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The Chemistry of Indoles. XVI.[1] A Convenient Synthesis of Substituted Indoles carrying a Hydroxy Group, a Halogeno Group, or a Carbon Side Chain at the 4-Position *via* 4-Indolediazonium Salts and a Total Synthesis of (±)-6,7-Secoagroclavine

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Various 4-indolediazonium salts were prepared for the first time by the diazotization of 4-aminoindole derivatives. They underwent various reactions parallel to those of general arene diazonium salts, and were found to be suitable intermediates for the preparation of substituted indoles carrying a hydroxy, halogeno, or cyano group at the 4-position. Attempts to introduce various carbon side chains into the 4-iodoindole derivatives gave satisfactory results and a key intermediate, 4-(3-hydroxy)3-methyl-1-buten-1-yl)indole, for the synthesis of (±)-6,7-secoagroclavine was also prepared.

Keywords——4-indolediazonium salts; titanium(III) chloride; 4-nitroindoles; 4-aminoindoles; 4-hydroxyindoles; 4-halogenoindoles; 4-cyanoindoles; 4-alkenylindoles; (±)-6,7-secoagroclavine; 4-substituted indoles

There are many biologically active compounds among 4-substituted indoles. Ergot alkaloids[2] are among them, carrying various carbon side chains at the 4-position of the indole nucleus. Psilocybin,[3] psilocin,[4] and 4-[2-hydroxy-3-(isopropylamino)propoxy]indole[5] have hydroxy groups, while teleocidin B[6] and dehydrobufotenin[7] have nitrogen functional groups at the same position. Some auxins[8] have a chlorine atom and chuaungxinmycin[9] carries a sulfur side chain.

Attempts to synthesize all these compounds have led us to investigate the reaction of 4-indolediazonium salts as common synthetic intermediates (Chart 1). Although these diazonium salts are an important class of reaction intermediates and are known to afford various types of compounds *via* appropriate reactions,[10] little attention has been paid to the chemistry

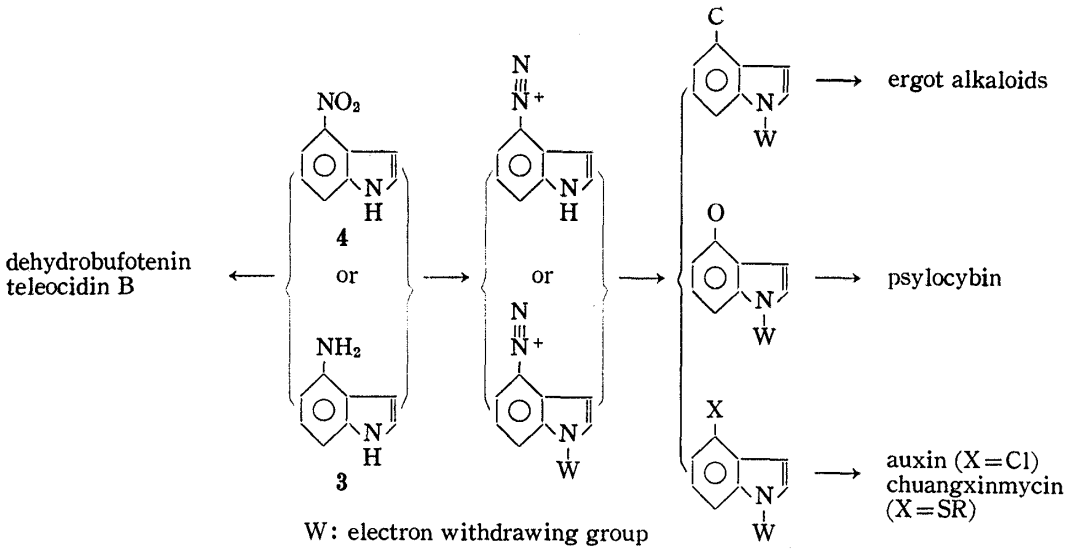


Chart 1

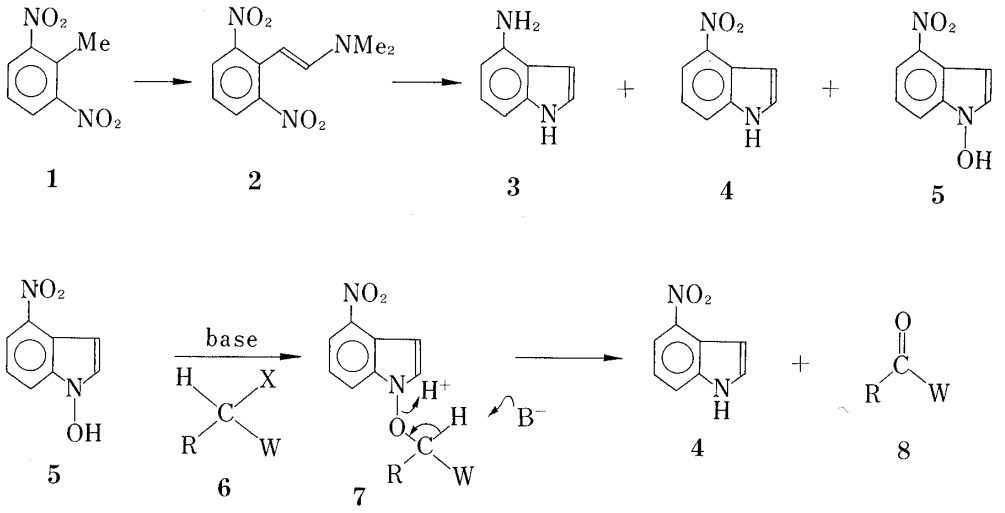
of indolediazonium salts. A discouraging factor in this field has doubtless been the lack of a method for the preparation of 4-aminoindole (**3**) or its precursor, 4-nitroindole (**4**). Furthermore, nitrosation of indoles having no substituent at the 3-position is well known to afford 3-nitroso compounds in poor yields together with large amounts of intractable tars.[11]

Taking into consideration our preliminary work showing that direct diazotization of 4-aminoindole (**3**) resulted in the formation of a polymer, we next planned to introduce an electron withdrawing group at the indole nitrogen (Chart 1). Using these 1-substituted 4-aminoindoles as starting materials, the difficulty mentioned above was overcome and the desired 1-substituted 4-hydroxyindoles were obtained. The optimum reaction conditions for diazotization, found in the above study, were successfully applied to 4-aminoindole (**3**) to give 4-hydroxyindole (**14**). It was also found that 1-substituted 4-indolediazonium salts underwent the Sandmeyer reaction to give 4-cyanoindole (**23**) and 4-halogenoindoles. Palladium-catalyzed alkenylation of the latter compound was then examined and 4-(3-hydroxy-3-methyl-1-buten-1-yl)indole (**26**), a key intermediate for the synthesis of (±)-6,7-secoagroclavine (**27**), was successfully obtained.

In this paper, we describe an efficient and convenient synthesis of 4-substituted indoles *via* 4-indolediazonium salts in detail.

I. Preparation of 4-Nitroindole

In the previous paper,[12] we reported the synthesis of 4-aminoindole (**3**), 4-nitroindole (**4**), and 1-hydroxy-4-nitroindole (**5**) by the reduction of 2,6-dinitro-*trans*-β-dimethylaminostyrene (**2**) with titanium (III) chloride. Although various attempts have hitherto been made to synthesize **4**,[13] our method described above seems to give the best results. However, the yield of **4** was still not satisfactory. Therefore, we planned to convert **5** into **4**.

