1019.

ii) 3-Dimethylaminomethyl-4-bromoindole (**24b**): In the general procedure, 781.1 mg of **22b**, 479.0 mg of 50% aq. Me_2NH, 362.4 mg of 37% formalin, and 4.0 ml of AcOH were used. The crude product, obtained after work-up as described above, was purified by column chromatography on Al_2O_3 with CH_2Cl_2–MeOH (98 : 2, v/v) as an eluent to give **24b** (971.2 mg, 96.3%). mp 146.0—147.0 °C (colorless needles from MeOH). IR (KBr): 3108, 1615, 1543 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (6H, s), 3.80 (2H, s), 6.65—7.23 (4H, m), 8.85 (1H, br s, NH). MS *m/e*: 254 and 252 (M^+). *Anal.* Calcd for $C_{11}H_{13}BrN_2$: C, 52.18; H, 5.17; N, 11.06. Found: C, 52.04; H, 5.01; N, 11.12.

iii) 3-Dimethylaminomethyl-4-iodoindole (**24c**): In the general procedure, 938.0 mg of **22c**, 467.8 mg of 50% aq. Me_2NH, 356.1 mg of 37% formalin, and 6.0 ml of AcOH were used. The crude product, obtained after work-up as described above, was purified by column chromatography on Al_2O_3 with CH_2Cl_2–MeOH (98 : 2, v/v) as an eluent to give **24c** (821.8 mg, 70.9%). mp 137.0—138.0 °C (colorless prisms from MeOH–H_2O). IR (KBr): 3095, 1613 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 2.32 (3H, s), 3.90 (2H, s), 6.67 (1H, t, J=8.0 Hz), 7.09 (1H, s), 7.23 (1H, dd, J= 8.0, 1.6 Hz), 7.43 (1H, dd, J=8.0, 1.6 Hz). MS *m/e*: 300 (M^+). *Anal.* Calcd for $C_{11}H_{13}IN_2$: C, 44.02; H, 4.37; N, 9.33. Found: C, 44.14; H, 4.24; N, 9.46.

iv) 4-Chloro-3-dimethylaminomethylindole (**24a**): Preparation of **24a** by Mannich reaction was reported in our previous paper.[8]

Preparation of 4-Halogeno-3-indoleacetonitrile (25a—d) from 3-Dimethylaminomethyl-4-halogenoindole (24a—d)——General Procedure: A solution of 3-dimethylaminomethyl-4-halogenoindole in DMF was added to a solution of KCN in H_2O and the mixture was refluxed for 1 h with stirring. After addition of H_2O, the whole was extracted

with benzene, washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product.

i) 4-Fluoro-3-indoleacetonitrile (**25d**): In the general procedure, 326.8 mg of **24d**, 10.0 ml of DMF, 1.153 g of KCN, and 10.0 ml of H_2O were used. The crude product, obtained after work-up as described above, was purified by column chromatography on SiO_2 with CH_2Cl_2 as a developing solvent to give **25d** (242.1 mg, 81.8%). mp 83.0—84.0 °C (colorless prisms from MeOH). IR (KBr): 3400, 2260, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.89 (2H, d, J= 0.8 Hz), 6.49—7.22 (4H, m), 8.22 (1H, br s, NH). High-resolution MS *m/e*: Calcd for $C_{10}H_7FN_2$: 174.0593. Found: 174.0619.

ii) 4-Bromo-3-indoleacetonitrile (**25b**): In the general procedure, 971.2 mg of **24b**, 15.0 ml of DMF, 2.567 g of KCN, and 15.0 ml of H_2O were used. The crude product, obtained after work-up as described above, was purified by column chromatography on SiO_2 with CH_2Cl_2–hexane (1 : 1, v/v) as an eluent to give **25b** (803.4 mg, 89.1%). mp 156.0—157.0 °C (colorless prisms from MeOH). IR (KBr): 3390, 2255, 1650, 1616 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 4.12 (2H, s), 6.75—7.34 (4H, m). MS *m/e*: 236 and 234 (M^+). *Anal.* Calcd for $C_{10}H_7BrN_2$: C, 51.09; H, 3.21; N, 11.91. Found: C, 51.19; H, 2.90; N, 11.93.

iii) 4-Iodo-3-indoleacetonitrile (**25c**): In the general procedure, 47.3 mg of **24c**, 2.0 ml of DMF, 114.6 mg of KCN, and 2.0 ml of H_2O were used. The crude product, obtained after work-up as described above, was purified by p-TLC on SiO_2 with CH_2Cl_2–hexane (3 : 1, v/v) as a developing solvent to give **25c** (41.6 mg, 93.6%). mp 168.0—169.0 °C (colorless prisms from MeOH). IR (KBr): 3370, 2230, 1646, 1609 cm^{-1}. ^{1}H-NMR (20% CD_3OD in $CDCl_3$) δ: 4.15 (2H, s), 6.72 (1H, dd, J=8.0, 7.0 Hz), 7.27 (1H, dd, J=8.0, 1.2 Hz), 7.41 (1H, dd, J=7.0, 1.2 Hz). MS *m/e*: 282 (M^+). *Anal.* Calcd for $C_{10}H_7IN_2$: C, 42.58; H, 2.50; N, 9.93. Found: C, 42.75; H, 2.45; N, 10.07.

iv) 4-Chloro-3-indoleacetonitrile (**25a**): This compound was prepared according to the procedure reported by Hansch and Godfrey[3] in 87.4% yield.

