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The Chemistry of Indoles. XIII.[1] Syntheses of Substituted Indoles carrying an Amino, Nitro, Methoxycarbonyl, or Benzyloxy Group at the 4-Position and Their 1-Hydroxy Derivatives

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Various 1-hydroxyindoles carrying a nitro, methoxycarbonyl, or benzyloxy group at the 4 position were prepared by the controlled reduction of 6-substituted *trans*-β-dimethylamino-2-nitrostyrenes with either aqueous titanium(III) chloride or zinc in aqueous ammonium chloride. The stability of 4-substituted 1-hydroxyindoles decreased in the following order: 4-nitro-$\gg$4-methoxycarbonyl-$>$4-benzyloxy-1-hydroxyindole. This result clearly indicates that an electron-withdrawing group at the 4-position can stabilize the 1-hydroxyindole structure. It was also found that 4-hydroxy- and 4-benzyloxy-indole were readily accessible by the reduction of 6-benzyloxy-2-nitrophenyl acetaldehyde. A unique route to 4- or 7-aminoindole from cinnoline is also described.

Keywords——4-substituted indoles; 4-substituted 1-hydroxyindoles; 1-hydroxy-4-nitroindoles; 1-hydroxy-4-methoxycarbonylindoles; 4-benzyloxy-1-hydroxyindoles; titanium (III) chloride; N,N-dimethylformamide dimethyl acetal; nitrocinnolines; aminocinnolines; reductive ring contraction

A lot of attention has been devoted to syntheses of 1-hydroxyindoles[2] since the isolation of their derivatives from plants.[3] In connection with our interest in 4-substituted indoles[4] and 1-hydroxyindoles,[5] we have attempted to synthesize 4-substituted 1-hydroxyindoles (**1**) which are new members of 1-hydroxyindoles.[2] The best synthetic method for these compounds so far reported in the literature seems to be the controlled reduction of 6-substituted 2-nitrophenyl acetaldehydes (**2**) or their enamine derivatives (**3**). The latter compounds are now readily available by the reaction of activated methyl groups on aromatics with N,N-dimethylformamide acetal, as first discolsed by Meerwein *et al.*,[6] and later extended by various workers.[7] Although an attempt to obtain 2-nitrophenyl acetaldehyde (**2**, R=H) by the conversion of 2-nitrotoluene to an enamine with *tert*-butoxy-bis(dimethylamino)methane followed by hydrolysis, was unsuccessful,[2,8] we have found that the use of N,N-dimethylformamide dimethyl acetal (DMFDMA) as the enamination reagent gives either various 4-substituted 1-hydroxyindoles carrying such substituents as amino, benzyloxy, methoxycarbonyl, and nitro functions or the corresponding 4-substituted indoles. The present paper describes these results in detail.

I. Preparation of 4-Aminoindole, 4-Nitroindole, and Their 1-Hydroxy Derivatives

Treatment of 2,6-dinitrotoluene with DMFDMA in abs. N,N-dimethylformamide (DMF) afforded 90.9% yield of 2,6-dinitro-*trans*-β-dimethylaminostyrene (**3a**). The structure of **3a** was established mainly on the basis of its nuclear magnetic resonance (NMR) spectrum, in which two protons on the double bond of the enamine part appeared at δ 5.28 and 6.41 as two sets of doublets (J=14 Hz), indicating *trans* geometry. When the mother liquor of **3a** was subjected to column chromatography on silica gel, 2,6-dinitrophenyl acetaldehyde (**2a**) was obtained in 2.2% yield. This result suggested that **3a** could be converted into **2a** under mild acidic conditions. Taking this into consideration, we chose titanium(III) chloride as a suitable reducing agent for **3a**, because the reagent can reduce nitro groups[9] and the reduction level was expected to be controllable by regulation of its amount. Furthermore, its acidic nature should catalyze the hydrolysis of **3a** to **2a** and promote intramolecular cyclization of the latter to give the desired product **1a**.

The above expectation was realized by the reaction of **3a** in aqueous acetic acid with titanium (III) chloride[9] to produce 4-nitroindole[10] (**4a**), 4-aminoindole[11] (**4b**), 1-hydroxy-4-nitroindole (**1a**), or 1-hydroxy-4-nitrooxyindole (**5a**) in various yields, depending on the reaction conditions. The results are summarized in Table I. With 12 mol eq. of titanium(III) chloride, which was sufficient to reduce two nitro groups at the same time, 4-aminoindole (**4b**) was obtained in 83.5% yield (entry 1). Theoretically, 4 mol eq of the reagent is needed to produce 1-hydroxy-4-nitroindole (**1a**), and indeed **1a** was formed predominantly under these conditions (entry 4). Although the use of 6 mol eq of titanium(III) chloride was expected to give 4-nitroindole (**4a**), **1a** was still the major product, with only a 7.9% yield of **4a** (entry 3).

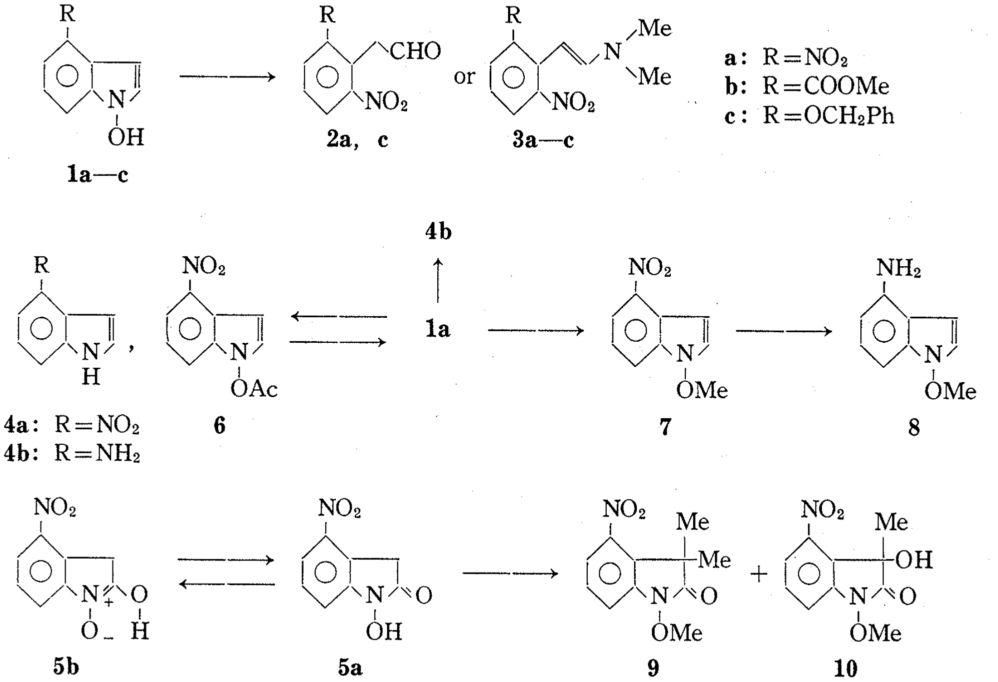
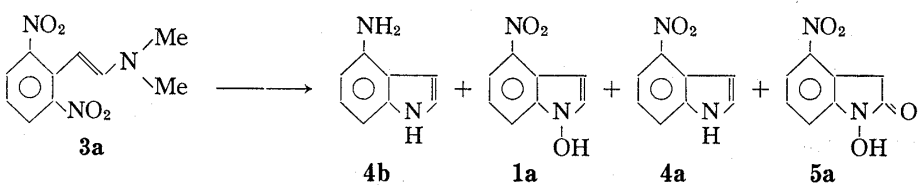


Chart 1

Table I. Reduction of 2,6-Dinitro-*trans*-β-dimethylaminostyrene with Titanium (III) Chloride[a)]



Entry	$TiCl_3$ (mol eq)	Solvent	Yield (%) 4b	1a	4a	5a
1	12	AcOH–H_2O (2: 1, v/v)	83.5	0	0	0
2	8	AcOH–H_2O (2: 1, v/v)	41.8	21.9	6.3	1.3
3	6	AcOH–H_2O (2: 1, v/v)	5.6	36.2	7.9	8.3
4	4	AcOH–H_2O (2: 1, v/v)	2.8	56.8	13.1	15.9
5	4	MeOH	3.6	47.3	31.3	5.6
6	6	MeOH	15.8	27.0	25.7	1.9

a) Reduction was carried out at room temperature for 7 min.