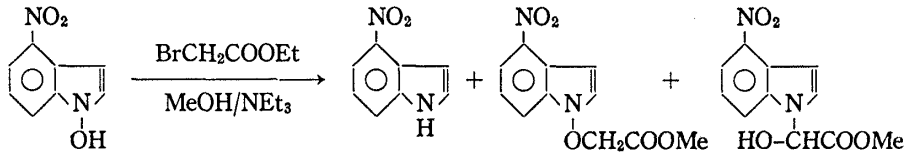


X: leaving group
R: alkyl group
W: electron withdrawing group

Chart 2

Our strategy to replace the 1-hydroxy group of **5** by hydrogen was as follows. Treatment of **5** with a reagent (**6**) in the presence of a base would give an alkylated intermediate (**7**). When the substituent W in **7** is an electron withdrawing group, an active methine proton might be produced. If the same base that is used for alkylation abstracts the proton, the intermediate (**7**) would split into **4** and a ketonic compound (**8**) as shown in Chart 2. Based upon this working plan, we selected the ethoxycarbonyl group, hydrogen, and bromine as functional groups W, R, and X, respectively, in the reagent (**6**), and triethylamine as a base.

TABLE I. Replacement of the 1-Hydroxy Group of 1-Hydroxy-4-nitroindole by Hydrogen[a)]



5 4 9 10

Entry	Reaction Time (h)	Yield (%) of 4	9	10
1	16	40.7	50.8	0
2	43	59.2	14.4	20.0
3	53	76.8	3.9	12.5
4	92.5	87.3[b)]	0	0

a) The compound (**5**) was reacted with 1.1—3.3 mol equivalents of ethyl bromoacetate in an excess of triethylamine in methanol at room temperature.
b) After being stirred for 92.5 h, the reaction mixture was heated with aqueous sodium bicarbonate under reflux for 5 min.
9→**4**, **10**→**4**.

Thus, 1-hydroxy-4-nitroindole (**5**) was treated with ethyl bromoacetate and triethylamine in methanol at room temperature and found to yield **4**, methyl 2-(4-nitroindol-1-yl)oxyacetate (**9**), and methyl 2-hydroxy-2-(4-nitroindol-1-yl)acetate (**10**). In the latter two compounds, the ester groups were exchanged to methyl ester. The effects of reaction time on the yields are summarized in Table I. These results clearly show that **9** is initially produced, and then gradually collapses to **4**, liberating methyl glyoxalate, as expected from the experimental design (entries 1—3). With the passage of time, methyl glyoxalate accumulates in the reaction mixture and it is trapped by **4** to afford **10**. The compound (**10**) was found to be unstable toward the action of base and protic solvent. Thus, treatment with methanol converted the pure oily compound (**10**) into prisms, which after isolation were found to contain a significant amount of **4**. When a methanol solution of **10** was heated with sodium bicarbonate, **4** was produced in 94.5% yield. Similarly, compound (**9**) was converted into **4** in 94.3% yield in methanol in the presence of triethylamine. Taking these findings into consideration, an 87.3% yield (entry 4) of **4** was attained by adopting a prolonged reaction time and subsequent brief heating with sodium bicarbonate in methanol. Hence, 4-nitroindole (**4**) can now be prepared from 2,6-dinitrotoluene (**1**) in three steps in 66.6% overall yield.

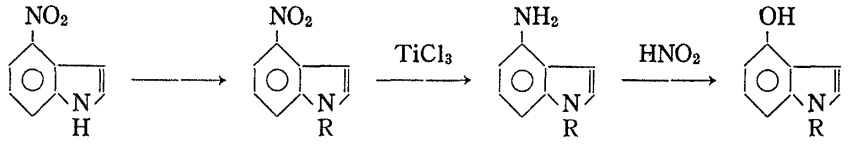
It is noteworthy that bromoacetate was oxidized to glyoxalate under these conditions. This result suggests that 1-hydroxy-4-nitroindole (**5**) can serve as a reagent for mild oxidation and this point is currently under investigation.

II. Preparation of 1-Substituted 4-Hydroxyindoles

Since 4-nitroindole (**4**) was now readily available, 1-substituted 4-nitroindoles were prepared from **4**. Thus, 4-nitroindole sodium salt, prepared by the treatment of **4** with sodium hydride in absolute dimethylformamide (DMF), was reacted with methyl chloroformate, tosyl chloride, or benzyl bromide to yield the corresponding 1-substituted 4-nitroindoles (**11a**—**c**) in 95.1%, 81.8%, or 96.8% yield, respectively (Table II). Subsequent reduction of **11a**—**c** with aqueous titanium (III) chloride[14)] gave the corresponding 1-substituted 4-aminoindoles (**12a**—**c**) in high yields (Table II).[15)]

Diazotization of **12a**—**c** with sodium nitrite and hydrogen chloride and subsequent pyrolysis gave the desired 1-substituted 4-hydroxyindoles (**13a**—**c**) in the yields listed in Table II.[16)] In this reaction, it was found that the starting materials (**12a**—**c**) should be diazotized in aqueous methanol solution. In cases where aqueous solutions of **12a**—**c** were diazotized,

TABLE II. Preparation of 1-Substituted 4-Nitro-, 4-Amino-, and 4-Hydroxyindoles

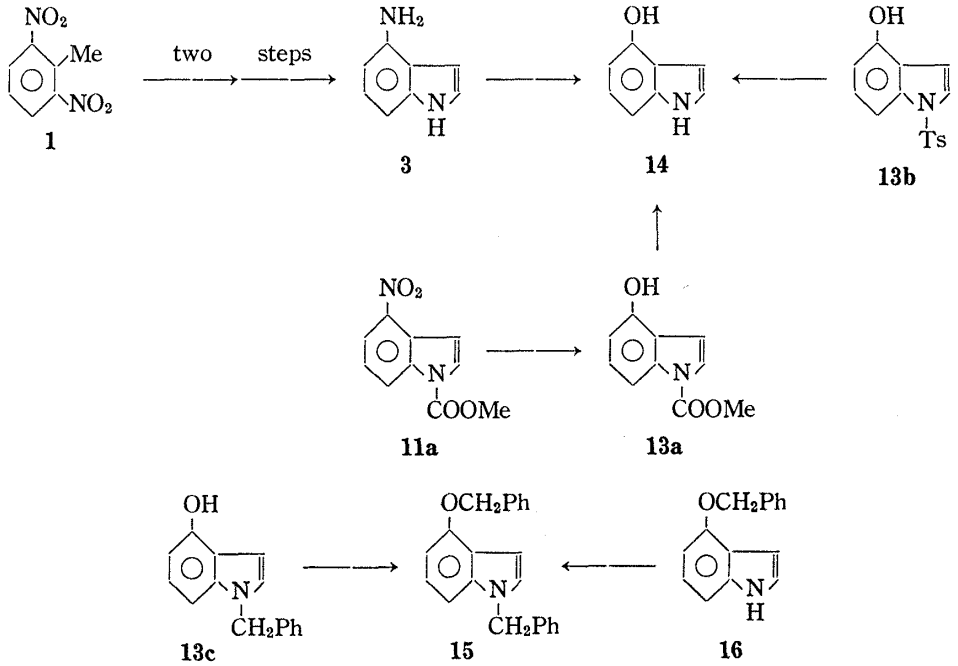


4 11 12 13

	R	Yield (%) of 11	12	13
a	COOMe	95.1	92.5	93.7
b	SO_2-C$_6$H$_4$-CH_3	81.8	91.8	58.0
c	CH_2Ph	96.8	85.0	43.9

the yields of **13a—c** became poor with concomitant formation of many unidentified products. It was also found that after diazotization, the solution containing the diazonium salt should be extracted with dichloromethane and the resultant aqueous layer should be pyrolyzed. The use of an excess or insufficient amount of sodium nitrite rather than 2.2 mol equivalents decreased the yields of phenols (**13a—c**) due to the formation of polymer.

Direct diazotization of **3** under the reaction conditions described above proceeded smoothyl and afforded 4-hydroxyindole[12,17] (**14**) in 38.8% yield. Since **3** is readily available from **1** in two steps in 75.9% yield, this route seems to be useful for the synthesis of **14** (Chart 3).



