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Synthesis and Some Reactions of 6-Bromooxindole

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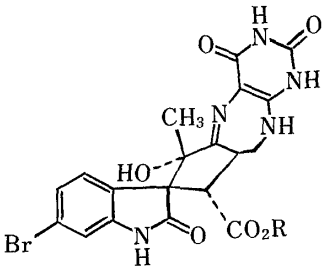
An efficient synthesis of 4- and 6-bromooxindoles, previously unknown compounds, from 6- and 4-amino-2-nitrotoluenes and the transformation of 6-bromooxindole to 3-acylated derivatives are described.

Keywords——neosurugatoxin; prosurugatoxin; 4-amino-2-nitrotoluene; 6-bromooxindole; 4-bromooxindole; 3-acyl-6-bromooxindole

During the course of our program aimed at developing a strategy for the construction of neosurugatoxin[1] (I) and prosurugatoxin[2] (II), which have an extremely high antinicotinic activity and strongly evoke mydriasis at a minimum dose of 3—20 ng in mice,[3] our retrosynthetic analysis of these compounds led us to consider routes based on the utilization of 3-C substituted 6-bromooxindoles as key precursor molecules. On the basis of this analysis,

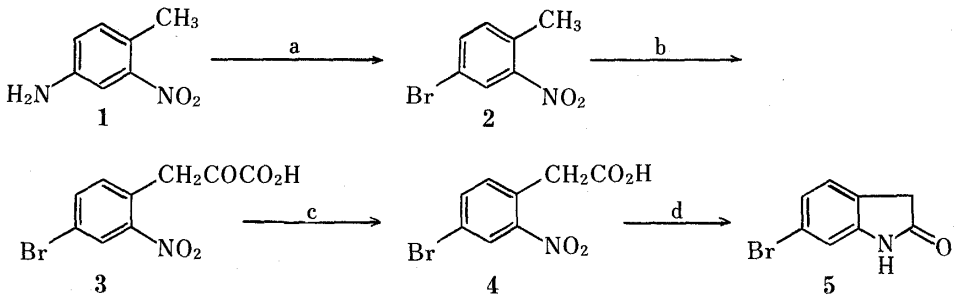


neosurugatoxin
R = β-*d*-xylopyranosyl-(1—5)-myoinositol

Fig. 1. Structure of Neosurugatoxin

we required 6-bromooxindole (**5**) as a starting material. Since no procedure has been developed for the synthesis of **5**,[4] we initiated a study geared toward multigram scale production. We wish to report here a method for producing 6-bromooxindole from commercially available 4-amino-2-nitrotoluene (**1**),[5] as well as some reactions of this compound.

Our synthesis of **5** is based on the application of a general oxindole synthesis reported by Reissert and Scherk[5c] as follows. Thus, 4-amino-2-nitrotoluene (**1**) was diazotized by reaction with sodium nitrite and hydrobromic acid in water. The diazonium salt was reacted with cuprous bromide in hydrobromic acid to yield the brominated compound (**2**). Reaction of **2** with diethyl oxalate and sodium ethoxide in ethanol led to ethyl 4-bromo-2-nitrophenylpyruvate. This ester was hydrolyzed with sodium hydroxide to yield 4-bromo-2-nitrophenylpyruvic acid (**3**) in 83% yield. Treatment of **3** with hydrogen peroxide in sodium hydroxide aqueous solution gave 4-bromo-2-nitrophenylacetic acid (**4**) as a crystalline solid in 86% yield.



a: (1) $NaNO_2$ and HBr, (2) CuBr and HBr. b: (1) $(CO_2Et)_2$, (2) NaOH. c: H_2O_2 and NaOH. d: Zn and H_2SO_4.