The yield of **4a** decreased to 6.3% and that of **4b** increased to 41.8% when 8 mol eq of the reagent was reacted. Change of the solvent system from aqueous acetic acid to methanol had a marked effect on the product distributions (entries 5 and 6). Thus, the yield of **4a** was increased to 31.3% by using 4 mol eq of the reagent, though **1a** was still the major product.

The structure of **4a** was established by comparing its melting point and spectral data with the reported values.[10] Confirmation was provided by the reaction of **4a** with 6 mol eq of titanium(III) chloride, which resulted in the formation of **4b** in 89.3% yield.

Compound **1a** gave acceptable combustion and mass data, and its structure was determined to be 1-hydroxy-4-nitroindole as follows: **1a** showed absorptions at 3140, 1520, and 1326 cm^{-1} in its infrared (IR) spectrum, suggesting the presence of both hydroxyl and nitro groups. Its NMR and ultraviolet (UV) spectra were quite similar in pattern to those of 4-nitroindole. All these data indicated a 1-hydroxyindole structure for **1a**. Therefore, characteristic reactions of 1-hydroxyindoles[2] were carried out to confirm its structure. Treatment of **1a** with either acetic anhydride–pyridine or methyl iodide in methanolic sodium hydroxide afforded 1-acetoxy-4-nitroindole (**6**) or 1-methoxy-4-nitroindole (**7**) in 84.2% or 97.4% yield, respectively. The IR spectrum of **6** exhibited absorption at 1809 cm^{-1}, ascribable to a 1-acetoxy group, and the mass fragmentation patterns of **6** and **7** were similar to those of the corresponding 1-hydroxyindole derivatives.[2] Hydrolysis of **6** in methanolic sodium hydroxide proceeded smoothly and **1a** was regenerated in 80.3% yield. Finally, reduction of **1a** with 8 mol eq of titanium(III) chloride afforded **4b** in quantitative yield.

The structure of **5a** was assigned on the basis of its elemental analysis, mass, and other spectral data. Thus, in its NMR spectrum, 3-methylene protons appeatred as a singlet at δ 3.89 (in pyridine-d_5) which, in accordance with its expected highly acidic nature, disappeared on addition of deuterium oxide. Due to its insolubility to various solvents, the IR spectrum was determined in the solid state. Strong absorption were seen at 1734 and 1678 cm^{-1}. A contribution of a tautomeric form such as **5b** might be considered to explain the latter absorption. Although **5a** dissolved in an alkaline medium, giving a violet color, and decomposed gradually, methylation with an excess of methyl iodide in methanolic sodium hydroxide procceded smoothly to give 1-methoxy-3,3-dimethyl-4-nitrooxyindole (**9**) and 3-hydroxy-1-methoxy-3-methyl-4-nitrooxyindole (**10**) in yields of 56.9% and 20.4%, respectively. Their IR spectra showed ordinary carbonyl absorptions at around 1725 cm^{-1} (Chart 1).

The structure of 4-aminoindole (**4b**) was determined by comparison of its melting point and spectral data with those of an authentic sample prepared as described below.

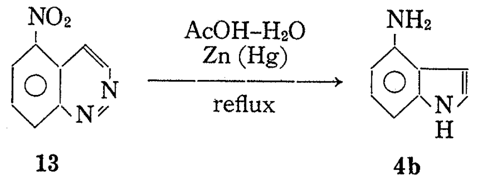
Reduction of 1-methoxy-4-nitroindole (**7**) with 6 mol eq of titanium(III) chloride afforded a 91.3% yield of 4-amino-1-methoxyindole (**8**), whose high resolution mass spectrum (MS) supported the assigned structure. Furthermore, its IR spectrum lacked nitro group absorption, but showed absorption bands ascribable to a primary amino group at around 3340 cm^{-1}. In its NMR spectrum, methoxy protons were observed at δ 3.94 in addition to amino protons at δ 3.55. This compound was found to be quite unstable and changed rapidly to a violet intractable tar on standing.

II. An Alternative Preparation of 4-Aminoindole together with 7-Aminoindole

We have already found that 1-aminoindole (**11**), which can be derived in 96.3% yield from indole,[12] affords cinnoline in 89.0% yield upon acid treatment in the presence of nitrobenzene.[13] Nitration of cinnoline, which is now readily available by the above procedure, with concd. nitric acid in concd. sulfuric acid at 75° afforded 5- and 8-nitrocinnolines (**13**[14] and **14**) in yields of 35.1%, and 43.7%, respectively. 3-Hydroxy-5-nitrocinnoline (**15**) was obtained in a small amount (0.5%) as a by-product. Elevation of the reaction temperature to 130° resulted in reduced yields of the nitrocinnolines.

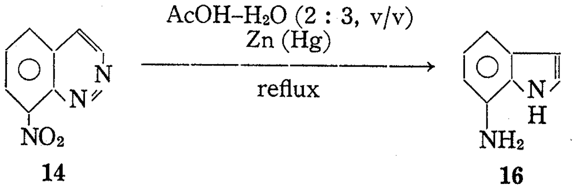
It has been reported that 4-alkyl- or 4-arylcinnolines are transformed to the corresponding 3-substituted indoles by the action of amalgamated zinc.[15] By applying this cinnoline–indole conversion procedure, **13** was converted by treatment with amalgamated zinc in aqueous

Table II. Preparation of 4-Aminoindole



Solvent	Reaction time (hr)	Zinc (mol eq)	Yield (%) of **4b**
AcOH–H_2O (1: 2, v/v)	12	78	4.3
AcOH–H_2O (1: 2, v/v)	3	20	7.6
AcOH–H_2O (2: 3, v/v)	0.5	20	40.2
AcOH–H_2O (2: 3, v/v)	0.25	21	65.8

Table III. Preparation of 7-Aminoindole



Reaction time (hr)	Zinc (mol eq)	Yield (%) of **16**
2	22	49.3
1.5	20	74.7
0.5	20	64.1

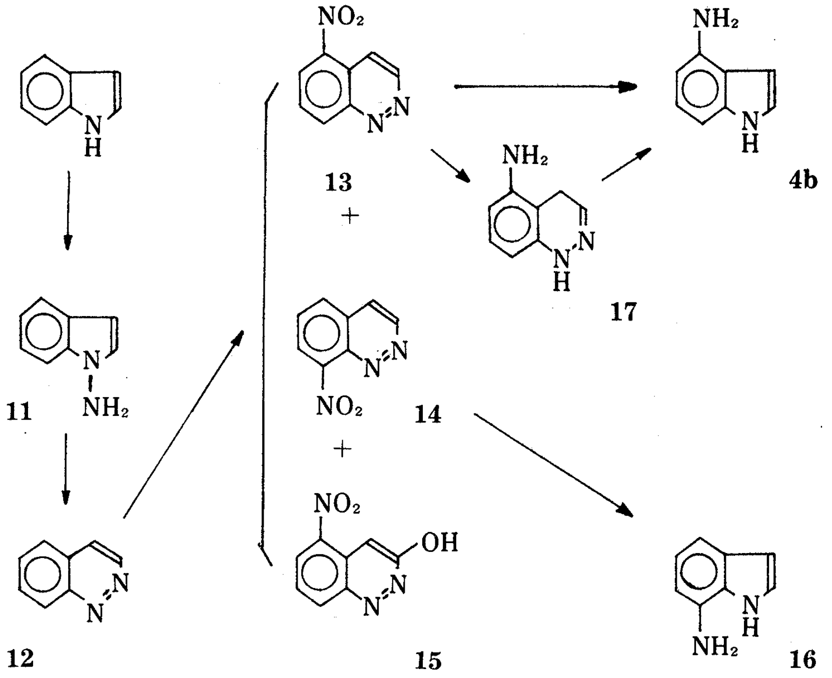


Chart 2

acetic acid into 4-aminoindole (**4b**) in 65.8% yield (optimal yield). Similarly, **14** was converted into 7-aminoindole[16] (**16**) in 74.7% yield. In these ring contraction reactions, the reduction of nitro functions proceeded concomitantly. The yields of the aminoindoles varied with the solvent system, reaction time, and amount of zinc, as summarized in Tables II and III. By the above four-step procedure, **4b** and **16** were obtained in overall yields of 19.7% and 27.9%, respectively, from indole (Chart 2).

