Structural determination of a natural alkaloid, 5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline and the synthesis of the corresponding 8-methoxy compound

STRUCTURAL DETERMINATION OF A NATURAL ALKALOID, 5-METHOXY-1-OXO-1,2,3,4-TETRAHYDRO-β-CARBOLINE AND THE SYNTHESIS OF THE CORRESPONDING 8-METHOXY COMPOUND[1]

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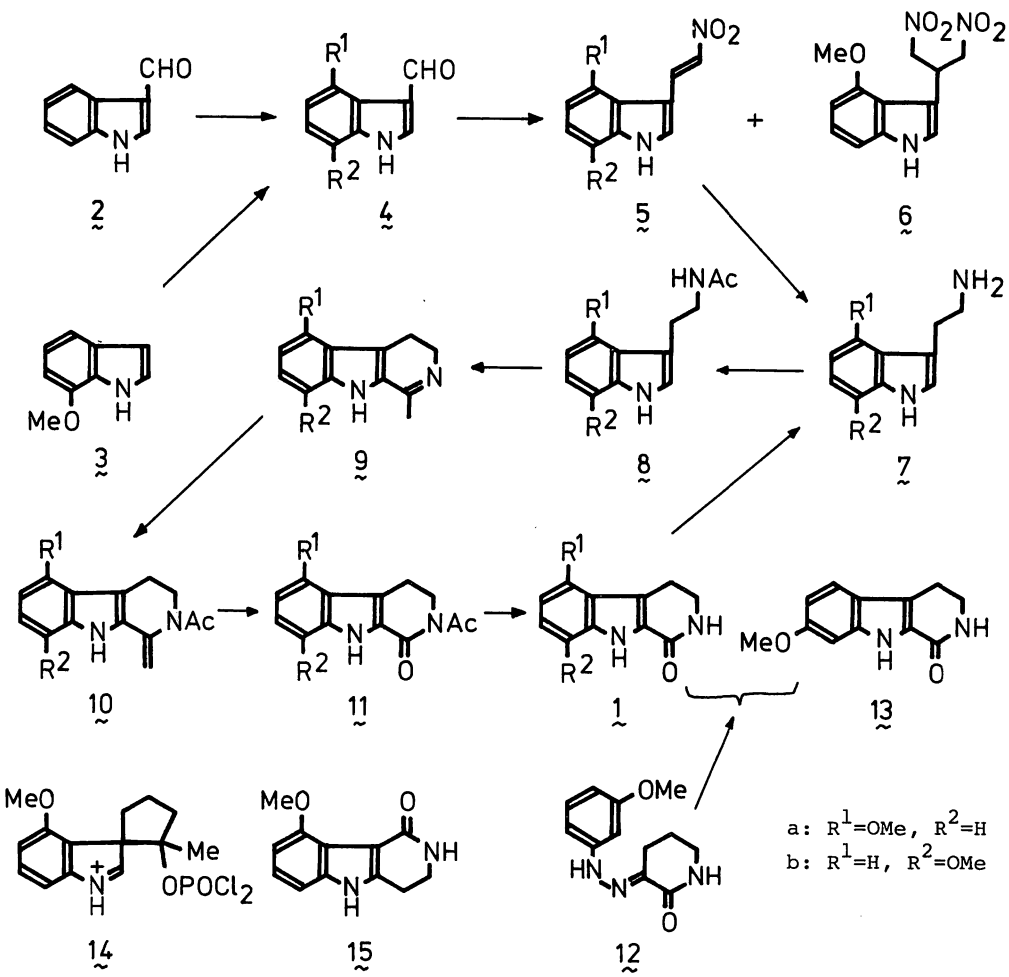
Abstract ——— Structure of a natural alkaloid, 5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline, was determined unequivocally by synthesis and the reported spectral data were found to be revised in some points.