1 3 14 13b 11a 13a 13c 15 16

Chart 3

1-Methoxycarbonyl-4-nitroindole (**11a**) could be converted in one pot in 85.1% yield to 4-hydroxy-1-methoxycarbonylindole (**13a**) by treatment with titanium (III) chloride in methanol, followed by the addition of 2.2 mol equivalents of sodium nitrite and subsequent pyrolysis.

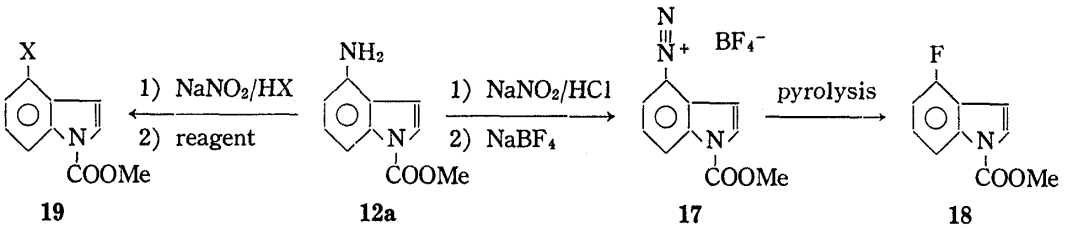
The structure of **13a** was established by the fact that hydrolysis with 20% aqueous sodium hydroxide afforded 4-hydroxyindole (**14**) in 74.9% yield. Under the same reaction conditions, 1-tosyl-4-hydroxyindole (**13b**) gave **14** and the starting material in 42.1% and 41.5% yields,

respectively. On the other hand, 1-benzyl-4-hydroxyindole (**13c**) resisted catalytic debenzylation under various reaction conditions using either 5% palladium on carbon or platinum oxide as a catalyst. Therefore, the compound (**13c**) was reacted with benzyl bromide in the presence of potassium carbonate to afford 1-benzyl-4-benzyloxyindole (**15**) in 52.6% yield, which was identical with the sample prepared in 95.8% yield from an authentic 4-benzyloxyindole[18] (**16**) by the reaction with sodium hydride and benzyl bromide (Chart 3).

III. Preparation of 4-Halogenoindoles

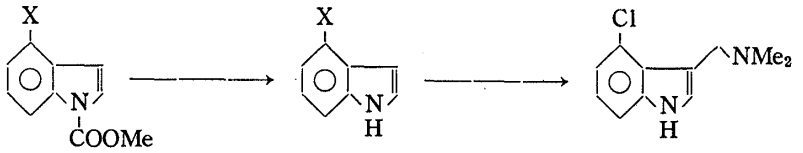
Treatment of an aqueous solution containing 1-methoxycarbonyl-4-indolediazonium chloride [prepared by diazotization of 4-amino-1-methoxycarbonylindole (**12a**) with sodium nitrite] with aqueous sodium tetrafluoroborate gave 1-methoxycarbonyl-4-indolediazonium tetrafluoroborate (**17**) as a stable crystalline compound in 78.3% yield. Pyrolysis of **17** over silica gel resulted in the Schiemann reaction[19] to afford a 50.6% yield of 4-fluoro-1-methoxycarbonylindole (**18**). Similarly, Sandmeyer reaction[20] of 1-methoxycarbonyl-4-indolediazonium salt with either cuprous chloride or cuprous bromide afforded 4-chloro- or 4-bromo-1-methoxycarbonylindole (**19a** or **19b**) in 77.9% or 82.6% yield, respectively. Treatment of the diazonium salt with potassium iodide gave a 76.2% yield of 4-iodo-1-methoxycarbonylindole (**19c**) as described in Table III.

Table III. Preparation of 4-Halogenoindoles



19 **12a** **17** **18**

	HX	Reagent	X	Yield (%) of **19**
a	HCl	CuCl	Cl	77.9
b	HBr	CuBr	Br	82.6
c	HCl	KI	I	76.2



19a: X=Cl
19c: X=I

20a: X=Cl
20b: X=I

21

Chart 4

Hydrolysis of **19a** or **19c** with 20% aqueous sodium hydroxide produced 4-chloroindole[21] (**20a**) or 4-iodoindole (**20b**) in 79.0% or 92.7% yield respectively (Chart 4). Reaction of **20a** with dimethyl(methylene)ammonium chloride[22] gave a 20.9% yield of starting material and a 59.9% yield of 4-chloro-3-dimethylaminoindole (**21**), whose physical data were identical with those reported in the literature.[23]

IV. Introduction of Carbon Side Chains into the 4-Position

Diazotization of 4-amino-1-methoxycarbonylindole (**12a**) and subsequent reaction with cuprous cyanide in the presence of potassium cyanide afforded 4-cyano-1-methoxycarbonylindole (**22**) in 82.0% yield (Chart 5). Confirmation of the structure of **22** was obtained by

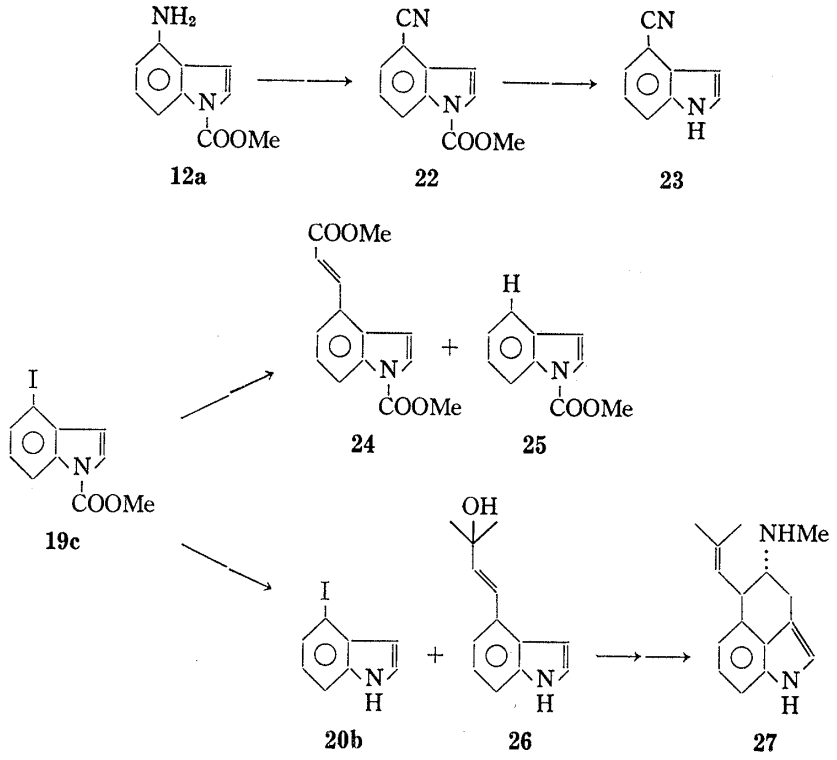


Chart 5

its hydrolysis with 20% aqueous sodium hydroxide to afford 4-cyanoindole[21] (**23**) in 91.8% yield.

Palladium–catalyzed alkenylation[24] was also effective for the synthesis of 4-substituted indoles. Thus, 4-iodo-1-methoxycarbonylindole (**19c**) was reacted with methyl acrylate in the presence of palladium acetate, triphenylphosphine, and triethylamine to afford methyl 3-(1-methoxycarbonylindol-4-yl)acrylate (**24**) and 1-methoxycarbonylindole (**25**) in 68.8% and 20.9% yields, respectively. The nuclear magnetic resonance (NMR) spectrum of **24** exhibited olefinic protons as two sets of doublets at δ 6.53 and 8.03 with a coupling constant 16.0 Hz, showing predominant formation of the E-isomer.