4-Iodo-3-indoleacetonitrile (25c) from 4-Amino-3-indoleacetonitrile (10)——A solution of $NaNO_2$ (66.0 mg) in H_2O (1.0 ml) was added dropwise to an ice-cooled solution of **10** (71.4 mg) in 2 N HCl (2.0 ml) and THF (1.0 ml) with stirring, while the reaction temperature was kept below 5 °C. The mixture was stirred for 5 min, then ice-cooled H_2O (2.0 ml) was added. The whole was extracted with ice-cooled CH_2Cl_2 (5.0 ml) and the separated aqueous layer was added to a solution of KI (4.020 g) in H_2O (10.0 ml). After being stirred for 10 min at room temperature, the whole was heated on a water bath (95 °C) for 10 min. The reaction mixture was cooled and extracted with CH_2Cl_2–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 subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **25c** (34.9 mg, 29.7%). All spectral data were identical with those of the sample prepared from 3-dimethylaminomethyl-4-iodoindole (**24c**).

4-Halogeno-3-indoleacetic Acid (1a—d) from 4-Halogeno-3-indoleacetonitrile (25a—d)——General Procedure: A 40% aq. NaOH was added to a solution of **25a—d** in MeOH and the mixture was refluxed for 2 h with stirring. After addition of brine, the whole was made acidic by adding concd. HCl, and extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crude product.

i) 4-Fluoro-3-indoleacetic Acid (**1d**): In the general procedure, 2.0 ml of 40% aq. NaOH, 52.9 mg of **25d**, and 2.0 ml of MeOH were used. The crude product, obtained after work-up as described above, was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (9 : 1, v/v) as a developing solvent to afford **1d** (51.4 mg, 87.6%). mp 128.0—129.0 °C (colorless prisms from MeOH). IR (KBr): 3440, 1737, 1632 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.82 (2H, s), 6.39—7.06 (4H, m), 8.57 (1H, br s, NH). High-resolution MS *m/e*: Calcd for $C_{10}H_8FNO_2$: 193.0538. Found: 193.0501.

ii) 4-Bromo-3-indoleacetic Acid (**1b**): In the general procedure, 20.0 ml of 40% aq. NaOH, 564.0 mg of **25b**, and 20.0 ml of MeOH were used. The crude product, obtained after work-up as described above, was purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as an eluent to give **1b** (473.6 mg, 77.7%). mp 185.0—187.0 °C (dec., colorless prisms from MeOH). IR (KBr): 3360, 3050, 1697 cm^{-1}. ^{1}H-NMR (50% CD_3OD in $CDCl_3$) δ: 3.96 (2H, s), 6.78 (1H, t, J=7.5 Hz), 7.01 (1H, br s), 7.05 (1H, dd, J=7.5, 1.6 Hz), 7.09 (1H, dd, J=7.5, 1.6 Hz). MS *m/e*: 255 and 253 (M^+). *Anal.* Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.37; H, 3.14; N, 5.49.

iii) 4-Iodo-3-indoleacetic Acid (**1c**): In the general procedure, 2.0 ml of aq. 40% NaOH, 81.4 mg of **25c**, and 3.0 ml of MeOH were used. The crude product, obtained after work-up as described above, was purified by column chromatography on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **1c** (83.1 mg, 99.0%). mp 170.0—171.0 °C (colorless prisms from MeOH). IR (KBr): 3360, 3030, 1698 cm^{-1}. ^{1}H-NMR (20% CD_3OD in $CDCl_3$) δ: 4.02 (2H, s), 6.71 (1H, t, J=7.0 Hz), 7.06 (1H, br s), 7.24 (1H, dd, J=7.0, 0.8 Hz), 7.44 (1H, dd, J=7.0, 0.8 Hz). MS *m/e*: 301 (M^+). *Anal.* Calcd for $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 39.97; H, 2.56; N, 4.85.

iv) 4-Chloro-3-indoleacetic Acid (**1a**): This compound was prepared according to the procedures reported by Hansch and Godfrey[3] in 48.9% yield.

3-(*N*,*N*-Dimethylaminomethyl)-4-indolecarbaldehyde (27) from 4-Indolecarbaldehyde (26)——A solution of 37% aq. HCHO (401.0 mg) in AcOH (10 ml) was added to a solution of 50% aq. Me_2NH (469.0 mg) in AcOH (1.0 ml) and stirred for 20 min. One-fifth of the resulting viscous mixture was added to a solution of **26** (136.0 mg) in AcOH (1.0 ml) and stirring was continued for 14 h at room temperature. The whole was made alkaline by adding 2 N NaOH,

then extracted with CH_2Cl_2–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 Al_2O_3 with CH_2Cl_2–MeOH (95:5, v/v) as a developing solvent to afford **27** (147.1 mg, 77.6%) as a colorless oil. IR (film): 1673 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (6H, s), 3.75 (2H, s), 7.05 (1H, t, J=7.0 Hz), 7.11 (1H, s), 7.43 (1H, dd, J=7.0, 1.5 Hz), 7.56 (1H, dd, J=7.0, 1.5 Hz). High-resolution MS *m/e*: Calcd for $C_{12}H_{14}N_2O$: 202.1105. Found: 202.1155.