In an attempt to improve the overall yield, reduction of **13** was carried out with titanium (III) chloride[9] to afford 5-amino-1,4-dihydrocinnoline[17] (**17**) in quantitative yield. Treatment of **17** with amalgamated zinc as above afforded **4b** in 85.1% yield. By this five-step alternative procedure, the overall yield of **4b** from indole was raised to 25.5%.

Although the overall yield is still inferior to that obtained by the reaction of 2,6-dinitrotoluene with DMFDMA followed by reduction with titanium (III) chloride, this reaction sequence for 4-substituted indoles from cinnoline offers a unique method for the introduction of a substituent into the 5 position of the latter.

III. Preparation of 4-Benzyloxyindole, 4-Benzyloxy-1-hydroxyindole, and Related Compounds

2-Benzyloxy-6-nitrotoluene[18] (**18**) was successfully converted by treatment with DMFDMA in abs. DMF into 2-benzyloxy-6-nitro-*trans*-β-dimethylaminostyrene (**3c**). The NMR spectrum of **3c** showed two sets of doublets at δ 5.09 and 7.21 (J=13.5 Hz), establishing

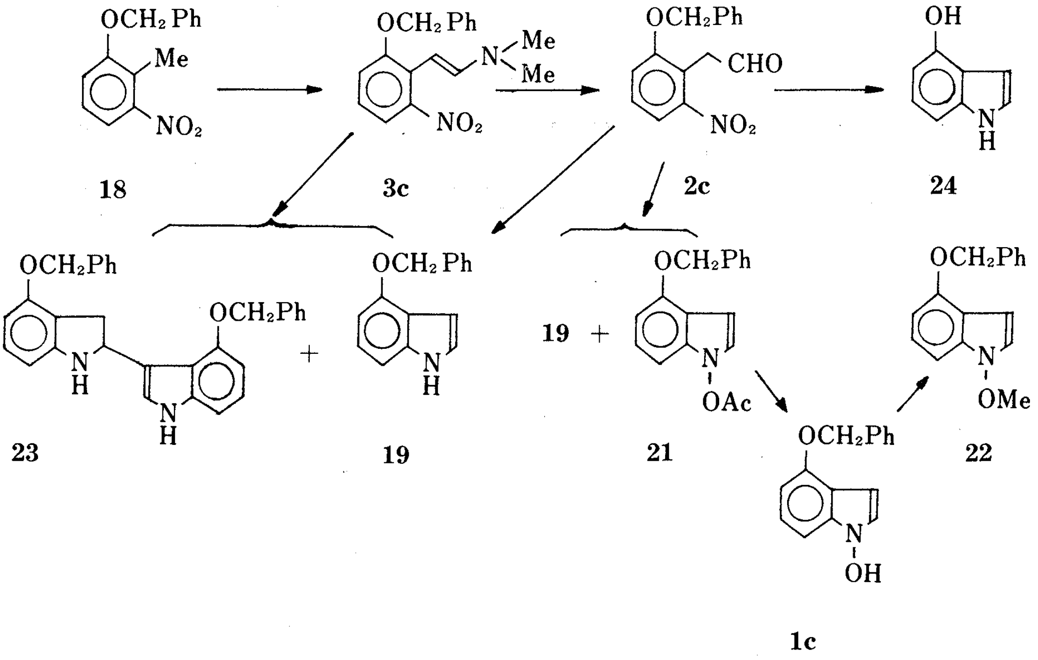
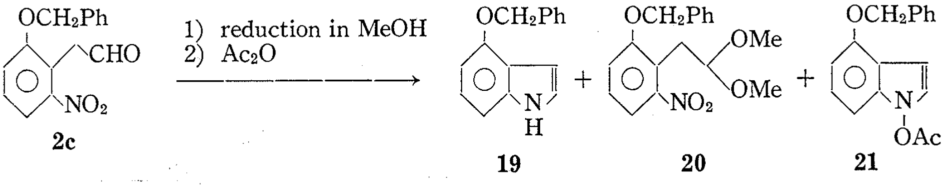


Chart 3

Table IV. Preparation of 1-Acetoxy-4-benzyloxyindole

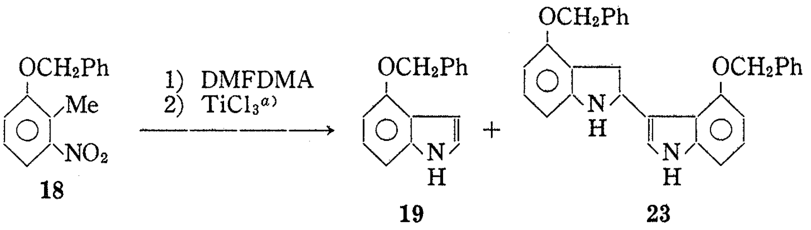


Reducing agent	Overall yield (%)		
	19	**20**	**21**
$TiCl_3$ (4 mol eq)	13.5	12.3	23.9
Zn/NH_4Cl	19.6	0	23.4

trans geometry of the enamine double bond. Because of its unstable nature, further reactions were carried out immediately on the crude product obtained after removal of DMF and DMFDMA from the above reaction mixture by evaporation. Thus, **3c** (crude) was hydrolyzed by the action of silica gel in a mixture of water and methylene chloride to 2-benzyloxy-6-nitrophenyl acetaldehyde (**2c**) in 83.6% yield (Chart 3). Compound **2c** was reduced with 4 mol eq of titanium(III) chloride, and subsequent acetylation with acetic anhydride–pyridine gave 4-benzyloxyindole[18] (**19**), 2-benzyloxy-6-nitrophenyl acetaldehyde dimethyl acetal (**20**), and 1-acetoxy-4-benzyloxyindole (**21**). Compound **21** showed a characteristic absorption band at 1815 cm^{-1} in its IR spectrum. The structure of **20** was determined based on its spectral data. In order to obtain a hydroxylamine by reducing a nitro group, zinc in aqueous ammonium chloride solution has usually been used.[2,3] Therefore, this reagent was also examined. Both reducing agents were found to give almost the same results, as shown in Table IV.

Treatment of **21** with methanolic sodium hydroxide solution produced a single product (**1c**, checked by thin–layer chromatography) which was too unstable to isolate. The following result, however, indicated it to be 4-benzyloxy-1-hydroxyindole (**1c**). Thus, immediately after the alkaline hydrolysis of **21**, an excess of methyl iodide was added to the reaction mixture to give 4-benzyloxy-1-methoxyindole (**22**) in 76.9% yield. An attempt to reduce **21** into **19** with titanium(III) chloride did not yield the desired product, but the starting material was recovered in almost quantitative yield. These results clearly indicate that titanium (III) chloride could not reduce benzyloxy, N-methoxy, and N-acetoxy groups[19] under our modified reaction conditions.