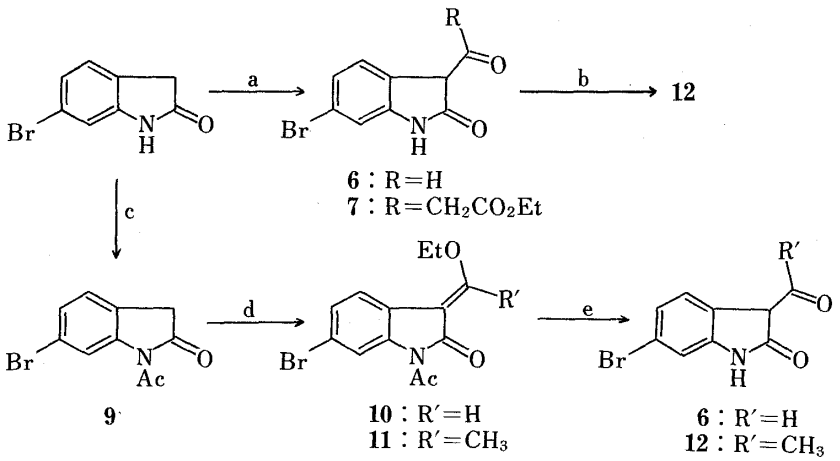
Chart 1

The 4-bromo-2-nitrophenylacetic acid (**4**) can be readily transformed into 6-bromooxindole by reduction with zinc and sulfuric acid as follows.[6] A solution of **4** in diluted sulfuric acid was reduced with zinc by heating at 90 °C for 2 h. The reaction mixture was extracted with ethyl acetate, and the extract was washed with 5% sodium bicarbonate, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude product was recrystallized from methanol to afford **5** as colorless needles in 97% yield.

This entire sequence can be executed on a multigram scale, thus providing an efficient route designed for the preparation of **5**. 4-Bromooxindole (**5'**) could also be readily prepared from 6-amino-2-nitrotoluene by use of the same sequence.

Some reactions were carried out with the newly synthesized 6-bromooxindole (**5**) in order to define some of the chemistry of this heterocyclic system. Condensation of **5** with ethyl esters provides the 3-C-acylated products. Ethyl formate gave an excellent yield of 3-hydroxymethylene-6-bromooxindole (**6**).

It is of considerable interest that **5** does not directly provide the 3-acetyl-6-bromooxindole (**12**) in the usual base-catalyzed acylation reaction, as used for the C-3 monoacylation of oxindole.[7] In contrast, condensation of **5** with some esters (ethyl formate and diethyl malonate) could be effected by sodium ethoxide to give the desired 3-acylated products (**6** and **7**). These results suggest that the electron-withdrawing effect of bromine changes the reactivity of the oxindole, especially toward base-catalyzed acylation at the C-3 position. However, further work is necessary on this point.



a: R–CO_2Et and NaOEt. b: (1) NaOH, (2) heated at 160 °C. c: Ac_2O. d: R–$C(OEt)_3$. e: NaOH.

Chart 2

The reaction of *N*-acetyl-6-bromooxindole (prepared by reaction of **5** with acetic anhydride) with an excess of orthoesters also proceeded readily to give excellent yields of condensation products. The new 6-bromooxidoles, **10** and **11**, were thus obtained on exposure of **9** to orthoesters, triethyl orthoformate and triethyl orthoacetate, respectively.

As mentioned above, an attempt to obtain 3-acetyl-6-bromooxindole (**12**) directly by the reaction of **5** with an acetylating agent was not successful. However, as shown in Chart 2, **12** could be readily prepared as follows. The enol ether (**11**) was reacted with 2 equivalents of sodium hydroxide to provide **12** quantitatively. Another useful procedure for the preparation of **12** is pyrolysis of the carboxylic acid (**8**), which was prepared by hydrolysis of **7** with sodium hydroxide, at 160 °C under a vacuum.

In summary, we have achieved the first preparations of 4- and 6-bromooxindole. Attempts to utilize 3-acetyl-6-bromooxindole in the synthesis of the new marine toxins neo- and prosurugatoxin (I and II) and a study of the reactivity of 6-bromooxindoles are under way, and will be reported elsewhere.

Experimental

Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were obtained with a JEOL FX-90 Fourier transform NMR spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard. Abbreviations used: s, singlet; d, doublet; dd, double doublet; m, multiplet; t, triplet; br s, broad singlet. The infrared (IR) spectra were recorded on a JASCO IRA-2 grating infrared spectrophotometer. Low- and high-resolution mass spectra (MS) were recorded on Hitachi M-80A and JEOL JMS D-100 instruments. Ultraviolet (UV) spectra were taken with a Shimadzu UV-360 spectrophotometer. Elemental analyses were done on a Perkin Elmer 240 analyzer. Melting points are uncorrected.