In 1982, Banerji and co-workers[2] have isolated 5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (1a) as a natural alkaloid from the root bark of Alstonia venenata. Although its structure was deduced based on spectral data, the corresponding 8-methoxy structure (1b) would also be an another possible candidate for the alkaloid.
In our continuing efforts on the syntheses of substituted indoles, we have developed facile synthetic methods for 7-methoxyindole[3] (3) and 4-methoxy-3-indolecarbaldehyde[4] (4a). As an extension of these findings, we have attempted the syntheses of 1a and 1b and found that the assigned structure (1a) for the alkaloid was correct but the reported spectral data should be revised in some points due to contamination of impurity.
First, we developed a convenient three step synthetic method for 4-methoxytryptamine,[5] which was a versatile intermediate for various indole alkaloids.[6] Thus, the compound (4a), prepared in one pot operation from 3-indolecarbaldehyde (2) in 86.1% yield,[4] reacted with nitromethane in the presence of ammonium acetate to produce 4-methoxy-3-(2-nitrovinyl(indole (5a) and 4-methoxy-3-[2-nitro-1-(nitromethyl)ethyl]indole (6) in 91.8% and 3.2% yields, respectively. Reduction of 5a with lithium aluminum hydride in tetrahydrofuran readily afforded 99.8% yield of 4-methoxytryptamine[5] (7a).
With the compound (7a) in hand, we next reacted 7a with acetic anhydride to afford

N_b-acetyltryptamine (8a) in 95.2% yield. Bischler-Napieralski reaction of 8a gave the cyclized 3,4-dihydro-β-carboline (9a) in 73.5% yield. Next, conversion of 9a to 1a was carried out according to Rahman's procedure.[7] Thus, treatment of 9a with acetic anhydride produced 2-acetyl-4-methoxy-1-methylene-1,2,3,4-tetrahydro-β-carboline (10a) in 76.3% yield. Successive oxidation of 10a with potassium permanganate in the presence of 18-crown-6 afforded 13.8% yield of 2-acetyl-5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (11a) together with 27.1% yield of the recovery of 10a. Treatment of 11a with aqueous sodium hydroxide in methanol afforded 5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline[5b] (1a) in 98.6% yield. The synthetic compound (1a) exhibited mp 216.0-217.0°C, different from that (mp 182-184°C) of the alkaloid.[2]



We have therefore attempted the synthesis of 8-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (1b) from 3 by essentially the same reaction sequences as used in the synthesis of 1a. Thus, 7-methoxy-3-indolecarbaldehyde (4b) was prepared in 91.7% yield by the Vilsmeier reaction. 7-Methoxy-3-(2-nitrovinyl)indole (5b), 7-methoxytryptamine (7b), N_b-acetyl-7-methoxytryptamine (8b), 8-methoxy-1-methyl-3,4-dihydro-β-carboline (9b), 2-acetyl-8-methoxy-1-methylene-1,2,3,4-tetrahydro-β-carboline (10b), 2-acetyl-8-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (11b), and 1b were prepared from the respective starting materials in 93.7%, 88.2%, 95.9%, 83.5%, 81.6 %, 28.2%, and 90.6% yields, respectively. Spectral data of 1b were found to be totally different from those of the natural alkaloid.

Alternatively, the compound (1a) was prepared in 7.0% yield according to Pouilhes's synthetic method[8] by cyclizing 3-methoxyphenyl hydrazone of 2,3-piperidinedione (12) together with 46.1% yield of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (13). The product obtained was identical with the synthetic compound (1a). It is however well known that Bischler-Napieralski cyclization proceed via indolenine intermediate[9] such as 14 and therefore hydrolysis of 1a became necessary to eliminate the possibility that the synthetic compound might be 5-methoxy-4-oxo-1,2,3,4-tetrahydro-γ-carboline (15). Alkaline hydrolysis of the synthetic compound actually produced 58.6% yield of 4-methoxytryptamine (7a) and this result clearly proved that the synthetic compound (1a) had the correct structure.

At this point, it became probable that the structure of the natural alkaloid might be either 15 or 8-methoxy-4-oxo-1,2,3,4-tetrahydro-γ-carboline, but the reported ^{13}C-NMR data were found to be identical with those of the synthetic compound (1a). Spectral data of 1a were therefore compared directly with those of the alkaloid, kindly provided by Banerji, and consequently we concluded that the alkaloid had the structure (1a) but it contained some impurities. In conclusion, mp, UV absorption value, IR data, and assigning of ^{1}H-NMR spectrum reported for the alkaloid should be revised as described in the experimental section.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infra-red (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer and ^{1}H-NMR spectra with a JEOL JNM PMX60 or JNM FX100S spectrometers with tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi M-80 spectrometer. Preparative thin layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (SiO_2, Type 60) or Merck Aluminium Oxide GF_{254} (Al_2O_3, Type 60/E). Column chromatography was performed on silica gel (SiO_2,

100-200 mesh, from Kanto Chemical Co., Inc.) or activated alumina (Al_2O_3, 300 mesh, from Wako Pure Chemical Industries, Ltd.) throughout present study.