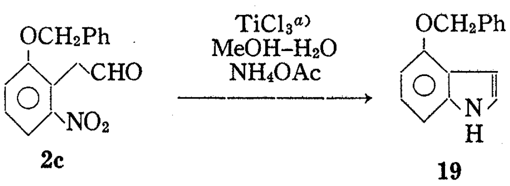
Table V. Preparation of 4-Benzyloxyindole



Reduction conditions		Overall yield (%)	
Solvent	Time (min)	**19**	**23**
AcOH	15	6.7	44.7
H_2O–AcOH (3: 7, v/v)	7	13.4	30.2
H_2O–MeOH[b)] (1: 9, v/v)	7	50.8	Trace

a) 6.5 mol eq of $TiCl_3$ was used.
b) The reaction was carried out in the presence of NH_4OAc (19.5 mol eq).

Table VI. Preparation of 4-Benzyloxyindole



NH_4OAc (mol eq to $TiCl_3$)	Yield (%) of **19**
3	59.6
4	74.9

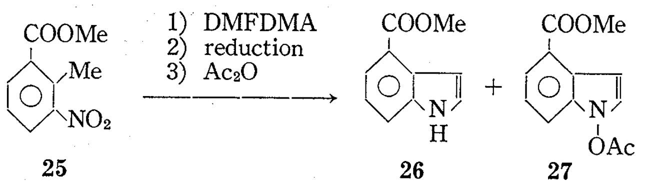
a) 6.5 Mol eq of $TiCl_3$ was used.

It was also found that **2c** and **3c** were both reduced with 6.5 mol eq of titanium(III) chloride to afford 4-benzyloxyindole (**19**). When the acidity of the solvent system was increased, dimerization of **19** was enhanced to give 4-benzyloxy-2-(4-benzyloxyindol-3-yl)-2,3-dihydroindole (**23**). To prevent this undesired reaction, various amounts of ammonium acetate were examined as a buffer; the resulting yields of **19** are summarized in Tables V and VI. On the other hand, catalytic hydrogenation of **2c** afforded 4-hydroxyindole[18] (**24**) in 67.7% yield.

IV. Preparation of 4-Methoxycarbonylindole, 1-Hydroxy-4-methoxycarbonylindole, and Their Derivatives

2-Methoxycarbonyl-6-nitro-*trans*-*β*-dimethylaminostyrene (**3b**) was prepared from methyl 2-methyl-3-nitrobenzoate (**25**) by the procedure of Ponticello *et al.*[20] Although we have already reported the formation of 4-methoxycarbonylindole[7] (**26**) in 73.6% overall yield from **25** *via* **3b** by the reaction with 7 mol eq of titanium(III) chloride, controlled reduction of **3b** was achieved by using 4 mol eq of the reagent. Subsequent acetylation with acetic anhydride–pyridine afforded 1-acetoxy-4-methoxycarbonylindole (**27**) and **26** in yields of 18.8% and 13.0%, respectively. When zinc in aqueous ammonium chloride solution was used as the reducing agent, **27** and **26** were produced in yields of 39.9% and 1.3%, respectively, as shown in Table VII. In this case, zinc is apparently superior to titanium(III) chloride for providing **27**, though the optimum reaction conditions with the latter reagent were not determined.

Table VII. Preparation of 1-Acetoxy-4-methoxycarbonylindole



Reducing agent	Overall yield (%)	
	26	**27**
$TiCl_3$ 3.5 mol eq	13.0	18.8
$TiCl_3$ 4.0	12.2	14.1
Zn/NH_4Cl	1.3	39.9

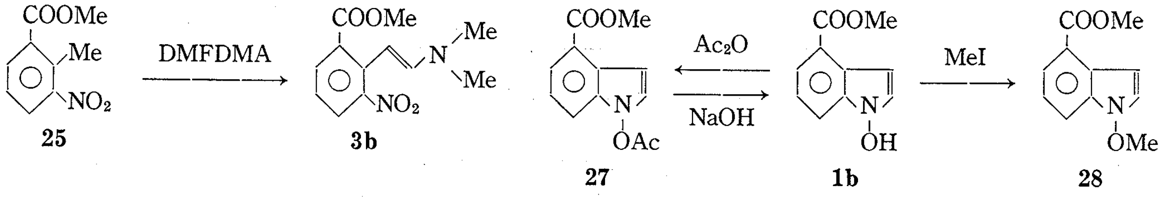


Chart 4

Hydrolysis of **27** with aqueous sodium hydroxide afforded a 64.9% yield of **1b**, which had an additional oxygen atom but a quite similar NMR signal pattern compared with **27**. Acetylation of **1b** with acetic anhydride–pyridine gave a 43.1% yield of **27**, whose IR spectrum exhibited a characteristic absorption band at 1802 cm^{-1}, ascribable to a 1-acetoxy group. 1-Methoxy-4-methoxycarbonylindole (**28**) was prepared in 78.4% yield from **1b** by treatment with methyl iodide in methanolic sodium hydroxide (Chart 4).

In general, 1-hydroxyindoles are known to be unstable unless they carry either an electron withdrawing group in the five-membered ring or a bulky group at the 2 position.[2,3] However 4-nitro-1-hydroxyindole derivatives, such as **1a**, **6**, and **7**, were stable compounds. The stability of 4-substituted 1-hydroxyindoles, synthesized for the first time in the present work, was found to decrease in the following order: 4-nitro-$\gg$4-methoxycarbonyl-$>$4-benzyloxy-1-hydroxyindole. These results clearly indicate that the presence of an electron-withdrawing substituent at the 4 position can also stabilize the 1-hydroxyindole structure.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. 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. N,N-Dimethylformamide dimethyl acetal (DMFDMA) was purchased from Aldrich Chemical Co., Inc. and used without further purification. Commercial aq. titanium (III) chloride (16%, $d=1.5$, from Kanto Chemical Co., Inc.) was used throughout the present study. Preparative thin-layer chromatography (p-TLC) was performed on Merck Aluminium oxid GF_{254} (Al_2O_3) or Kiesel-gel GF_{254} (Type 60) (SiO_2).

2,6-Dinitro-*trans*-β-dimethylaminostyrene (3a) from 2,6-Dinitrotoluene——A solution of 2,6-dinitrotoluene (2.315 g) in abs. N,N-dimethylformamide (DMF, 7.0 ml) and DMFDMA (3.028 g) was refluxed for 9 hr. The solvent was evaporated off *in vacuo*, and the resultant reddish-black oil was treated with CH_2Cl_2–hexane (1: 1, v/v, 10 ml). The residue gradually changed into dark-red prisms, which were collected by filtration, washed with H_2O–MeOH (1: 1, v/v), and dried to yield **3a** (2.739 g, 90.9%). mp 96—97°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1618, 1592, 1515, 1344. NMR ($CDCl_3$) δ: 2.84 (6H, s), 5.28 (1H, d, $J=14$ Hz), 6.41 (1H, d, $J=14$ Hz), 7.00 (1H, d.d, $J=7$ and 9 Hz), 7.62 (1H, d, $J=7$ Hz), 7.63 (1H, d, $J=9$ Hz). MS *m/e*: 237 (M^+).

The filtrate and the washings were combined and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil, which was chromatographed on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as an eluent to afford **2a** (59.0 mg, 2.2%). Recrystallization from MeOH afforded pale yellow prisms. mp 123—124°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1723, 1524, 1340. NMR ($CDCl_3$) δ: 4.25 (2H, s), 7.56 (1H, d.d, $J=7$ and 9 Hz), 8.10 (1H, d, $J=7$ Hz), 8.11 (1H, d, $J=9$ Hz), 9.67 (1H, s). MS *m/e*: 210 (M^+).