Cuprous bromide was prepared from cupric sulfate, sodium bromide, and sodium sulfite.[8]

4-Bromo-2-nitrotoluene (2)——Sodium nitrite (7 g, 0.1 mol) in 13 ml of H_2O was added slowly to a stirred solution of finely divided 4-amino-2-nitrotoluene (15.2 g, 0.1 mol) in 30 ml of 48% HBr below 0 °C. The precipitate was removed by filtration, and the filtrate of the diazonium salt solution was added dropwise to a stirred solution of cuprous bromide (0.7 g, 0.05 mol) in 8 ml of 48% HBr without external cooling. After being stirred for a few min, the mixture was heated at 90 °C for 0.5 h, and the resulting mixture was extracted with ether (2 × 200 ml). The combined organic portions were washed with water and saturated sodium chloride, then dried ($MgSO_4$), and concentrated by rotary evaporation. The crude product was bulb-to-bulb distilled (143 °C, 19 mmHg) to yield 11.3 g (91%) of **2** as yellow prisms; mp 45—46 °C (lit.[5a] mp 47 °C). IR (KBr): 1523, 1441, 1339, 1100, 874, 792 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 7.92 (d, 1H, J=2.2 Hz), 7.04 (dd, 1H, J=8.3, 2.2 Hz), 7.08 (d, 1H, J=8.3 Hz), 2.51 (s, 3H). MS (70 eV) *m/z*: 217 (M^+), 215 (M^+), 200, 198, 172, 170, 145, 143.

6-Bromo-2-nitrotoluene (2′)——In 84.3% yield from 6-amino-2-nitrotoluene; mp 39—40 °C (yellow prisms) (lit.[5a] mp 42 °C). IR (KBr): 1521, 1442, 1357, 1098, 1004, 865, 792, 738, 710 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 7.76 (d, 1H, J=7.3 Hz), 7.76 (d, 1H, J=7.6 Hz), 7.18 (t, 1H, J=7.3 Hz), 2.54 (s, 3H). MS (70 eV) *m/z*: 217 (M^+), 215 (M^+), 200, 198, 172, 171, 170, 169.

4-Bromo-2-nitrophenylpyruvic Acid (3)——Diethyl oxalate (29.2 g, 0.2 mol) and 4-bromo-2-nitrotoluene (21.6 g, 0.1 mol) were poured into a cooled sodium ethoxide solution, prepared from sodium (4.6 g, 0.2 mol) and 90 ml of dry ethanol. The mixture was stirred overnight at room temperature and then refluxed for 10 min at the end of the reaction. Next, 30 ml of water was added to the reaction mixture, and the whole was refluxed for 2 h in order to hydrolyze the ethyl 4-bromo-2-nitrophenylpyruvate. The reaction mixture was cooled and concentrated to remove excess ethanol by rotary evaporation. The precipitate was filtered off, washed with ether to remove unreacted starting material, and dried. This crude sodium salt of **3** was dissolved in 300 ml of H_2O and acidified with conc. HCl. The white precipitate of **3** was filtered, washed with water, and then dried. The crude product was recrystallized from hexane and ethyl acetate to afford 15.2 g (83.0%) of **3** as yellow prisms; mp 145 °C (lit.[5b] mp 138—140 °C. IR (KBr): 1739, 1726, 1520, 1341 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 8.34 (d, 1H, J=2.2 Hz), 7.77 (dd, 1H, J=8.0, 2.2 Hz), 7.23 (d, 1H, J=8.0 Hz). MS (70 eV) *m/z*: 244 ($M-CO_2$), 242 ($M-CO_2$), 216, 214, 172, 170.

6-Bromo-2-nitrophenylpyruvic Acid (3′)——In 88.8% yield from **2′**; mp 115—116 °C (colorless prisms recryst. from benzene) (lit.[5b] mp 117 °C). IR (KBr): 3400, 1768, 1738, 1533, 1376, 1354, 1319, 1060, 803, 745 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 8.01 (d, 1H, J=7.1 Hz), 7.95 (d, 1H, J=7.1 Hz), 7.39 (t, 1H, J=7.1 Hz), 4.81 (s, 2H). MS (70 eV) *m/z*: 244, 242, 216, 214, 200, 199, 198, 197, 172, 170.