E-4-Methoxy-3-(2-nitrovinyl)indole (5a) and 4-Methoxy-3-[2-nitro-1-(nitromethyl)-ethyl]indole (6) from 4-Methoxy-3-indolecarbaldehyde (4a) ———— A mixture of 4a (99.5 mg), dried NH_4OAc (109.3 mg), and CH_3NO_2 (3.0 ml) was heated under reflux for 30 min. After evaporation of the solvent under reduced pressure, H_2O was added to the residue and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave a crystalline solid, which was recrystallized from MeOH to give 5a (97.7 mg) as red prisms. Mother liquor was subjected to p-TLC on SiO_2 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent. Under UV light, two bands were detected. Extraction of the upper band with CH_2Cl_2-MeOH (95:5, v/v) afforded 6 (5.1 mg, 3.2%). Extraction of the lower band with the same solvent afforded further crop of 5a (16.1 mg). Total yield of 5a was 113.8 mg (91.8%). 5a: mp 185.0-188.0°C (Lit.[5a] mp 189-190°C, red prisms, recrystallized from MeOH). IR (KBr): 3250, 1608, 1510 cm^{-1}. ^{1}H-NMR (10% DMSO-d_6 in $CDCl_3$) δ: 3.92 (3H, s), 6.54 (1H, dd, J=6 and 2.5 Hz), 6.68-7.28 (2H, m), 7.58 (1H, d, J=3.2 Hz), 7.81 (1H, d, J=13 Hz), 8.39 (1H, d, J=13 Hz), 11.39 (1H, br s). MS m/z: 218 (M^+). 6: mp 115.0-116.0°C (pale yellow prisms, recrystallized from MeOH). IR (KBr): 3400, 1615, 1541, 1377 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.90 (3H, s), 4.49-5.07 (5H, m), 6.43 (1H, dd, J=6.5 and 1.8 Hz), 6.74-7.23 (3H, m), 9.39 (1H, br s). MS m/z: 279 (M^+). Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.65; H, 4.69; N, 15.05. Found: C, 51.76; H, 4.64; N, 15.09.

4-Methoxytryptamine (7a) from 5a ———— A solution of 5a (316.2 mg) in abs. THF (14.0 ml) was added to a suspension of $LiAlH_4$ (596.8 mg) in abs. THF (6.0 ml) and heated under reflux for 1 h with stirring. Excess $LiAlH_4$ was destroyed by adding MeOH with caution under cooling in an ice bath. H_2O and aq. Rochelle salt were added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v), washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with $CHCl_3$-MeOH-NH_4OH (20:5:1, v/v) as a developing solvent. Extraction with the same solvent system from the band having Rf value of 0.47-0.19 afforded 7a (275.1 mg, 99.8%), mp 146.0-147.0°C (Lit.[5b] mp 139-140°C, colorless prisms, recrystallized from MeOH-CH_2Cl_2). IR (KBr): 3360, 3290, 1615, 1592 cm^{-1}. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 1.45 (2H, br s), 3.01 (4H, s), 3.91 (3H, s), 6.48 (1H, dd, J=7.3 and 1.4 Hz), 6.87 (1H, d, J=2.4 Hz), 6.94 (1H, dd, J=8.2 and 1.4 Hz), 7.05 (1H, dd, J=8.2 and 1.4 Hz), 8.13 (1H, br s). MS m/z: 190 (M^+). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.40; H, 7.51; N, 14.77.

N_b-Acetyl-4-methoxytryptamine (8a) from 7a ———— Acetic anhydride (0.5 ml) was added to a solution of 7a (25.8 mg) in pyridine (1.0 ml). After being stirred at room temperature for 15 h, solvent was evaporated off under reduced pressure 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 to give 8a (30.0 mg, 95.2%), mp 100.0-101.0°C (colorless prisms, recrystallized from ether-hexane). IR (KBr): 3420, 1649 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, s), 3.00 (2H, t, J=6 Hz), 3.51 (2H, q, J=6 Hz), 3.84 (3H, s), 5.97 (1H, br s, NH), 6.35 (1H, dd, J=6.2 and 2.1 Hz), 6.59-7.17 (3H, m), 8.49 (1H, br s). MS m/z: 232 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.14; H, 7.01; N, 11.93.