Next, we attempted to prepare 4-(3-hydroxy-3-methyl-1-buten-1-yl)indole (**26**) by the reaction of **19c** with 2-methyl-3-buten-2-ol under palladium acetate catalysis and obtained **20b** and the desired product (**26**) in 30.1% and 46.7% yields, respectively. Since we have already reported a total synthesis of (±)-6,7-secoagroclavine[25] (**27**) through **26** as a key intermediate, this constitutes an alternative total synthesis of **27** *via* the 4-indolediazonium salt.

It is noteworthy that hydrogen nuclei on C-3 and C-7 were found to be spin coupled with a coupling constant of 0.8 Hz in the NMR spectra of almost all 4-substituted indoles described in the present study.

The present study disclosed the versatility of 4-indolediazonium salts for the synthesis of various 4-substituted indoles. Extensive further study of the reaction of 4-indolediazonium salts is in progress.

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 NMR spectra with a JEOL JNM-C-60H spectrometer (with tetramethylsilane as an internal standard). Mass spectra (MS) were recorded on a JEOL JNM-01SG spectrometer. Commercial aq. titanium(III) chloride (16%, d=1.5, from Kanto Chemical Co., Inc.) was used. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kieselgel GF_{254} (Type 60) (SiO_2). Silica gel (100—200 mesh, from Kanto Chemical Co., Inc.) was used for column chromatography throughout the present study.

4-Nitroindole (4), Methyl 2-(4-Nitroindol-1-yl)oxyacetate (9), and Methyl 2-Hydroxy-2-(4-nitroindol-1-yl)-acetate (10) from 1-Hydroxy-4-nitroindole (5)——i) Entry 1: Triethylamine (NEt_3, 0.4 ml) was added to a solution of **5** (58.0 mg, 0.32 mmol) and ethyl bromoacetate (176.4 mg, 1.05 mmol) in MeOH(3.0 ml). The mixture was stirred for 16 h at room temperature, then the solvent was evaporated off under reduced pressure. The residue was made acidic by adding 2 N HCl and the whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent. Extraction of the upper yellow band with CH_2Cl_2–MeOH (95: 5, v/v) gave **9** (41.4 mg, yield. 50.8%). Recrystallization from MeOH gave yellow needles. mp 73.5—74.5°C. IR ν_{max}^{KBr} cm^{-1}: 1767, 1514, 1333. MS *m/e*: 250 (M^+). NMR ($CDCl_3$) δ: 3.73 (3H, s), 4.79 (2H, s), 7.01 (1H, dd, $J=3.2$ and 0.8 Hz), 7.23 (1H, t, $J=8.0$ Hz), 7.64 (1H, d, $J=3.2$ Hz), 7.77 (1H, ddd, $J=8.0$, 1.2, and 0.8 Hz), 8.04 (1H, dd, $J=8.0$ and 1.2 Hz). *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.89; H, 3.91; N, 11.38. Extraction from the lower yellow band with the same solvent gave **4** (21.5 mg, yield. 40.7%), which was identical with an authentic sample.[12]

ii) Entry 2: NEt_3 (1.0 ml) was added to a solution of **5** (156.5 mg, 0.87 mmol) and ethyl bromoacetate (169.5 mg, 0.96 mmol) in MeOH (5.0 ml). The mixture was stirred for 43 h at room temperature, then the solvent was removed *in vacuo*. The residue was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent. Extraction from the upper yellow band or middle yellow band with CH_2Cl_2–MeOH (95: 5, v/v) afforded **9** (31.6 mg, yield. 14.4%) or **4** (84.3 mg, yield. 59.2%), respectively. Extraction with the same solvent from the lower yellow band gave **10** (41.7 mg, yield. 20.0%) as a yellow oil. **10**: MS *m/e*: 250 (M^+). IR ν_{max}^{film} cm^{-1}: 3400, 1756, 1503, 1313. NMR ($CDCl_3$) δ: 3.78 (3H, s), 4.35 (1H, br s, OH), 6.11 (1H, s), 7.19 (1H, t, $J=8.0$ Hz), 7.21 (1H, dd, $J=3.2$ and 0.8 Hz), 7.31 (1H, d, $J=3.2$ Hz), 7.66 (1H, ddd, $J=8.0$, 1.2, and 0.8 Hz), 8.05 (1H, dd, $J=8.0$ and 1.2 Hz). The compound (**10**) was rather stable in CH_2Cl_2, $CHCl_3$, or in methanol containing a small amount of dilute HCl. Although treatment with MeOH converted the oily compound (**10**) to prisms, the crystals, obtained by filtration, turned out to be a mixture of **4** and **10** in various ratios depending on the time required for recrystallization. In basic media, **10** decomposed rapidly to **4**.

iii) Entry 3: In the procedure described in item ii, 56.5 mg (0.32 mmol) of **5**, 177.0 mg (1.06 mmol) of ethyl bromoacetate, 3.0 ml of MeOH, and 0.4 ml of NEt_3 were used. The mixture was stirred for 53 h at room temperature. After work-up as described in item ii, **9** (3.1 mg, yield. 3.9%), **4** (39.5 mg, yield. 76.8%), and **10** (9.9 mg, yield. 12.5%) were obtained.

iv) Entry 4: NEt_3 (8.0 ml) was added to a solution of **5** (1.921 g, 10.8 mmol) and ethyl bromoacetate (2.201 g, 13.2 mmol) in MeOH (40.0 ml). After being stirred for 92.5 h at room temperature, the reaction mixture was made basic (pH 8.0) by adding sat. aq. $NaHCO_3$ and heated under reflux for 15 min. The solvent was evaporated off under reduced pressure and H_2O was added. The whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v), washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave crystals. Recrystallization from MeOH gave **4** (1.096 g) as yellow prisms. The mother liquor was subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent to afford a further crop of **4** (430.0 mg). Total yield: 1.526 g (yield. 87.3%).

4-Nitroindole (4) from Methyl 2-(4-Nitroindol-1-yl)oxyacetate (9)——NEt_3 (0.5 ml) was added to a solution of **9** (18.0 mg) in MeOH (2.0 ml). The mixture was stirred for 16 h at room temperature, then the solvent was evoporated off under reduced pressure. The residue was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to give **4** (11.0 mg, yield. 94.3%) as yellow prisms.

4-Nitroindole (4) from Methyl 2-Hydroxy-2-(4-nitroindol-1-yl)acetate (10)——A solution of **10** (16.0 mg) in MeOH (2.0 ml) and sat. aq. $NaHCO_3$ (1.0 ml) was refluxed for 5 min. After removal of the solvent under reduced pressure, the whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v), washed with sat. aq. NaCl and dried over Na_2SO_4. Removal of the solvent by evaporation *in vacuo* afforded homogeneous **4** (9.8 mg, yield. 94.5%) as yellow prisms.