4-Bromo-2-nitrophenylacetic Acid (4)——A 30% H_2O_2 solution (11.3 ml, 0.1 mol) was added dropwise to a solution of 4-bromo-2-nitrophenylpyruvic acid (28.8 g, 0.1 mol) and sodium hydroxide (12 g, 0.3 mol) in 300 ml of H_2O with stirring at 0 °C.[5c] The reaction solution was stirred for 1 h at 5 °C and then acidified with dil. HCl. The

white precipitate was filtered off, washed with water, dried, and recrystallized from hexane and ethyl acetate to yield 22.2 g (85.4%) of **4** as a white powder; mp 168 °C (lit.[5c] mp 167—167.5 °C). IR (KBr): 1695, 1524, 1349, 1236, 883 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 12.44 (br s, 1H) 8.18 (d, 1H, J=2.2 Hz), 7.84 (dd, 1H, J=8.4, 2.2 Hz), 7.47 (d, 1H, J=8.4 Hz), 3.95 (s, 3H). MS (70 eV) m/z: 261 (M^+), 259 (M^+), 217, 215, 199, 197, 172, 170.

6-Bromo-2-nitrophenylacetic Acid (4')——In 86.4% yield from **3'**; mp 193—194 °C (colorless needles recryst. from hexane and ethyl acetate) (lit.[9] mp 196.5—197 °C). IR (KBr): 1708, 1524, 1423, 1343, 1242, 1092, 936, 804, 743, 709 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 12.66 (br s, 1H), 8.00 (d, 1H, J=8.2 Hz), 8.00 (d, 1H, J=8.2 Hz), 7.48 (t, 1H, J=8.2 Hz), 4.00 (s, 2H). MS (70 eV) m/z: 200, 198, 180, 172, 170, 158, 156, 145, 143.

6-Bromooxindole (5)——Zinc dust (26.2 g, 0.4 mol) was added slowly to a solution of 4-bromo-2-nitrophenylacetic acid (26 g, 0.1 mol) in 400 ml of 50% sulfuric acid and 600 ml of ethanol at 90 °C during 1 h. The mixture was heated at this temperature for 2 h with stirring and then excess ethanol was distilled off. After cooling, the resulting mixture was filtered and the filtrate was extracted with ethyl acetate (2 × 300 ml). The combined organic portions were washed with 5% sodium bicarbonate and then saturated sodium chloride, dried ($MgSO_4$), and concentrated by rotary evaporation. The isolated product was recrystallized from methanol to yield 20.48 g (97%) of **5** as colorless needles; mp 216 °C. IR (KBr): 3160, 1698, 1614, 1480, 1330, 1254 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 10.45 (br s, 1H), 7.20 (m, 2H), 6.93 (s, 1H), 3.43 (s, 2H). ^{13}C-NMR (22.5 MHz, d_6-DMSO): 175.8 (s, C_2), 145.3 (s, C_8), 125.9 (d, C_4), 124.9 (s, C_9), 123.5 (d, C_5), 119.9 (s, C_6), 111.9 (s, C_7), 35.3 (t, C_3). UV λ_{max}^{MeOH} nm (log ε): 252 (3.87), 285 (3.29), 295 (3.19). MS (70 eV) m/z: 213 (M^+), 211 (M^+), 173, 171, 131; m/z: Calcd for C_8H_6BrNO: 212.9613, 210.9613. Obsd: 210.9615, 212.9613.

4-Bromooxindole (5')——In 87.1% yield from **4'**; mp 217—220 °C (colorless needles recryst. from methanol). IR (KBr): 1710, 1616, 1584, 1451, 1317, 1292, 1260, 1163, 1139, 918, 874 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 10.57 (br s, 1H), 7.10 (m, 2H), 6.8 (m, 1H), 3.39 (s, 2H). ^{13}C-NMR (22.5 MHz, d_6-DMSO): 174 (s), 145 (s), 129 (d), 126 (s), 124 (d), 118 (d), 108 (d), 37.0 (t). MS (70 eV) m/z: 213 (M^+), 211 (M^+), 184, 183, 182, 181; m/z Calcd for C_8H_6BrNO: 212.9612, 210.9637. Obsd: 212.9612, 210.9641.