3,4-Dihydro-5-methoxy-1-methyl-β-carboline (9a) from 8a ——— Phosphorus pentoxide (10.134 g) was added to a suspension of 8a (502.6 mg) in xylene (25.0 ml) and the mixture was heated at 140°C for 3.5 h with stirring. Excess P_2O_5 was destroyed by adding H_2O cautiously under ice cooling. The whole was made alkaline by adding 10% aq. NaOH and extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a cryatalline solid. Crystallization from benzene afforded 9a (287.2 mg). Mother liquor was purified by p-TLC on Al_2O_3 with CH_2Cl_2-MeOH (97:3, v/v) as a developing solvent to give a further crop of 9a (53.4 mg), mp 200.0-202.0°C (dec., colorless needles, recrystallized from CH_2Cl_2-n-hexane). Total yield of 9a was 340.6 mg (73.5%). IR (KBr): 1620, 1580, 1548, 1518 cm^{-1}. ^{1}H-NMR (10% DMSO-d_6 in $CDCl_3$) δ: 2.31 (3H, br s), 2.97 (2H, t, J=8 Hz), 3.73 (2H, t, J=8 Hz), 3.82 (3H, s), 6.29 (1H, dd, J=6.4 and 2 Hz), 6.73-7.15 (2H, m). MS m/z: 214 (M^+). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.58; H, 6.47; N, 13.14.

2-Acetyl-5-methoxy-1-methylene-1,2,3,4-tetrahydro-β-carboline (10a) from 9a ——— Acetic anhydride (2.0 ml) was added to a solution of 9a (256.0 mg) in pyridine (4.0 ml) and the mixture was stirred at 13°C for 3.5 h. Evaporation of the solvent under reduced pressure afforded a crystalline solid, which was recrystallized from MeOH to give 10a (183.7 mg). Mother liquor was concentrated in vacuo to leave an oil, which was dissolved in CH_2Cl_2-MeOH (95:5, v/v). The solution was washed with sat. aq. $NaHCO_3$, then with H_2O, dried over Na_2SO_4, and evaporated to leave an oil, which was purified by p-TLC on Al_2O_3 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent to give a further crop of 10a (50.0 mg), mp 217.0-219.0°C (dec., colorless prisms, recrystallized from MeOH). Total yield of 10a was 233.7 mg (76.3%). IR (KBr): 3220, 1622, 1583, 1397, 1250 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 2.21 (3H, s), 3.03 (2H, t, J=5.6 Hz), 3.79 (3H, s), 3.98 (2H, t, J=5.6 Hz), 4.85 (1H, br s), 5.29 (1H, br s), 6.30 (1H, dd, J=6.4 and 1.6 Hz), 6.76 (1H, dd, J=8 and 1.6 Hz), 6.95 (1H, dd, J=8 and 6.4 Hz). MS m/z: 256 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.47; H, 6.49; N, 10.86.

2-Acetyl-5-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (11a) from 10a ——— Powdered $KMnO_4$ (12.6 mg) was added to a solution of 10a (21.0 mg) and 18-crown-6 (4.3 mg) in benzene (6.0 ml) and the mixture was stirred at 17°C for 3 h. After addition of CH_2Cl_2-MeOH (95:5, v/v, 6.0 ml), the whole was filtered through SiO_2 to remove precipitates. The filtrate was concentrated under reduced pressure to leave an oil, which was subjected to p-TLC on Al_2O_3 with CH_2Cl_2-MeOH (99:1, v/v) as a developing solvent. Under UV light, two bands were detected. Extraction of the upper band with CH_2Cl_2-MeOH (95:5, v/v) afforded 11a (2.9 mg, 13.8%). Extraction of the lower band with the same solvent afforded the recovered 10a (5.7 mg, 27.1%). 11a: mp 210.0-212.0°C (colorless needles, recrystallized from MeOH). IR (KBr): 3290, 1687, 1655, 1615, 1579 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 3.20 (2H, t, J=6.4 Hz), 3.86 (3H, s), 4.24 (2H, t, J=6.4 Hz), 6.38 (1H, dd, J=7.2 and 0.8 Hz), 6.87 (1H, dd, J=8.4 and 0.8 Hz), 7.15 (1H, dd, J=8.4 and 7.2 Hz), 9.27 (1H, br s). MS m/z: 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.86; H, 5.51; N, 10.56.