1-Substituted 4-Nitroindoles (11a—c) from 4-Nitroindole (4)——General Procedure: A solution of an appropriate amount of **4** in abs. dimethylformamide (DMF) was added to stirred 50% NaH (1.5—2.0 mol eq., washed twice with benzene). The mixture was stirred for 5 min at room temperature, then a solution of alkylating or acylating reagent (1.5—2.0 mol eq) in benzene (or abs. DMF) was added as a single portion. The mixture was stirred for an appropriate time, then three drops of H_2O were added and the solvent was evaporated off *in vacuo*. H_2O was added and the whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to column chromatography on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as an eluent to give products.

i) 1-Methoxycarbonyl-4-nitroindole (**11a**) from **4**: In the above procedure, 504.0 mg of **4**, 10.0 ml of abs. DMF, and 229.0 mg of 50% NaH were used. A solution of methyl chloroformate (596.9 mg) in abs. DMF (5.0 ml) was added and stirring was continued for 4 h. After work-up and subsequent column chromatography, as described above, **11a** (650.9 mg, yield. 95.1%) was obtained as crystals from the early part of the fraction. From the later part of the fraction, unreacted starting material was obtained (13.0 mg, yield. 2.6%). **11a**: mp 132.0—133.0°C (yellow needles, recrystallized from MeOH). MS *m/e*: 220 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1738, 1515, 1450, 1330. NMR ($CDCl_3$) δ: 4.04 (3H, s), 7.13 (1H, d, $J=3.2$ Hz), 7.24 (1H, t, $J=8.0$ Hz), 7.67 (1H, d, $J=3.2$ Hz), 8.06 (1H, dd, $J=8.0$ and 1.2 Hz), 8.41 (1H, dd, $J=8.0$ and 1.2 Hz). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.53; H, 3.60; N, 12.68.

ii) 4-Nitro-1-tosylindole (**11b**) from **4**: In the general procedure, 577.1 mg of **4**, 15.0 ml of abs. DMF, and 267.5 mg of 50% NaH were used. A solution of tosyl chloride (1.338 g) in benzene (7.0 ml) was added and stirring was continued for 17 h. After work-up and subsequent column chromatography, as described above, **11b** (921.4 mg, yield. 81.8%) was obtained as crystals from the early part of the fraction. From the later part of the fraction, unreacted starting material was recovered (85.8 mg, y. 14.9%). **11b**: mp 166.0—167.0°C (yellow needles, recrystallized from MeOH). MS *m/e*: 316 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1596, 1572, 1526, 1509, 1348, 1332. NMR ($CDCl_3$) δ: 2.33 (3H, s), 7.18 (2H, d, J=8.0 Hz), 7.33 (1H, t, J=8.0 Hz), 7.34 (1H, dd, J=3.2 and 0.8 Hz), 7.70 (2H, d, J=8.0 Hz), 7.74 (1H, d, J=3.2 Hz), 8.10 (1H, dd, J=8.0 and 1.2 Hz), 8.26 (1H, ddd, J=8.0, 1.2, and 0.8 Hz). *Anal.* Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.96; H, 3.82; N, 8.86. Found: C, 56.96; H, 3.67; N, 8.65.

iii) 1-Benzyl-4-nitroindole (**11c**) from **4**: In the general procedure, 22.3 mg of **4**, 7.0 ml of abs. DMF, and 15.0 mg of 50% NaH were used. A solution of benzyl bromide (33.5 mg) in benzene (2.0 ml) was added and the mixture was stirred for 17 h. After work-up and subsequent column chromatogrophy, as described above, **11c** (31.4 mg, yield. 96.8%) was obtained. mp 129.5—130.5°C (yellow needles, recrystallized from MeOH). MS *m/e*: 252 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1500 (br), 1318, 1280. NMR ($CDCl_3$) δ: 5.32 (2H, s), 6.87—7.38 (8H, m), 7.50 (1H, dd, J=8.0 and 1.2 Hz), 8.03 (1H, dd, J=8.0 and 1.2 Hz). *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.23; H, 4.69; N, 10.89.

4-Amino-1-methoxycarbonylindole (12a) from 1-Methoxycarbonyl-4-nitroindole (11a)——Aq. titanium (III) chloride ($TiCl_3$, 6.0 ml, 9.35 mmol) was added as a single portion to a stirred solution of **11a** (317.0 mg, 1.44 mmol) in MeOH (40.0 ml). After being stirred for 7 min at room temperature, the whole was ice-cooled. The reaction mixture was adjusted to pH 4 by adding sat. aq. $NaHCO_3$, then the solvent was evaporated off under reduced pressure. The whole was made alkaline by adding sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated. to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2 as an eluent to afford **12a** (253.4 mg, yield. 92.5%). Recrystallization from CH_2Cl_2 gave colorless prisms. mp 109.5—110.5°C. MS *m/e*: 190 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3475, 3385, 1732, 1628. NMR ($CDCl_3$) δ: 3.62 (2H, br s, NH_2), 3.93 (3H, s), 6.38 (1H, d, J=3.2 Hz), 6.38 (1H, d, J=8.0 Hz), 6.99 (1H, t, J=8.0 Hz), 7.35 (1H, d, J=3.2 Hz), 7.46 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.20; H, 5.28; N, 14.53.

4-Amino-1-tosylindole (12b) from 4-Nitro-1-tosylindole (11b)——Aq. $TiCl_3$ (11.0 ml, 17.14 mmol) was added as a single portion to a stirred solution of **11b** (858.0 mg, 2.71 mmol) in MeOH (16.0 ml). After being stirred for 7 min at room temperature, the whole was ice-cooled. The reaction mixture was adjusted to pH 4 by adding sat. aq. $NaHCO_3$, then the solvent was evaporated off under reduced pressure. The whole was made alkaline by adding sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2 as an eluent to afford **12b** (712.8 mg, yield. 91.8%). Recrystallization from CH_2Cl_2 afforded colorless prisms. mp 131.0—132.0°C. MS *m/e*: 286 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 3390, 1623, 1593, 1359. NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.58 (2H, br s, NH_2), 6.32 (1H, d, J=8.0 Hz), 6.42 (1H, d, J=3.2 Hz), 6.93 (1H, t, J=8.0 Hz), 7.02 (2H, d, J=8.0 Hz), 7.25 (1H, d, J=8.0 Hz), 7.30 (1H, d, J=3.2 Hz), 7.59 (2H, d, J=8.0 Hz). *Anal.* Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.78; H, 4.85; N, 9.83.

4-Amino-1-benzylindole (12c) from 1-Benzyl-4-nitroindole (11c)——Aq. $TiCl_3$ (9.22 ml, 14.36 mmol) was added as a single portion to a stirred solution of **11c** (481.8 mg, 1.91 mmol) and NH_4OAc (2.226 g, 28.9 mmol) in MeOH (40.0 ml). After being stirred for 7 min at room temperature, the whole was made basic by adding sat. aq. $NaHCO_3$. The solvent was evaporated off under reduced pressure and the residue was extracted with CH_2Cl_2–MeOH (95: 5, v/v), washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as an eluent to give **12c** (360.9 mg, yield. 85.0%). Recrystallization from CH_2Cl_2 afforded colorless needles. mp 114.5—115.5°C. MS *m/e*: 222 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3440, 3335, 1625, 1606, 1581. NMR ($CDCl_3$) δ: 3.60 (2H, br s, NH_2), 5.16 (2H, s, CH_2), 6.18—7.50 (10H, m). *Anal.* Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.73; H, 6.24; N, 12.32.

1-Substituted 4-Hydroxyindoles (13a—c) from 1-Substituted 4-Aminoindoles (12a—c)——General Procedure: A solution of $NaNO_2$ (2.2 mol eq.) in H_2O (1.0 ml) was added dropwise with stirring to an ice-cooled suspension of an appropriate amount (*ca.* 0.25 mmol) of 1-substituted 4-aminoindole in MeOH (2.0 ml) and 2 N HCl (0.45 ml); during this time the temperature was maintained below 5°C. After being stirred for 5 min, the reaction mixture was poured into ice-cooled H_2O (100 ml). The whole was extracted with CH_2Cl_2 (50 ml) and the separated aqueous layer was heated on a water bath (97°C) for an appropriate time. The reaction mixture was cooled and extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–MeOH (99: 1, v/v) as a developing solvent to give the product.

i) 4-Hydroxy-1-methoxycarbonylindole (**13a**) from 4-Amino-1-methoxycarbonylindole (**12a**): In the above procedure, 49.8 mg of **12a** and 41.0 mg of $NaNO_2$ were used. The aqueous layer containing diazonium salt was heated for 50 min. After work-up and subsequent p-TLC, as described above, **13a** (46.9 mg, yield. 93.7%) was obtained. mp 171.0—173.0°C (colorless prisms, recrystallized from MeOH). MS *m/e*: 191