3-Hydroxymethylene-6-bromooxindole (6)——A slurry of 6-bromooxindole (212 mg, 1 mmol) and ethyl formate (0.25 ml, 3 mmol) was added to a warm sodium ethoxide solution, prepared from sodium (31 mg, 1.35 mmol) and 1 ml of dry ethanol, with stirring. The mixture set to a solid immediately. After standing at room temperature for 1 h and then being heated at 90 °C for 0.5 h, the mixture was neutralized with dil. HCl, and the resulting precipitate was filtered off and dried. Recrystallization of the crude product from dil. methanol provided 221 mg (92.1%) of pure **6** as yellow needles; mp 227—228 °C. *Anal.* Calcd for $C_9H_6BrNO_2$: C, 45.03; H, 2.52; N, 5.84. Found: C, 44.99; H, 2.48; N, 5.77. IR (KBr): 3600, 3150, 3030, 2740, 1704, 1658, 1613, 1480, 1263, 1194, 1057, 816 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 10.24 (s, 1H), 7.81 (s, 1H), 7.43 (d, 1H, J=7.9 Hz), 7.07 (dd, 1H, J=7.9, 1.8 Hz), 6.92 (d, 1H, J=1.8 Hz). MS (70 eV) m/z: 241 (M^+), 239 (M^+), 224, 222, 213, 212, 211, 210, 184, 182, 132.

6-Bromo-3-(2-ethoxycarbonyl-1-oxo-ethyl)oxindole (7)——Freshly distilled diethyl malonate (1.2 g, 7.5 mmol) was added to a stirred sodium ethoxide solution [prepared from sodium (184 mg, 8 mmol) and 3 ml of dry ethanol] and then a solution of 6-bromooxindole (424 mg, 2 mmol) in 20 ml of dry ethanol was further added dropwise during 2 h. The reaction mixture was refluxed with stirring for 6 h under nitrogen, during which time 10 ml of ethanol was distilled off. The resulting mixture was poured into 20 ml of ice-water and the solution was extracted with ether. The aqueous portion was acidified with cold conc. HCl. The precipitate was collected by filtration and dried. Recrystallization of the product from *n*-hexane and ethyl acetate provided 456 mg (70.0%) of **7** as yellow prisms; mp 162—163 °C. *Anal.* Calcd for $C_{13}H_{12}BrNO_4$: C, 47.87; H, 3.71; N, 4.30. Found: C, 47.83; H, 3.62; N, 4.41. IR (KBr): 3180, 2990, 1734, 1677, 1613, 1486, 1335, 1284, 1222, 1191, 1068, 978, 813 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 10.47 (br s, 1H), 7.55 (d, 1H, J=7.9 Hz), 7.08 (dd, 1H, J=7.9, 1.8 Hz), 6.95 (d, 1H, J=1.8 Hz), 4.15 (s, 2H), 4.10 (q, 2H, J=7.0 Hz), 1.21 (t, 3H, J=7.0 Hz). MS (70 eV) m/z: 327 (M^+), 325 (M^+), 280, 278, 239, 237, 211, 158, 145, 130.

6-Bromo-3-(2-carboxy-1-oxo ethyl)oxindole (8)——A solution of 6-bromo-3-(2-ethoxycarbonyl-1-oxo ethyl)-oxindole (326 mg, 1 mmol) and sodium hydroxide (120 mg, 3 mmol) in 10 ml of water was heated at 90 °C for 5 min. After cooling, the resulting solution was acidified with dil. HCl and extracted with ethyl acetate (2 × 20 ml). The combined organic portions were washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated by rotary evaporation. The isolated product was recrystallized from dil. ethanol to yield 272 mg (91.0%) of **8** as a colorless powder; mp 244—245 °C. *Anal.* Calcd for $C_{11}H_8BrNO_4$: C, 44.32; H, 2.66; N, 4.70. Found: C, 44.38; H, 2.66; N, 4.74. IR (KBr): 3320, 1702, 1660, 1612, 1480, 1282, 1251, 1200, 1065, 977, 817 cm^{-1}. ^{1}H-NMR (90 MHz, d_8-THF) 10.11 (br s, 1H), 7.21 (d, 1H, J=8.8 Hz), 7.09 (d, 1H, J=8.8 Hz), 7.05 (s, 1H), 3.75 (s, 3H). MS (70 eV) m/z: 254, 252, 240, 238, 213, 211, 184, 182.

***N*-Acetyl-6-bromooxindole (9)**——A solution of 6-bromooxindole (2.12 g, 0.01 mol) in 50 ml of acetic anhydride was heated at 110 °C for 3 h and then allowed to cool. The precipitate was filtered off, dried, and recrystallized from ethanol to yield 2.448 g (96%) of **9** as orange needles; mp 158—159 °C. *Anal.* Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.28; H, 3.12; N, 5.51. IR (KBr): 1790, 1762, 1697, 1471, 1416, 1380, 1283, 1030 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 8.21 (d, 1H, J=1.6 Hz), 7.36 (dd, 1H, J=8.7, 1.6 Hz), 7.26 (d, 1H, J=8.7 Hz), 3.75 (s, 2H), 2.55 (s, 3H). MS (70 eV) m/z: 255 (M^+), 253 (M^+), 213, 211, 185, 184, 183, 182, 132.