5-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (1a) from 11a ——— 30% Aq. KOH (0.136 ml) was added to a solution of 11a (40.7 mg) in EtOH (10.0 ml) and the mix-

ture was heated at 55-60°C for 30 min with stirring. After evaporation of the solvent under reduced pressure, H_2O was added to the residue and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent to afford 1a (33.6 mg, 98.6%), mp 216.0-217.0°C (colorless prisms, recrystallized from MeOH). UV λ_{max}^{EtOH}nm (log ε): 236 (4.46), 295 (4.16). λ_{min}^{EtOH}nm (log ε): 258 (3.31). IR (KBr): 3180, 1652 cm^{-1}. ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 3.06 (2H, t, J=7 Hz), 3.47 (2H, t, J=7 Hz), 3.84 (3H, s), 6.46 (1H, dd, J=7.4 and 1 Hz), 6.95 (1H, dd, J=8 and 1 Hz), 7.10 (1H, dd, J=8 and 7.4 Hz), 7.44 (1H, br s), 11.50 (1H, br s). MS m/z: 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.64; H, 5.52; N, 12.90. ^{13}C-NMR spectrum was identical with that of the natural alkaloid, kindly provided by Dr. J. Banerji. IR spectrum of the natural alkaloid exhibited two extra bands at 1575 (sh) and 1535 cm^{-1} when compared with our sample, showing the presence of some impurity.

4-Methoxytryptamine (7a) from 1a ——— A mixture of 1a (35.3 mg) in MeOH (2.0 ml) and 40% aq. NaOH (2.0 ml) was heated under reflux for 2 h with stirring. After evaporation of MeOH, concd. HCl (1.8 ml) was added to the residue and the whole was heated under reflux for 2 h. The whole was made alkaline by adding 10% aq. NaOH and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was purified by p-TLC on SiO_2 with $CHCl_3$-MeOH-NH_4OH (20:5:1, v/v) as a developing solvent. Extraction of the band having Rf value of 0.47-0.19 with the same solvent system gave 7a (18.2 mg, 58.6%) as colorless prisms. This product was identical with the sample prepared by the reduction of 5a with $LiAlH_4$.

7-Methoxy-3-indolecarbaldehyde (4b) from 7-Methoxyindole (3) ——— A solution of 3 (203.3 mg) in abs. DMF (2.0 ml) was added to the Vilsmeier reagent, prepared from $POCl_3$ (424.9 mg) and abs. DMF (1.0 ml). After being stirred at room temperature for 5 h, ice and H_2O were added. The whole was made alkaline by adding 10% aq. NaOH and extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline solid, which was subjected to column chromatography on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as an eluent to afford 4b (222.4 mg, 91.7%), mp 165.0-165.0°C (colorless prisms, recrystallized from CH_2Cl_2-MeOH). IR (KBr): 3120 (br), 1621 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.87 (3H, s), 6.61 (1H, dd, J=7.8 and 1.2 Hz), 7.06 (1H, t, J=7.8 Hz), 7.62 (1H, br d, J=1.6 Hz), 7.70 (1H, dd, J=7.8 and 1.2 Hz), 9.74 (1H, s). MS m/z: 175 (M^+). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.25; H, 5.03; N, 7.93.

E-7-Methoxy-3-(2-nitrovinyl)indole (5b) from 4b ——— A mixture of 4b (610.6 mg), dried NH_4OAc (348.2 mg), and CH_3NO_2 (15.0 ml) was heated at 103-107°C for 2.5 h with stirring. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2-MeOH (95:5, v/v). The whole was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave the crude product which was recrystallized from AcOEt-n-hexane to afford 5b as orange needles (661.5 mg). Mother liquor was purified by p-TLC on SiO_2 with CH_2Cl_2 as a developing solvent to afford a further crop of 5b (51.1 mg), mp 172.5-173.0°C. Total yield of 5b was 712.6 mg (93.7%). IR (KBr): 3305, 1615, 1583, 1309 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 3.92

(3H, s), 6.64 (1H, dd, J=6.4 and 2 Hz), 7.07 (1H, t, J=8 and 6.4 Hz), 7.23 (1H, dd, J=8 and 2 Hz), 7.49 (1H, br d, J=2.4 Hz), 7.58 (1H, d, J=12.8 Hz), 8.15 (1H, d, J=12.8 Hz), 10.42 (1H, br s). MS m/z: 218 (M^+). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.24; H, 4.51; N, 12.78.