(M^+). IR ν_{max}^{KBr} cm^{-1}: 3335, 1708, 1595, 1467, 1305. NMR (10% CD_3OD in $CDCl_3$) δ: 4.00 (3H, s), 6.59 (1H, d, J=8.0 Hz), 6.69 (1H, d, J=4.0 Hz), 7.07 (1H, t, J=8.0 Hz), 7.39 (1H, d, J=4.0 Hz), 7.62 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.52; H, 4.73; N, 7.19.

ii) 4-Hydroxy-1-tosylindole (**13b**) from 4-Amino-1-tosylindole (**12b**): In the general procedure, 48.8 mg of **12b** and 26.6 mg of $NaNO_2$ were used. The aqueous layer containing diazonium salt was heated for 20 min. After work-up and subsequent p-TLC, as described above, **13b** (28.4 mg, y. 58.0%) was obtained. mp 147.5—149.0°C (colorless prisms, recrystallized from CH_2Cl_2). MS *m/e*: 287 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3460, 1597, 1360. NMR (10% CD_3OD in $CDCl_3$) δ: 2.29 (3H, s), 6.48 (1H, dd, J=8.0 and 0.8 Hz), 6.67 (1H, dd, J=4.0 and 0.8 Hz), 7.01 (1H, t, J=8.0 Hz), 7.08 (2H, d, J=8.0 Hz), 7.31 (1H, d, J=4.0 Hz), 7.38 (1H, ddd, J=8.0, 0.8, and 0.8 Hz), 7.61 (2H, d, J=8.0 Hz). *Anal.* Calcd for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.56; N, 4.62. Found: C, 62.42; H, 4.40; N, 4.62.

iii) 1-Benzyl-4-hydroxyindole (**13c**) from 4-Amino-1-benzylindole (**12c**): In the general procedure, 46.0 mg of **12c** and 33.2 mg of $NaNO_2$ were used. The aqueous layer containing diazonium salt was heated for 10 min. After work-up and subsequent p-TLC, as described above, **13c** (20.3 mg, y. 43.9%) was obtained. mp 96.5—98.0°C (colorless prisms, recrystallized from ether–hexane). MS *m/e*: 223 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3230, 1580, 1260. NMR ($CDCl_3$) δ: 4.98 (1H, br s, OH), 5.19 (2H, s), 6.40 (1H, dd, J=7.0 and 1.5 Hz), 6.49 (1H, d, J=3.2 Hz), 6.73—7.36 (8H, m). *Anal.* Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.50; H, 5.89; N, 6.35.

4-Hydroxyindole (14) from 4-Aminoindole (3)——A solution of $NaNO_2$ (45.5 mg, 0.65 mmol) in H_2O (1.0 ml) was added dropwise to a stirred ice-cooled solution of **3** (37.1 mg, 0.28 mmol) in MeOH (2.0 ml) and 2 N HCl (0.45 ml), maintaining the temperature below 5°C. After being stirred for 5 min, the reaction mixture was poured into ice–cold H_2O (100 ml) and the whole was extracted with CH_2Cl_2 (50 ml). The aqueous layer was separated and heated on a water bath (97°C) for 50 min. The reaction mixture was cooled and extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (96: 4, v/v) as a developing solvent to afford **14** (14.5 mg, yield. 38.8%) as crystals. mp 101.0—103.0°C (lit.[17] mp 97—99°C). All spectral data were identical with those of authentic 4-hydroxyindole.[17]

4-Hydroxy-1-methoxycarbonylindole (13a) from 1-Methoxycarbonyl-4-nitroindole (11a)——Aq. $TiCl_3$ (1.04 ml, 1.62 mmol) was added as a single portion to a stirred suspension of **11a** (50.6 mg, 0.23 mmol) in MeOH (2.0 ml). After being stirred for 25 min, the whole was cooled in an ice bath. A solution of $NaNO_2$ (36 mg, 0.52 mmol) in H_2O (1.0 ml) was added dropwise with stirring, maintaining the temperature below 5°C. After being stirred for 5 min, the reaction mixture was poured into ice–cold H_2O (100 ml) and extracted with CH_2Cl_2 (50 ml). The aqueous layer was separated and heated on a water bath (97°C) for 50 min. The whole was cooled and extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evoporated to dryness under reduced pressure. The residue was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (99: 1, v/v) as a developing solvent to afford **13a** (37.4 mg, yield. 85.1%) as colorless prisms. The compound was identical with the sample prepared from **12a**.

4-Hydroxyindole (14) from 4-Hydroxy-1-methoxycarbonylindole (13a)——A solution of **13a** (33.0 mg) in MeOH (2.0 ml) and 40% aq. NaOH (2.0 ml) was refluxed for 10 min. The reaction mixture was cooled in an ice bath and CH_2Cl_2 was added. The whole was made acidic by adding 2 N HCl and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2–MeOH (95: 5, v/v). The combined extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evoporated to dryness under reduced pressure. The residue was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95: 5, v/v) as a developing solvent to give **14** (17.2 mg, yield. 74.9%) as colorless prisms. All spectral data were identical with those of authentic 4-hydroxyindole.[17]

4-Hydroxyindole (14) from 4-Hydroxy-1-tosylindole (13b)——A solution of **13b** (16.6 mg) in MeOH (2.0 ml) and 40% aq. NaOH (2.0 ml) was refluxed for 10 min. The reaction mixture was cooled in an ice bath and CH_2Cl_2 was added. The whole was made acidic by adding 2 N HCl and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2–MeOH (95: 5, v/v). The combined extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2–MeOH (95: 5, v/v) as a developing solvent. Under a UV lamp, two dark bands were detected. Extraction of the upper band with CH_2Cl_2–MeOH (95: 5, v/v) gave the starting material (6.8 mg, yield 41.5%). From the lower band, **14** (3.2 mg, yield 42.1%) was extracted with the same solvent. All spectral data were identical with those of authentic 4-hydroxyindole.[17]

1-Benzyl-4-benzyloxyindole (15) from 4-Benzyloxyindole (16)——A solution of **16** (102.0 mg, 0.45 mmol) in abs. DMF (5.0 ml) was added to stirred 50% NaH (39.0 mg, 0.81 mmol, washed three times with benzene). The mixture was stirred for 5 min, then a solution of benzyl bromide (130.5 mg, 0.76 mmol) in benzene (2.0 ml) was added. Stirring was continued for 5 h at room temperature, then H_2O (1.0 ml) was added. The solvent was evaporated off under reduced pressure and H_2O was added. The whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v), then washed with sat. aq. NaCl, dried aver Na_2SO_4, and concentrated to leave **15** (137.2 mg, yield 96.0%) as crystals. mp 122.5—123.0°C (colorless needles, recrystallized from MeOH). MS *m/e*: 313 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1609, 1577, 1492, 1252. NMR ($CDCl_3$) δ: 5.17 (2H, s), 5.21 (2H, s), 6.39—7.64

(15H, m). *Anal.* Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.10; H, 6.08; N, 4.31.