***N*-Acetyl-3-ethoxymethylene-6-bromooxindole (10)**——A solution of *N*-acetyl-6-bromooxindole (2.54 g,

0.01 mol) and triethyl orthoformate (1.924 g, 0.013 mol) in 12 ml of acetic anhydride was heated at 110 °C for 2 h and then allowed to cool. The precipitate was filtered off, dried, and recrystallized from ethanol to yield 2.945 g (95%) of **10** as orange needles; mp 136—137 °C. *Anal.* Calcd for $C_{13}H_{12}BrNO_3$: C, 50.30; H, 3.90; N, 4.52. Found: C, 50.22; H, 3.77; N, 4.47. IR (KBr): 1740, 1705, 1660, 1376, 1288, 1265, 1157, 1144, 1105, 1023 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO and $CDCl_3$): 8.27 (d, 1H, J=1.8 Hz), 7.86 (s, 1H), 7.49 (d, 1H, J=8.1 Hz), 7.27 (dd, 1H, J=8.1, 1.8 Hz), 4.46 (q, 2H, J=7.2 Hz), 2.61 (s, 3H), 1.47 (t, 3H, J=7.2 Hz). MS (70 eV) *m/z*: 311 (M^+), 309 (M^+), 269, 267, 241, 239, 213, 212, 211, 210, 184, 182.

***N*-Acetyl-3-(α-ethoxyethylidene)-6-bromooxindole (11)**——A solution of *N*-acetyl-6-bromooxindole (2.54 g, 0.01 mol), and triethyl orthoacetate (2.11 g, 0.013 mol) in 12 ml of acetic anhydride was heated at 110 °C for 2 h and then allowed to cool. The precipitate was filtered off, dried, and recrystallized from ethanol to yield 3.11 g (96.0%) of **11** as orange needles; mp 185—186 °C. *Anal.* Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.72; H, 4.31; N, 4.2. IR (KBr): 1716, 1693, 1609, 1462, 1420, 1289, 1133, 940, 920 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 8.34 (d, 1H, J=1.5 Hz), 7.45 (d, 1H, J=8.3 Hz), 7.16 (dd, 1H, J=8.3, 1.5 Hz), 4.28 (q, 2H, J=7.0 Hz), 2.65 (s, 3H), 2.63 (s, 3H), 1.51 (t, 3H, J=7.0 Hz). MS (70 eV) *m/z*: 325 (M^+), 323 (M^+), 283, 281, 255, 253, 240, 238, 226, 224, 145.

3-Acetyl-6-bromooxindole (12)——(a) Sodium hydroxide (0.8 g, 0.02 mol) in 20 ml of water was added dropwise to a solution of *N*-acetyl-(α-ethoxyethylidene)-6-bromooxindole (3.24 g, 0.01 mol) in 120 ml of ethanol. The resulting solution was heated at 90 °C for 5 min. After cooling, the solution was concentrated by rotary evaporation, and the residue was dissolved in 120 ml of water. This solution was acidified with dil. HCl. The precipitate was filtered off, dried, and recrystallized from ethanol to yield 2.448 g (96.0%) of **12** as colorless needles.

(b) 6-Bromo-3-(2-carboxyl-1-oxo ethyl)oxindole (298 mg, 1 mmol) was pyrolyzed at 160 °C for 1 h under a vacuum (0.1 mmHg). The product was purified by silica gel chromatography with 25% (v/v) ethyl acetate–*n*-hexane as the eluent to yield 178 mg (71%) of **12**; mp 257—259 °C. *Anal.* Calcd for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51. Found: C, 47.22; H, 3.09; N, 5.53. IR (KBr): 3200, 1688, 1613, 1284, 1255, 1067, 962 cm^{-1}. ^{1}H-NMR (90 MHz, d_6-DMSO): 10.45 (br s, 1H), 7.46 (d, 1H, J=7.9 Hz), 7.06 (d, 1H, J=7.9 Hz), 6.96 (s, 1H), 5.50 (br s, 1H), 2.50 (s, 3H). MS (70 eV) *m/z*: 255 (M^+), 253 (M^+), 240, 238, 237, 235, 213, 211, 184, 182.

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