7-Methoxytryptamine (7b) from 5b ——— $LiAlH_4$ (104.1 mg) was added to a solution of 5b (54.9 mg) in abs. THF (3.0 ml) and the mixture was heated under reflux for 1 h. Excess $LiAlH_4$ was destroyed by adding AcOEt, and then with H_2O. After addition of aq. Rochelle salt, the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline solid, which was purified by p-TLC on Al_2O_3 with AcOEt-$CHCl_3$-MeOH-NH_4OH (20:27:3:2, v/v) as a developing solvent to afford 7b (42.2 mg, 88.2%), mp 133.0-135.0°C (colorless prisms, recrystallized from CH_2Cl_2-n-hexane). IR (KBr): 3335, 3280, 1623, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (2H, br s), 2.63-3.16 (4H, m, A_2B_2), 3.86 (3H, s), 6.49 (1H, dd, J=7.4 and 1.6 Hz), 6.71-7.00 (2H, m), 7.08 (1H, dd, J=7.4 and 1.6 Hz), 8.19 (1H, br s). MS m/z: 190 (M^+). Anal. Calcd for $C_{11}H_{14}N_2O \cdot 1/4H_2O$: C, 67.83; H, 7.25; N, 14.39. Found: C, 67.49; H, 7.21; N, 14.06.

N_b-Acetyl-7-methoxytryptamine (8b) from 7b ——— Acetic anhydride (0.5 ml) was added to a solution of 7b (48.1 mg) in pyridine (1.0 ml). After being stirred at room temperature for 4h, the solvent was evaporated under reduced pressure to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent to give 8b (56.3 mg, 95.9%) as a colorless oil. IR (film): 3400, 3280, 1645 (br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, s), 2.89 (2H, t, J=6.4 Hz), 3.52 (2H, q, J=6.4 Hz), 3.88 (3H, s), 5.41 (1H, br s), 6.50 (1H, dd, J=7 and 1.6 Hz), 6.73-7.16 (3H, m), 8.14 (1H, br s). High resolution MS m/z: Calcd for $C_{13}H_{16}N_2O_2$: 232.1211. Found: 232.1215.

3,4-Dihydro-8-methoxy-1-methyl-β-carboline (9b) from 8b ——— A mixture of 8b (18.7 mg) and freshly distilled $POCl_3$ (1.0 ml) was heated at 108-109°C for 20 min with stirring. After evaporation of $POCl_3$ under reduced pressure, ice and H_2O were added and the whole was made alkaline by adding 10% aq. NaOH and extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline solid, which was purified by p-TLC on Al_2O_3 with CH_2Cl_2-AcOEt-MeOH (19:2:1, v/v) as a developing solvent to give 9b (14.4 mg, 83.5%), mp 170.5-171.0°C (yellow prisms, recrystallized from CH_2Cl_2-n-hexane). IR (KBr): 3410, 1608, 1574, 1551, 1260 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.45-2.57 (3H, t, J=1.3 Hz), 2.79 (2H, dd, J=8.3 and 7.2 Hz), 3.62 (3H, s), 3.87 (2H, dd, J=8.3 and 7.2 Hz), 6.59 (1H, dd, J=6.7 and 1.6 Hz), 6.99 (1H, dd, J=7.4 and 6.7 Hz), 7.20 (1H, dd, J=7.4 and 1.6 Hz), 12.04 (1H, br). MS m/z: 214 (M^+). Anal. Calcd for $C_{13}H_{14}N_2O \cdot 1/4H_2O$: C, 71.36; H, 6.45; N, 12.81. Found: C, 70.96; H, 6.50; N, 12.41.