1-Benzyl-4-benzyloxyindole (15) from 1-Benzyl-4-hydroxyindole (13c)——A solution of benzyl bromide (33.3 mg, 0.19 mmol) in acetone (0.5 ml) was added to a solution of **13c** (10.3 mg, 0.046 mmol) and K_2CO_3 (22.0 mg) in acetone (3.0 ml). The mixture was heated under reflux for 6.75 h, then the solvent was evaporated off under reduced pressure and H_2O was added. The whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v), washed with sat. aq. NaCl, 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 (1: 1, v/v) as a developing solvent to afford **15** (7.6 mg, yield 52.6%) as crystals. Recrystallization from MeOH afforded colorless needles. All spectral data and the melting point were identical with those of the sample prepared from **16.**

1-Methoxycarbonyl-4-indolediazonium Tetrafluoroborate (17) from 4-Amino-1-methoxycarbonylindole (12a)——A solution of $NaNO_2$ (88.0 mg, 1.27 mmol) in H_2O (2.0 ml) was added dropwise to an ice-cooled suspension of **12a** (100.0 mg, 0.52 mmol) in H_2O (4.0 ml) and 2 N HCl (0.9 ml) with stirring. During addition, the temperature was kept below 5°C. The mixture was stirred f aBF$_4$ (1.0 ml) was added. Stirring was continued for 20 min in an ice bath, then for ire. Precipitates were collected by filtration, washed well with CH_2Cl_2, and drie 9.0 mg, yield 78.3%) as a yellow powder. Recrystallization from MeOH gave 163.0°C. IR ν_{max}^{KBr} cm^{-1}: 2260, 1763. NMR (DMSO-d_6) δ: 4.06 (3H, s), 7.33 (1H, d , J=8.0 Hz), 8.30 (1H, d, J=4.0 Hz), 8.60 (1H, d, J=8.0 Hz), 8.85 (1H, d, J=8. trum, no M$^+$ peak was detected and the base peak was 193 (m/e), which correspond arbonylindole cation radical.

4-Fluoro-1-methoxycarbonylindole (18) from 1-Methoxycarbonyl-4- oroborate (17)——Diazonium salt (**17**, 49.1 mg) was mixed with SiO_2 (300 mg, 100 Chemical Co, Inc.) and the whole was heated at 175—180°C in a round-bottome denser. The mixture was heated for 20 min, and tarry matter adhering to the cond H_2Cl_2 into the flask. The whole was made alkaline by adding sat. aq. $NaHCO_3$. Tl ated, washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil, whic on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as a developing solvent to give **18** (16.6 mg . mp 30.5—31.5°C (colorless prisms by sublimation). MS m/e: 193 (M$^+$). IR (CCl_4) δ: 4.00 (3H, s), 6.63 (1H, dd, J=4.0 and 0.8 Hz, C_3–H), 6.85 (1H, ddd, J=9.6, 8.0, and 1.2 Hz, C_5–H; J_{HCCF}=9.6 Hz), 7.19 (1H, dt, J=8.0 and 5.4 Hz, C_6–H; J_{HCCCF}=5.4 Hz), 7.47 (1H, d, J=4.0 Hz, C_2–H), 7.90 (1H, ddd, J=8.0, 1.2, and 0.8 Hz, C_7–H).

4-Chloro-1-methoxycarbonylindole (19a) from 4-Amino-1-methoxycarbonylindole (12a)——A solution of $NaNO_2$ (40.5 mg, 0.58 mmol) in H_2O (1.0 ml) was added to an ice-cooled suspension of **12a** (49.0 mg, 0.25 mmol) in H_2O (1.0 ml) and 2 N HCl (1.0 ml) with stirring, maintaining the temperature below 5°C. After being stirred for 20 min, the whole was extracted with ice-cooled CH_2Cl_2 (5.0 ml). The separated aqueous layer was added to a cold solution of CuCl (640.0 mg) in conc. HCl (2.0 ml) with stirring. After being stirred for 30 min at room temperature, the whole was heated on a water bath (97°C) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2–MeOH (99: 1, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by p-TLC on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as a developing solvent to afford **19a** (42.1 mg, yield 77.9%) as crystals. mp 43.5—44.0°C (colorless prisms, recrystallized from hexane). MS m/e: 211 (M$^+$) and 209 (M$^+$). IR ν_{max}^{KBr} cm^{-1}: 1754, 743. NMR ($CDCl_3$) δ: 4.03 (3H, s), 6.67 (1H, d, J=4.0 Hz), 7.18 (1H, d, J=5.0 Hz), 7.19 (1H, d, J=5.4 Hz), 7.57 (1H, d, J=4.0 Hz), 8.03 (1H, dd, J=5.4 and 5.0 Hz). *Anal.* Calcd for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.84; N, 6.68. Found: C, 57.68; H, 3.86; N, 6.95.

4-Bromo-1-methoxycarbonylindole (19b) from 4-Amino-1-methoxycarbonylindole (12a)——A solution of $NaNO_2$ (39.9 mg, 0.58 mmol) in H_2O (1.0 ml) was added to an ice-cooled suspension of **12a** (51.0 mg, 0.27 mmol) in 4.7% aq. HBr 1.990 g) with stirring, maintaining the temperature below 5°C. After being stirred for 15 min, the reaction mixture was extracted with ice-cooled CH_2Cl_2 (5.0 ml). The separated aqueous layer was added to a cold solution of CuBr (795.0 mg) in conc. HBr (2.0 ml) with stirring. After being stirred for 2 h at room temperature, the whole was heated on a water bath (94°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 sat. aq. NaCl, 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 (1: 1, v/v) as a developing solvent to give **19b** (56.3 mg, yield 82.6%) as a colorless oil. MS m/e: 255 (M$^+$) and 253 (M$^+$). IR ν_{max}^{film} cm^{-1}: 1744, 754. NMR (CCl_4) δ: 4.00 (3H, s), 6.58 (1H, d, J=4.0 Hz), 7.06 (1H, t, J=8.0 Hz), 7.33 (1H, dd, J=8.0 and 1.6 Hz), 7.52 (1H, d, J=4.0 Hz), 8.06 (1H, br.dd, J=8.0 and 1.6 Hz). *Anal.* Calcd for $C_{10}H_8BrNO_2$: C, 47.26; H, 3.17; N, 5.51. Found: C, 47.09; H, 3.15; N, 5.75.

4-Iodo-1-methoxycarbonylindole (19c) from 4-Amino-1-methoxycarbonylindole (12a)——A solution of $NaNO_2$ (41.0 mg, 0.59 mmol) in H_2O (1.0 ml) was added to an ice-cooled suspension of **12a** (51.5 mg, 0.27 mmol) in H_2O (1.0 ml) and 2 N HCl (1.0 ml) with stirring, maintaining the temperature below 5°C. After being stirred for 15 min, the reaction mixture was extracted with ice-cooled CH_2Cl_2 (5.0 ml). The separated aqueous layer was added to a cold solution of KI (1.137 g) in H_2O (2.0 ml) with stirring. After being stirred for 30 min at room temperature, the whole was heated on a water bath (85°C) for 5 min. The reaction mixture was cooled and extracted with CH_2Cl_2–MeOH (99: 1, v/v). The extract was washed with sat. aq. NaCl,

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 (1: 1, v/v) to give **19c** (62.2 mg, yield 76.2%) as crystals. mp 63.0—64.0°C (colorless prisms, recrystallized from Et_2O–hexane). MS *m/e*: 301 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1730, 752. NMR ($CDCl_3$) δ: 3.97 (3H, s), 6.44 (1H, d, J=3.5 Hz), 6.92 (1H, t, J=8.0 Hz), 7.51 (1H, d, J=8.0 Hz), 7.61 (1H, d, J=3.5 Hz), 8.04 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 40.03; H, 2.70; N, 4.30.

4-Chloroindole (20a) from 4-Chloro-1-methoxycarbonylindole (19a)——A solution of **19a** (38.5 mg) in MeOH (2.5 ml) and 40% aq. NaOH (2.5 ml) was refluxed for 15 min. The solvent was evaporated off and the residue was extracted with CH_2Cl_2–MeOH (99: 1, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave pure **20a** (22.0 mg, yield 79.0%) as a colorless oil.[21] MS *m/e*: 153 (M^+) and 151 (M^+). IR ν_{max}^{film} cm^{-1}: 3455, 1615, 1573, 750. NMR (CCl_4) δ: 6.55 (1H, dd, J=4.0 and 2.5 Hz), 6.80—7.23 (4H, m), 7.84 (1H, br.s, NH).