4-Aminoindole (4b), 1-Hydroxy-4-nitroindole (1a), 4-Nitroindole (4a), and 1-Hydroxy-4-nitrooxyindole (5a) from 2,6-Dinitro-*trans*-β-dimethylaminostyrene (3a)——General Procedure: An appropriate amount of aq. $TiCl_3$ was added to a solution of **3a** in AcOH–H_2O (2: 1, v/v) as a single portion. The mixture was stirred for 7 min at room temperature, then H_2O was added and the whole was extracted with MeOH–CH_2Cl_2 (1: 9, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under a reduced pressure to leave an oil, which was subjected to p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent. Under a UV lamp, three dark bands were detected on the whole luminescent plate. Extraction from the upper band with MeOH–CH_2Cl_2 (5: 95, v/v) afforded **4a**. Using the same solvent, **1a** or **5a** was extracted from the middle or lower band, respectively. The water layer and the washings of the organic layer were combined and the mixture was basified with 30% aq. NaOH. After addition of concd. aq. NH_3, the whole was extracted with MeOH–CH_2Cl_2 (1: 9, v/v), washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to give an oil. Subsequent purification by p-TLC on Al_2O_3 with CH_2Cl_2 as a developing solvent gave **4b**.

i) Entry 1: In the above procedure, 106.5 mg of **3a**, 6.0 ml of AcOH–H_2O (2: 1, v/v), and 3.50 ml (12 mol eq) of aq. $TiCl_3$ were used. After work-up and subsequent p-TLC, as described above, **4b** (49.5 mg, 83.5%) was obtained. mp 106—108.5° (lit.[11] mp 105—107°). All spectral data were identical with those of the reported 4-aminoindole. The structure of **4b** was confirmed by preparing 4-acetamidoindole (mp 156.5—157.5°, lit.[11] mp 154—156°) by treatment of **4b** with Ac_2O–pyridine.

ii) Entry 4: In the general procedure, 108.0 mg of **3a**, 4.50 ml of AcOH–H_2O (2: 1, v/v), and 1.17 ml (4 mol eq) of aq. $TiCl_3$ were used. After work-up and subsequent p-TLC, as described above, **4a** (9.7 mg, 13.1%), **1a** (46.1 mg, 56.8%), **5a** (14.1 mg, 15.9%), and **4b** (1.7 mg, 2.8%) were obtained. **4a**: mp 206—207° (yellow prisms, recrystallized from MeOH–H_2O). Lit.[10] mp 205—206°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1508, 1313. NMR (10% CD_3OD in $CDCl_3$) δ: 7.12 (1H, t, $J=8$ Hz), 7.17 (1H, d, $J=3.2$ Hz), 7.41 (1H, d, $J=3.2$ Hz), 7.70 (1H, d, $J=8$ Hz), 8.06 (1H, d, $J=8$ Hz). MS *m/e*: 162 (M^+). **1a**: mp 154—156° (dec., orange prisms, recrystallized from MeOH–H_2O). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3140, 1520, 1326, 1308. NMR (10% CD_3OD in $CDCl_3$) δ: 6.93 (1H, d.d, $J=3.2$ and 1 Hz), 7.15 (1H, t, $J=8$ Hz), 7.40 (1H, d, $J=3.2$ Hz), 7.72 (1H, d.t, $J=8$ and 1 Hz), 8.00 (1H, d.d, $J=8$ and 1 Hz). MS *m/e*: 178 (M^+), 162 (M^+-16). *Anal.* Calcd for $C_8H_6N_2O_3$: C, 53.93; H, 3.40; N, 15.73. Found: C, 54.10; H, 3.30; N, 15.61. **5a**: mp 226—229° (dec., colorless prisms, recrystallized from MeOH–H_2O). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3060, 1734, 1678, 1630, 1520, 1345. IR (CH_2Cl_2–MeOH, 1: 1, v/v) cm^{-1}: 1728, 1700 (sh.), 1632. NMR (pyridine-d_5) δ: 3.89 (2H, s, disappeared on addition of D_2O), 7.32 (1H, d, $J=6$ Hz), 7.34 (1H, d, $J=4$ Hz), 7.67 (1H, q, $J=4$ and 6 Hz). MS *m/e*: 194 (M^+), 178 (M^+-16). *Anal.* Calcd for $C_8H_6N_2O_4$: C, 49.47; H, 3.12; N, 14.43. Found: C, 49.53; H, 3.05; N, 14.28.

iii) Entry 2: In the general procedure, 111.0 mg of **3a**, 4.50 ml of AcOH–H_2O (2: 1, v/v), and 1.75 ml (6 mol eq) of aq. $TiCl_3$ were used. After work-up and subsequent p-TLC, as described above, **4a** (6.0 mg, 7.9%), **1a** (30.2 mg, 36.2%), **5a** (7.6 mg, 8.3%), and **4b** (3.5 mg, 5.6%) were obtained.

iv) Entry 3: In the general procedure, 102.6 mg of **3a**, 4.50 ml of AcOH–H_2O (2: 1, v/v), and 2.22 ml (8 mol eq) of aq. $TiCl_3$ were used. After work-up and subsequent p-TLC, as described above, **4a** (3.6 mg, 6.3%), **1a** (15.4 mg, 21.9%), **5a** (1.1 mg, 1.3%), and **4b** (23.9 mg, 41.8%) were obtained.

v) Entry 5: Aq. $TiCl_3$ (11.7 ml, 4 mol eq.) was added to a stirred solution of **3a** (1.012 g) in MeOH (35.0 ml) as a single portion. The mixture was stirred for 7 min, then CH_2Cl_2 (250 ml) and solid NaCl were added. The organic layer was separated and the water layer was further extracted with CH_2Cl_2. The combined organic layer was worked up as described in the general procedure. The water layer was basified with 30% aq. NaOH and worked up as described in the general procedure. **4a** (216.7 mg, 31.3%), **1a** (359.4 mg, 47.3%), **5a** (46.5 mg, 5.6%), and **4b** (29.5 mg, 3.6%) were obtained.

vi) Entry 6: Aq. $TiCl_3$ (1.70 ml, 6 mol eq) was added to a stirred solution of **3a** (105.5 mg) in MeOH (3.5 ml) as a single portion. After work-up as described in item v, **4a** (18.5 mg, 25.7%), **1a** (21.4 mg, 27.0%), **5a** (1.7 mg, 1.9%), and **4b** (9.3 mg, 15.8%) were obtained.

1-Acetoxy-4-nitroindole (6) from 1-Hydroxy-4-nitroindole (1a)——A solution of **1a** (46.1 mg) in abs. pyridine (2.0 ml) and Ac_2O (1.0 ml) was stirred for 4 hr at room temperature. The solvent was evaporated off under reduced pressure, and the residue was extracted with CH_2Cl_2, washed with aq. $NaHCO_3$, then with H_2O, dried over Na_2SO_4, and concentrated to give pure **6** (47.9 mg, 84.2%). Recrystallization from MeOH–H_2O gave yellow prisms. mp 70—70.5°. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1809, 1509, 1332. NMR (CCl_4) δ: 2.36 (3H, s), 7.06 (1H, d, $J=3.2$ Hz), 7.09 (1H, t, $J=7.6$ Hz), 7.19 (1H, d, $J=3.2$ Hz), 7.33 (1H, br.d, $J=7.6$ Hz), 7.94 (1H, d.d, $J=7.6$ and 1.5 Hz). MS *m/e*: 220 (M^+), 178 ($M^+-C_2H_2O$), 162 ($M^+-C_2H_2O_2$).

Hydrolysis of 1-Acetoxy-4-nitroindole (6) to 1-Hydroxy-4-nitroindole (1a)——A solution of **6** (22.0 mg) in MeOH (4.0 ml) and 30% aq. NaOH was refluxed for 2 hr. The solvent was evaporated off, and the residue was acidified with 2 N HCl. The whole was extracted with MeOH–CH_2Cl_2 (5: 95, v/v), washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave **1a** as yellow prisms (14.3 mg, 80.3%).