2-Acetyl-8-methoxy-1-methylene-1,2,3,4-tetrahydro-β-carboline (10b) from 9b ——— Acetic anhydride (0.5 ml) was added to a solution of 9b (52.5 mg) in pyridine (1.0 ml). After being stirred at room temperature for 30 min, the whole was ice cooled. Ice-cooled sat. aq. $NaHCO_3$ was added until the whole became alkaline and then extracted with CH_2Cl_2-MeOH (95:5, v/v), washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent to afford 10b

(51.3 mg, 81.6%), mp 223.0-223.5°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3140, 1648, 1615, 1572 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 2.22 (3H, s), 2.80 (2H, t, J=5.4 Hz), 3.88 (3H, s), 4.01 (2H, t, J=5.4 Hz), 4.90 (1H, br s), 5.38 (1H, br s), 6.53 (1H, dd, J=6 and 3.2 Hz), 6.66-7.03 (2H, m), 9.15 (1H, br s). MS m/z: 256 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.27; H, 6.28; N, 10.89. Found: C, 70.29; H, 6.29; N, 10.93.

2-Acetyl-8-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (11b) from 10b ——— A solution of 18-crown-6 (8.5 mg) in benzene (4.0 ml) was added to a solution of 10b (35.8 mg) in benzene (16.0 ml). $KMnO_4$ (87.9 mg) was added to the solution in four portions at every 1 h interval with stirring. After being stirred at room temperature for 4 h, CH_2Cl_2-MeOH (95:5, v/v) was added and allowed to stand for 30 min. Precipitates were removed by filtration through SiO_2 and the filtrate was concentrated in vacuo to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent to afford 11b (10.2 mg, 28.2%), mp 181.5-182.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3320, 1690, 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s), 2.97 (2H, t, J=6.4 Hz), 3.89 (3H, s), 4.24 (2H, t, J=6.4 Hz), 6.60 (1H, dd, J=6.2 and 2.4 Hz), 6.77-7.15 (2H, m), 8.99 (1H, br s). MS m/z: 258 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.43; N, 10.82. Found: C, 65.10; H, 5.46; N, 10.85.

8-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (1b) from 11b ——— A solution of 11b (19.1 mg) in EtOH (4.0 ml) and 30% aq. KOH (0.064 ml) was heated at 56°C for 15 min with stirring. H_2O was added and the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2-MeOH (95:5, v/v) as a developing solvent to afford 1b (14.5 mg, 90.6%), mp 244.0-246.0°C (colorless needles, recrystallized from MeOH). IR (KBr): 3170, 1648 cm^{-1}. ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 2.89 (2H, t, J=6.8 Hz), 3.50 (2H, t, J=6.8 Hz), 3.89 (3H, s), 6.74 (1H, d, J=7.3 Hz), 6.98 (1H, t, J=7.3 Hz), 7.16 (1H, d, J=7.3 Hz), 7.45 (1H, br s), 11.44 (1H, br s). MS m/z: 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.54; H, 5.53; N, 13.11.

5-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (1a) and 7-Methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline (13) from 3-Methoxyphenylhydrazone of 2,3-Piperidinedione (12) ——— A solution of 12 (975.6 mg) in 88% HCOOH (10.0 ml) was heated under reflux for 2 h with stirring. After evaporation of HCOOH in vacuo, the black residue was subjected to column chromatography repeatedly on SiO_2 with CH_2Cl_2-MeOH (98:2, v/v) as an eluent. From the early part of the fractions, 63.0 mg (7.0%) of 1a was obtained. This compound was identical with the sample prepared from 11a via the Bischler-Napieralski cyclization reaction. From the later part of the fractions, 13 (416.9 mg, 46.1%) was obtained. 13: mp 204.0-206.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3180, 1642, 1615 cm^{-1}. ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 2.85 (2H, t, J=7 Hz), 3.16 (3/6H, d, J=5.2 Hz, CH_3OH of crystallization), 3.47 (2H, dt, J=7 and 2.4 Hz), 3.75 (3H, s), 4.06 (1/6H, q, J=5.2 Hz, CH_3OH of crystallization), 6.65 (1H, dd, J=8.7 and 2.2 Hz), 6.79 (1H, d, J=2.2 Hz), 7.34 (1H, br s, NH), 7.41 (1H, d, J=8.7 Hz), 11.33 (1H, br s, NH). MS m/z: 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2 \cdot 1/6CH_3OH$: C, 65.95; H, 5.76; N, 12.64. Found: C, 65.86; H, 5.64; N, 12.90.

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