4-(1,3-Dithiolan-2-yl)indole (28) from 4-Indolecarbaldehyde (26)——Boron trifluoride etherate (0.05 ml) was added to a solution of **26** (106.2 mg) in ethanedithiol (120.7 mg) and CH_2Cl_2 (10.0 ml). After being stirred for 15 min at room temperature, the whole was made alkaline by adding 2 N NaOH and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent to give **28** (134.5 mg, 83.1%). Recrystallization from hexane afforded unstable colorless needles, which gradually became red oily crystals on standing. mp 77.5—78.5 °C. IR (KBr): 3360, 1609, 1592 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.06—3.50 (4H, A_2B_2 pattern), 5.95 (1H, s), 6.46 (1H, dd, J=3.2, 0.8 Hz), 6.73—7.27 (4H, m). MS *m/e*: 221 (M^+). *Anal.* Calcd for $C_{11}H_{11}NS_2$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.42; H, 4.90; N, 6.44.

3-Dimethylaminomethyl-4-(1,3-dithiolan-2-yl)indole (29) from 4-(1,3-Dithiolan-2-yl)indole (28)——A solution of 37% aq. HCHO (630.0 mg) in AcOH (1.0 ml) was added with stirring to a solution of 50% aq. dimethylamine (836.5 mg) in AcOH (1.0 ml), and stirring was continued for 20 min at room temperature. One-tenth of the resulting viscous mixture was dissolved in AcOH (1.0 ml), and the solution was added to a solution of **28** (134.0 mg) in AcOH (1.0 ml). Stirring was continued for 8 h at room temperature. The whole was made alkaline by adding 2 N NaOH, then extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave **29** (174.5 mg, 94.2%) as prisms. mp 137.5—138.5 °C (colorless prisms from MeOH). IR (KBr): 3125—2500 (br), 1615, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (6H, s), 3.18—3.52 (4H, A_2B_2 pattern), 3.55 (2H, s), 6.85—7.18 (3H, m), 7.07 (1H, s), 7.43 (1H, dd, J=5.6, 3.0 Hz), 7.86 (1H, br s). MS *m/e*: 278 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2S_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.16; H, 6.38; N, 10.27.

4-(1,3-Dithiolan-2-yl)-3-indoleacetonitrile (30) from 3-Dimethylaminomethyl-4-(1,3-dithiolan-2-yl)indole (29)——A mixture of **29** (59.7 mg), KCN (395.0 mg), DMF (3.0 ml), and H_2O (2.0 ml) was refluxed for 1 h with stirring. After evaporation of the solvent under reduced pressure, H_2O was added to the residue. The whole was extracted with CH_2Cl_2–MeOH (97:3, v/v), and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **30** (47.2 mg, 84.5%). mp 155.0—156.0 °C (colorless prisms from CH_2Cl_2–MeOH). IR (KBr): 3295, 2220, 1610 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 3.14—3.53 (4H, A_2B_2 pattern), 4.41 (2H, d, J=1.2 Hz), 6.47 (1H, s), 7.06 (1H, dd, J=8.0, 7.0 Hz), 7.33 (1H, dd, J=8.0, 1.5 Hz), 7.40 (1H, t, J=1.2 Hz), 7.71 (1H, dd, J=7.0, 1.5 Hz). MS *m/e*: 260 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2S_2$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.68; H, 4.64; N, 10.76.

4-Formyl-3-indoleacetonitrile (31) from 4-(1,3-Dithiolan-2-yl)-3-indoleacetonitrile (30)——A solution of **30** (15.0 mg) in CH_3CN (2.0 ml) was added to suspension of $CaCO_3$ (44.2 mg) and $HgCl_2$ (57.8 mg) in H_2O (0.5 ml). The mixture was stirred for 5.5 h at room temperature, then CH_2Cl_2–MeOH (95:5, v/v) was added and the whole was filtered through silica gel, which was washed well with brine. After the organic layer had been separated, the water layer was further extracted with CH_2Cl_2–MeOH (95:5, v/v). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95:5, v/v) as a developing solvent to give **31** (7.1 mg, 66.9%). mp 178.0—179.0 °C (pale yellow prisms from MeOH–H_2O). IR (KBr): 3210, 2240, 1670 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 4.44 (2H, s), 7.12 (1H, t, J=8.0 Hz), 7.38—7.71 (3H, m), 10.00 (1H, s). MS *m/e*: 184 (M^+). *Anal.* Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.54; H, 4.38; N, 15.34.

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