1-Methoxy-4-nitroindole (7) from 1-Hydroxy-4-nitroindole (1a)——A solution of methyl iodide (180 mg) in MeOH (0.5 ml) was added to a solution of **1a** (20.0 mg) in MeOH (1.0 ml) and 2 N NaOH (0.5 ml). The mixture was stirred for 16 hr at room temperature, then H_2O (5.0 ml) and CH_2Cl_2 (10 ml) were added. The organic layer was separated and the water layer was further extracted with CH_2Cl_2. The combined extracts was washed with H_2O, dried over Na_2SO_4, and concentrated to give **7** (21.0 mg, 97.4%). Recrystallization from MeOH–H_2O afforded yellow needles. mp 82.5—83.0°. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1515, 1316. NMR ($CDCl_3$) δ: 4.10 (3H, s), 7.01 (1H, d, $J=3.2$ Hz), 7.20 (1H, t, $J=8$ Hz), 7.42 (1H, d, $J=3.2$ Hz), 7.68 (1H, d, $J=8$ Hz), 8.07 (1H, d, $J=8$ Hz), MS *m/e*: 192 (M^+), 177 (M^+-CH_3), 162 (M^+-CH_2O). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.16; H, 4.07; N, 14.54.

1-Methoxy-3,3-dimethyl-4-nitrooxyindole (9) and 3-Hydroxy-1-methoxy-3-methyl-4-nitrooxyindole (10) from 1-Hydroxy-4-nitrooxyindole (5a)——A stirred solution of **5a** (44.0 mg) and methyl iodide (0.5 ml) in MeOH (4.0 ml) was treated with 2 N NaOH (2.0 ml) under an argon atmosphere. The reaction mixture was stirred for 2 hr at room temperature, then the solvent was evaporated off under reduced pressure. The residue was diluted with H_2O and the whole 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 as a developing solvent. Under a UV lamp, two dark bands were detected on the whole luminescent plate. Extraction of the upper band with MeOH–CH_2Cl_2 (5: 95, v/v) afforded **9** (30.5 mg, 56.9%). Extraction from the lower band with the same solvent gave **10** (11.0 mg, 20.4%). **9**: mp 118—119° (pale yellow prisms, recrystallized from MeOH–H_2O). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1722, 1620, 1536, 1348. NMR (CCl_4) δ: 1.54 (6H, s), 3.96 (3H, s), 7.08 (1H, d.d, $J=7$ and 2 Hz), 7.32 (1H, t, $J=7$ Hz), 7.61 (1H, d.d, $J=7$ and 2 Hz). MS *m/e*: 236 (M^+), 206 (M^+-CH_2O). *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.90; H, 5.02; N, 11.67. **10**: mp 121.5—122.5° (colorless prisms, recrystallized from benzene). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 3380, 1730, 1618, 1523, 1343. NMR ($CDCl_3$) δ: 1.76 (3H, s), 4.02 (3H, s), 3.56—4.16 (1H, br., O$\underline{\mathrm{H}}$), 7.23 (1H, d.d, $J=8$ and 2 Hz), 7.46 (1H, t, $J=8$ Hz), 7.77 (1H, d.d, $J=8$ and 2 Hz). MS *m/e*: 238 (M^+), 210 (M^+-CO), 207 (M^+-CH_3O). *Anal.* Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.66; H, 4.10; N, 11.79.

4-Aminoindole (4b) from 1-Hydroxy-4-nitroindole (1a)——Aq. $TiCl_3$ (0.67 ml, 8 mol eq) was added to a stirred solution of **1a** (23.0 mg) in AcOH–H_2O (2: 1, v/v, 4.5 ml) as a single portion. The mixture was stirred for 7 min at room temperature, then made basic by adding 30% aq. NaOH. Concd. aq. NH_3 was added and the whole was extracted with MeOH–CH_2Cl_2 (5: 95, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to give **4b** as colorless prisms (17.1 mg, 99.6%).

4-Aminoindole (4b) from 4-Nitroindole (4a)——To a solution of **4a** (26.8 mg) in MeOH (2.5 ml), NH_4OAc (305.0 mg, 16 mol eq) and H_2O (0.1 ml) were added. Aq. $TiCl_3$ (0.64 ml, 4 mol eq) was added to the mixture as a single portion and stirring was continued for 7 min at room temperature. The whole was made basic by adding 2 N NaOH and extracted with CH_2Cl_2. The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave **4b** as colorless prisms (19.5 mg, 89.3%).

4-Amino-1-methoxyindole (8) from 1-Methoxy-4-nitroindole (7)——NH_4OAc (135.0 mg, 26 mol eq) and H_2O (0.1 ml) were added to a solution of **7** (13.0 mg) in MeOH (1.0 ml). Aq. $TiCl_3$ (0.28 ml, 6.5 mol eq) was added to the mixture as a single portion and the whole was stirred for 5 min at room temperature. The reaction mixture was made basic by adding 2 N NaOH, and 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 dissolved in CCl_4. The solution was filtered and the filtrate was concentrated to leave pure **8** (pale pink oil, 10.1 mg, 91.3%). On standing, **8** changed gradually into a reddish-violet tar. From this violet tar, unchanged **8** could be extracted with CCl_4. **8**: IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3340, 1615, 1579. NMR (CCl_4) δ: 3.55 (2H, br.s, NH_2), 3.94 (3H, s), 6.00 (1H, d, *J*=4 Hz), 6.09 (1H, d.d, *J*=7.5 and 2 Hz), 6.65 (1H, t, *J*=7.5 Hz), 6.75 (1H, d.d, *J*=7.5 and 2 Hz), 6.90 (1H, d, *J*=4 Hz). High resolution MS *m/e*: 162.076 (M^+, Calcd for $C_9H_{10}N_2O$: 162.079), 147.056 (M^+-CH_3, Calcd for $C_8H_7N_2O$: 147.057), 132.069 (M^+-CH_2O, Calcd for $C_8H_8N_2$: 132.069), 131.061 (M^+-CH_3O, Calcd for $C_8H_7N_2$: 131.061).

2-Benzyloxy-6-nitro-*trans*-*β*-dimethylaminostyrene (3c) from 2-Benzyloxy-6-nitrotoluene (18)——A solution of **18** (2.002 g) in abs. DMF (20.0 ml) and DMFDMA (2.980 g, 3 mol eq) was heated under reflux for 30 hr. After removal of the solvent *in vacuo*, crude **3c** (2.718 g) was obtained as a red oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1673, 1608, 1588, 1508, 1370. NMR (CCl_4) δ: 2.64 (6H, s), 4.92 (2H, s), 5.09 (1H, d, *J*=13.5 Hz), 7.21 (1H, d, *J*=13.5 Hz), 6.61—7.39 (3H, m), 7.22 (5H, br.s). MS *m/e*: 298 (M^+), 281, 207 ($M^+-CH_2C_6H_5$). This crude **3c** was used for further reactions without purification.

2-Benzyloxy-6-nitrophenyl Acetaldehyde (2c) from 2-Benzyloxy-6-nitro-*trans*-*β*-dimethylaminostyrene (3c)——Silica gel (10.004 g, Kanto Chemical Co. Inc., 100—200 mesh) was added to a solution of **3c** (1.083 g) [prepared from **18** (807.9 mg)] in CH_2Cl_2 (90.0 ml) and H_2O (10.0 ml), and the mixture was stirred for 4 hr in two phases at room temperature. Silica gel was removed by filtration and washed with CH_2Cl_2. The combined CH_2Cl_2 layer was dried and concentrated to give an oil. Subsequent column chromatography on the silica gel with CH_2Cl_2–hexane (1: 1, v/v) as an eluent afforded **2c** (752.8 mg, 83.6%) as a colorless, relatively unstable oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2820, 2720, 1725, 1525, 1345. NMR ($CDCl_3$) δ: 4.04 (2H, d, *J*=0.8 Hz), 5.05 (2H, s), 7.07 (1H, d.d, *J*=7 and 2.5 Hz), 7.26 (5H, s), 6.96—7.60 (1H, m), 7.51 (1H, d.d, *J*=6.5 and 2.5 Hz), 9.61 (1H, t, *J*=0.8 Hz). MS *m/e*: 271 (M^+), 242 (M^+-CHO).