4-Iodoindole (20b) from 4-Iodo-1-methoxycarbonylindole (19c)——A solution of **19c** (35.4 mg) in MeOH (3.0 ml) and 40% aq. NaOH (3.0 ml) was refluxed for 10 min. The solvent was evaporated off and the residue was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (1: 1.4, v/v) as a developing solvent to afford **20b** (52.1 mg, yield 92.7%) as crystals. mp 98.5—99.5°C (colorless needles, recrystallized from hexane). MS *m/e*: 243 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3385, 1605, 1557, 760, 748. NMR ($CDCl_3$) δ: 6.36 (1H, ddd, J=3.2, 3.2, and 0.8 Hz), 6.78 (1H, dd, J=8.0 and 7.2 Hz), 7.09 (1H, t, J=3.2 Hz), 7.22 (1H, br.d, J=8.0 Hz), 7.41 (1H, dd, J=7.2 and 0.8 Hz), 8.10 (1H, br.s). *Anal.* Calcd for C_8H_6IN: C, 39.52; H, 2.48; N, 5.76. Found: C, 39.43; H, 2.50; N, 5.98.

4-Chloro-3-dimethylaminomethylindole (21) from 4-Chloroindole (20a)——Dimethyl(methylene)ammonium chloride[22] (19.0 mg, 1.5 mol eq.) was added to a stirred solution of **20a** (20.5 mg) in CH_3CN (2.0 ml). The mixture was stirred for 18 h at room temperature, then the solvent was evaporated off under reduced pressure. Water was added to the residue and 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 sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was subjected to p-TLC on Merck Al_2O_3 (GF_{254}) with CH_2Cl_2–MeOH (98: 2, v/v) as a developing solvent. Under UV light, two dark bands were detected. Extraction from the upper band with CH_2Cl_2–MeOH (95: 5, v/v) afforded the starting material (4.3 mg, yield 20.9%). Extraction from the lower band with the same solvent afforded **21** (16.9 mg, yield 59.9%). mp 149.5—150.5°C (colorless prisms, recrystallized from MeOH; lit.[23] mp 147—148°C). MS *m/e*: 210 (M^+) and 208 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3120 (br.), 1616, 1548, 1452, 1344. NMR (5% CD_3OD in $CDCl_3$) δ: 2.33 (6H, s), 3.92 (2H, s), 6.90—7.31 (4H, m).

4-Cyano-1-methoxycarbonylindole (22) from 4-Amino-1-methoxycarbonylindole (12a)——A solution of $NaNO_2$ (43.3 mg, 0.62 mmol) in H_2O (1.0 ml) was added to an ice-cooled suspension of **12a** (52.0 mg, 0.27 mmol) in H_2O (1.0 ml) and 2 N HCl (1.0 ml) with stirring, maintaining the temperature below 5°C. After being stirred for 20 min, the reaction mixture was extracted with ice-cooled CH_2Cl_2 (5.0 ml). The separated aqueous layer was added to a cold solution of CuCN (653.4 mg) and NaCN (729.0 mg) in H_2O (4.0 ml) with stirring. Stirring was continued for 1 h at room temperature, then the reaction mixture was heated on a water bath (94°C) for 5 min and cooled. The whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v), washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by p-TLC with CH_2Cl_2–hexane (2: 1, v/v) as a developing solvent to give **22** (44.9 mg, yield 82.0%) as crystals. mp 129.5—130.5°C (pale yellow needles, recrystallized from MeOH). MS *m/e*: 200 (M^+). IR ν_{max}^{film} cm^{-1}: 2230, 1748. NMR ($CDCl_3$) δ: 4.07 (3H, s), 6.77 (1H, dd, J=4.0 and 0.8 Hz), 7.32 (1H, t, J=8.0 Hz), 7.55 (1H, dd, J=8.0 and 1.6 Hz), 7.72 (1H, d, J=4.0 Hz), 8.38 (1H, ddd, J=8.0, 1.6, and 0.8 Hz). *Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.85; H, 3.94; N, 13.63.

4-Cyanoindole (23) from 4-Cyano-1-methoxycarbonylindole (22)——A solution of **22** (29.0 mg) in MeOH (2.0 ml) and 40% aq. NaOH (2.0 ml) was refluxed for 10 min. The solvent was evaporated off under reduced pressure and H_2O was added. The whole was made acidic by adding 2 N HCl and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to leave crystals, which were purified by p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to afford **23** (18.9 mg, yield 91.8%). Recrystallization from MeOH–H_2O gave colorless needles. mp 120.5—121.5°C (lit.[21] mp 120—121°C). All spectral data were identical with those of authentic 4-cyanoindole.[21]

Methyl 3-(1-Methoxycarbonylindol-4-yl)acrylate (24) from 4-Iodo-1-methoxycarbonylindole (19c)——A mixture of **19c** (60.0 mg, 0.20 mmol), $P(Ph)_3$ (9.5 mg, 0.036 mmol), methyl acrylate (26.0 mg, 0.30 mmol, freshly distilled), NEt_3 (26.3 mg, 0.26 mmol), and $Pd(OAc)_2$ (1.0 mg, 0.004 mmol) in CH_3CN (4.0 ml) was heated in a sealed tube at 110—115°C for 13 h. The solvent was evaporated off *in vacuo* and the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as a developing solvent. Under a UV lamp, two bands were detected. Extraction from the upper band with CH_2Cl_2–MeOH (95: 5, v/v) gave 1-methoxycarbonylindole (**25**, 7.3 mg, yield 20.9%) as a colorless oil. Extraction from the fluorescent lower band with the same solvent gave **24** (35.5 mg, yield 68.8%) as crystals. **25**: MS *m/e*: 175 (M^+). IR ν_{max}^{film} cm^{-1}: 1740. NMR ($CDCl_3$) δ: 4.05 (3H, s), 6.56 (1H, dd, J=4.0 and 0.8 Hz), 7.11—7.61 (4H, m), 8.02—8.30 (1H, m). **24**: mp 126.5—127.5°C (colorless prisms, recrystallized from MeOH). MS *m/e*: 259 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1737, 1703. NMR ($CDCl_3$) δ: 3.83 (3H, s), 4.04 (3H, s), 6.53 (1H, d, J=16.0 Hz), 6.85 (1H, dd, J=4.0 and

0.8 Hz), 7.28 (1H, t, J=7.5 Hz), 7.50 (1H, dd, J=7.5 and 1.6 Hz), 7.66 (1H, d, J=4.0 Hz), 8.03 (1H, d, J=16.0 Hz), 8.22 (1H, ddd, J=7.5, 1.6, and 0.8 Hz). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.91; H, 4.97; N, 5.18.

4-(3-Hydroxy-3-methyl-1-buten-1-yl)indole (26) from 4-Iodo-1-methoxycarbonylindole (19c)——A mixture of **19c** (126.0 mg, 0.42 mmol), $P(Ph)_3$ (20.8 mg, 0.08 mmol), 2-methyl-3-buten-2-ol (56.9 mg, 0.66 mmol, freshly distilled), NEt_3 (64.0 mg, 0.63 mmol), and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol) in CH_3CN (4.0 ml) was heated in a sealed tube at 110—115°C for 16 h. The solvent was evaporated off *in vacuo* and the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent. Under a UV lamp, two bands were detected. Extraction from the upper band with CH_2Cl_2–MeOH (95: 5, v/v) gave 4-iodoindole (**20b**, 30.6 mg, yield 30.1%). Extraction from the lower band with the same solvent afforded **26** (39.3 mg, yield 46.7%) as crystals. mp 98.0—99.0°C (colorless prisms, recrystallized from benzene). MS m/e: 201 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3527, 3238, 1605. NMR ($CDCl_3$) δ: 1.50 (6H, s), 6.40 (1H, d, J=15.6 Hz), 6.61 (1H, dd, J=3.2 and 0.8 Hz), 6.93 (1H, d, J=15.6 Hz), 6.93—7.36 (4H, m). *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.71; H, 7.68; N, 6.69. Found: C, 77.58; H, 7.51; N, 6.96.

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