1-Acetoxy-4-benzyloxyindole (21), 4-Benzyloxyindole (19), and 2-Benzyloxy-6-nitrophenyl Acetaldehyde Dimethyl Acetal (20) from 2-Benzyloxy-6-nitrophenyl Acetaldehyde (2c)——i) Aq. $TiCl_3$ (0.75 ml, 4 mol eq) was added to a solution of **2c** (76.5 mg) in MeOH (7.0 ml) as a single portion. The mixture was stirred for 5 min, then H_2O (10.0 ml) was added and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil. The oil was dissolved in Ac_2O (1.5 ml) and pyridine (3.0 ml) and the solution was stirred for 8 hr at room temperature. The solvent was then removed *in vacuo*. The residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (7: 5, v/v). Under a UV lamp, three dark bands were detected on the whole luminescent plate. Extraction of the upper band with CH_2Cl_2–MeOH (95: 5, v/v) afforded **21** (19.0 mg, 23.9%). Extraction with the same solvent from the middle band or lower band gave **19** (8.5 mg, 13.5%) or **20** (11.0 mg, 12.3%), respectively. **21**: mp 68.5—69° (colorless prisms, recrystallized from CCl_4–hexane). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1819, 1808. IR $\nu_{\max}^{\text{CCl}_4}$ cm^{-1}: 1815. NMR ($CDCl_3$) δ: 2.30 (3H, s), 5.12 (2H, s), 6.40—7.46 (10H, m). High resolution MS *m/e*: 281.104 (M^+, Calcd for $C_{17}H_{15}NO_3$: 281.105), 239.096 ($M^+-C_2H_2O$, Calcd for $C_{15}H_{13}NO_2$: 239.095), 223.102 ($M^+-C_2H_2O_2$, Calcd for $C_{15}H_{13}NO$: 223.104), 222.096 ($M^+-C_2H_3O_2$, Calcd for $C_{15}H_{12}NO$: 222.092). This compound changed to a black tar even when in the crystalline state. **19**: mp 73—74° (lit.[18] mp 72—74°). All spectral data were identical with those of an authentic sample. **20**: colorless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1524, 1356. NMR ($CDCl_3$) δ: 3.20 (6H, s), 3.31 (2H, d, *J*=6 Hz), 4.43 (1H, t, *J*=6 Hz), 5.03 (2H, s), 6.83—7.41 (8H, m). MS *m/e*: 317 (M^+), 285 (M^+-CH_4O).

ii) Zinc (500.5 mg) and NH_4Cl (503.4 mg) were added to a solution of **2c** (98.6 mg) in MeOH (9.0 ml) and H_2O (1.0 ml). The solution was stirred for 4 hr at room temperature, then zinc was removed by filtration through Celite, and washed with MeOH. The combined filtrate was evaporated to dryness and the residue 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 evaporated to dryness. The residue was dissolved in Ac_2O (2.0 ml) and pyridine (4.0 ml) and the solution was stirred for 4 hr. The solvent was evaporated off under reduced pressure, the residue was subjected to p-TLC on SiO_2 with CH_2Cl_2–hexane (7: 3, v/v) as a developing solvent to afford **21** (23.9 mg, 23.4%) and **19** (15.9 mg, 19.6%).

4-Benzyloxyindole (19) and 4-Benzyloxy-2-(4-benzyloxyindol-3-yl)-2,3-dihydroindole (23) from 2-Benzyloxy-6-nitrotoluene (18)——i) The enamine **3c** (200.2 mg) was prepared by the reaction of **18** (149.3 mg) with DMFDMA (219.0 mg) in abs. DMF (2.0 ml). Aq. $TiCl_3$ (2.8 ml, 6.5 mol eq) was added to a solution of the enamine in AcOH–H_2O (7: 3, v/v, 10.0 ml) as a single portion, and the mixture was stirred for 7 min at room temperature. The whole was poured into H_2O, made basic by adding solid $NaHCO_3$, and extracted with MeOH–CH_2Cl_2 (5: 95, 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–hexane (4: 1, v/v) as a developing solvent. Under a UV lamp, two dark bands were detected on the whole luminescent plate. Extraction of the upper band with MeOH–CH_2Cl_2 (5: 95, v/v) gave **19** (18.3 mg) in an overall yield of 13.4% from **18**. Extraction of the lower band with the same solvent afforded **23** (41.4 mg) in an overall yield of 30.2% from **18**. **23**: mp 163—164° (colorless prisms, recrystallized from MeOH–CH_2Cl_2). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3350, 1612—1598 (br.), 1455, 1317, 1256. NMR ($CDCl_3$) δ: 2.98 (1H, d.d, *J*=14.5 and 9.5 Hz), 3.38 (1H, d.d, *J*=14.5 and 8 Hz), 4.97 (2H, s), 5.10 (2H, s), 5.32 (1H, q, *J*=9.5 and 8 Hz), 5.91—7.56 (8H, m), 7.27 (10H, br.s), 7.93 (1H, br.s). MS *m/e*: 446 (M^+), 223. *Anal.* Calcd for $C_{30}H_{26}N_2O_2$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.40; H, 5.62; N, 6.13.

ii) The enamine **3c** (105.2 mg) was prepared from **18** (78.4 mg) and dissolved in AcOH (5 ml). Aq. $TiCl_3$ (1.5 ml, 6.5 mol eq) was added as a single portion and the mixture was stirred for 15 min at room temperature. The whole was poured into H_2O and worked up as described in item i to afford **19** (4.8 mg) and **23** (32.2 mg) in overall yields of 6.7% and 44.7%, respectively, from **18**.

iii) The enamine **3c** (100.1 mg) was prepared from **18** (74.6 mg) and dissolved in MeOH (9.0 ml) and H_2O (1.0 ml). Solid NH_4OAc (509.4 mg, 19.5 mol eq) was added, then aq. $TiCl_3$ (1.40 ml, 6.5 mol eq) was added as a single portion and the mixture was stirred for 7 min at room temperature. The whole was poured into H_2O and worked up as described in item i to afford **19** (34.8 mg) in an overall yield of 50.8% from **18**. Only a trace amount of **23** (<1 mg) was obtained.

4-Benzyloxyindole (19) from 2-Benzyloxy-6-nitrophenyl Acetaldehyde (2c)——i) Solid NH_4OAc (732.6 mg, 26.0 mol eq) was added to a solution of **2c** (98.8 mg) in MeOH (9.0 ml) and H_2O (1.0 ml), then aq. $TiCl_3$ (1.50 ml, 6.5 mol eq) was added as a single portion. The mixture was stirred for 7 min at room temperature, then poured into H_2O and extracted with CH_2Cl_2. The extract was washed with sat. aq. $NaHCO_3$, then 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 (7: 3, v/v) as a developing solvent to afford **19** (60.9 mg, 74.9%).

ii) Compound **2c** (55.7 mg), NH_4OAc (309.2 mg, 19.5 mol eq), and aq. $TiCl_3$ (0.86 ml, 6.5 mol eq) were treated according to the procedure described in item i. Work-up as described above afforded **19** (27.3 mg, 59.6%).

4-Hydroxyindole (24) from 2-Benzyloxy-6-nitrophenyl Acetaldehyde (2c)——The nitroaldehyde (**2c**, 100.9 mg) was dissolved in MeOH (30.0 ml) and catalytic hydrogenation was carried out with 10% Pd/C (30.7 mg) and $PtO_2 \cdot 2H_2O$ (1.3 mg) at 60° and 72 kg/cm^2 for 15 hr. The catalysts were removed by filtration through Celite and the filtrate was concentrated to leave an oil. Purification by p-TLC on SiO_2 with MeOH–CH_2Cl_2 (5: 95, v/v) as a developing solvent afforded **24** (33.5 mg, 67.7%). mp 102—104° (lit.[18]) mp 97—99°). All spectral data were identical with those of authentic 4-hydroxyindole.

4-Benzyloxy-1-methoxyindole (22) from 1-Acetoxy-4-benzyloxyindole (21)——A stirred solution of **21** (19.5 mg) in MeOH (0.9 ml) was treated with 30% aq. NaOH (0.1 ml) and stirring was continued for 7 min at room temperature. [At this point, the reaction mixture was checked by thin-layer chromatography on an SiO_2 plate with CH_2Cl_2–hexane (1: 1, v/v) as a developing solvent; it showed only one spot which adsorbed iodine strongly and gave a reddish-violet color. This behavior is similar to that of **1a** or **1b**]. Methyl iodide (70.0 mg) was added to the reaction mixture, and stirring was continued for 5.5 hr. The solvent was evaporated off under reduced pressure and the residue was extracted with MeOH–CH_2Cl_2 (1: 99, v/v). The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to leave an oil. Purification by p-TLC on SiO_2 with CH_2Cl_2–hexane (1: 1, v/v) as a developing solvent gave **22** (13.5 mg, 76.9%). mp 77—78° (colorless prisms, recrystallized from CCl_4–hexane). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1606, 1570, 1340, 1241, 1025. NMR (CCl_4) δ: 3.97 (3H, s), 5.09 (2H, s), 6.25—6.43 (2H, m), 6.80—7.01 (3H, m), 7.01—7.50 (5H, m). High resolution MS *m/e*: 253.105 (M^+, Calcd for $C_{16}H_{15}NO_2$: 253.110), 223.102 (M^+-CH_2O, Calcd for $C_{15}H_{13}NO$: 223.100), 222.093 (M^+-CH_3O, Calcd for $C_{15}H_{12}NO$: 222.092), 162.056 ($M^+-CH_2C_6H_5$, Calcd for $C_9H_8NO_2$: 162.056). Even in the solid state, **22** decomposed slowly on exposure to light.

1-Acetoxy-4-methoxycarbonylindole (27) and 4-Methoxycarbonylindole (26) from Methyl 2-Methyl-3-nitrobenzoate (25)——i) A solution of **25** (199.0 mg) and DMFDMA (330.5 mg) in abs. DMF (2.0 ml) was heated under reflux for 15.5 hr.[20]) Removal of the solvent *in vacuo* afforded an almost quantitative yield of **3b** (checked by NMR spectroscopy). The crude **3b** was dissolved in MeOH (7.0 ml), then aq. $TiCl_3$ (2.40 ml, 3.7 mol eq) was added as a single portion. The mixture was stirred for 5 min at room temperature, then CH_2Cl_2 (40.0 ml) and H_2O (10.0 ml) were added. The whole was salted out, then the organic layer was separated and the water layer was further extracted with CH_2Cl_2. The combined extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was dissolved in Ac_2O (1.5 ml) and pyridine (3.0 ml). The mixture was stirred for 20.5 hr at room temperature, and the solvent was evaporated off under reduced pressure. The residue was extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$, then 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 (13: 5, v/v) as a developing solvent. Under a UV lamp, two luminescent bands were detected. Extraction of the upper band with MeOH–CH_2Cl_2 (1: 99, v/v) gave **27** (44.6 mg) in an overall yield of 18.8% from **25**. From the lower band, **26** (23.2 mg) was extracted with the same solvent in an overall yield of 13.0% from **25**. **27**: mp 76—77° (pale pink prisms, recrystallized from CCl_4). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1802, 1701, 1439, 1258, 1172. NMR (CCl_4) δ: 2.15 (3H, s), 3.83 (3H, s), 6.84—7.30 (4H, m), 7.73 (1H, d.d, $J=6$ and 2 Hz). MS *m/e*: 233 (M^+), 202, 192, 175. *Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.64; H, 4.61; N, 5.96. **26**: mp 66—67° (lit.[7]) mp 64—65°). All spectral data were identical with those of an authentic sample.

ii) The crude **3b**, prepared from **25** (215.0 mg), was treated with aq. $TiCl_3$ (2.80 ml, 4.0 mol eq) followed by acetylation as described in item i. After the usual work-up, **27** (36.1 mg) and **26** (23.5 mg) were obtained in overall yields of 14.1% and 12.2%, respectively, from **25**.

iii) The crude **3b**, prepared from **25** (513.7 mg), was dissolved in MeOH (10.0 ml) and H_2O (2.0 ml). Zinc powder (504.9 mg) and solid NH_4Cl (501.5 mg) were added and the mixture was stirred for 2.5 hr at room temperature. Zinc was removed by filtration through Celite and washed well with MeOH. The combined filtrate was evaporated to dryness under reduced pressure and the residue was extracted with MeOH–CH_2Cl_2 (5: 95, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated to leave an oil, which was treated with Ac_2O (2.0 ml) and pyridine (4.0 ml) for 15.5 hr. After work-up as described in item i, **27** (244.9 mg) and **26** (6.0 mg) were obtained in overall yields of 39.9% and 1.3%, respectively, from **25**.

1-Acetoxy-4-methoxycarbonylindole (27) from 1-Hydroxy-4-methoxycarbonylindole (1b)——A solution of **1b** (133.4 mg) in abs. pyridine (4.0 ml) was treated with Ac_2O (2.0 ml) and the mixture was stirred for 4.5 hr at room temperature. After usual work-up and purification by p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent, **27** (70.2 mg, 43.1%) was obtained.

1-Hydroxy-4-methoxycarbonylindole (1b) from 1-Acetoxy-4-methoxycarbonylindole (27)——A solution of **27** (34.0 mg) in MeOH (1.8 ml) was treated with 2 N NaOH (0.2 ml) and the mixture was stirred for 15 min at room temperature, then made acidic by adding 2 N HCl and extracted with CH_2Cl_2. The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by p-TLC on SiO_2 with MeOH–CH_2Cl_2 (1: 99, v/v) as a developing solvent to give **1b** (18.1 mg, 64.9%) as a colorless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3250, 1690 (br.). NMR ($CDCl_3$) δ: 3.73 (3H, s), 6.60 (1H, d, $J=3.2$ Hz), 6.92 (1H, t, $J=8$ Hz), 7.09 (1H, d, $J=3.2$ Hz), 7.41 (1H, br.d, $J=8$ Hz), 7.58 (1H, d.d, $J=8$ and 1.2 Hz). MS m/e: 191 (M^+), 175 (M^+-16), 160, 145, 144. This compound gradually decomposed to a black tar on standing.

1-Methoxy-4-methoxycarbonylindole (28) from 1-Hydroxy-4-methoxycarbonylindole (1b)——Methyl iodide (140.0 mg) was added to a solution of **1b** (21.4 mg) in MeOH (1.0 ml) and 2 N NaOH (0.5 ml), and the mixture was stirred for 5 hr at room temperature, then poured into H_2O and extracted with CH_2Cl_2. 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 **28** (18.0 mg, 78.4%) as a colorless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1710 (br.). NMR (CCl_4) δ: 3.82 (3H, s), 3.90 (3H, s), 6.82 (1H, d.d, $J=3.2$ and 0.8 Hz), 7.02 (1H, t, $J=7$ Hz), 7.11 (1H, d, $J=3.2$ Hz), 7.38 (1H, d.d.d, $J=7$, 1.2, and 0.8 Hz), 7.68 (1H, d.d, $J=7$ and 1.2 Hz). MS m/e: 205 (M^+), 190 (M^+-CH_3). In solution, **28** gradually changed to a black tar on standing.

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