Reactions of the Cyclic Tautomer of 3-Indoleacetamides. Synthesis of *N*_b-Methyl-4,5,6-tribromo-3-indoleacetamide¹⁾

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The cyclic tautomer (**5**) of *N*_b-methyl-3-indoleacetamide (**4**) has been prepared by dissolving **4** in phosphoric acid. The bromination of **5** with 1 or 2 mol of *N*-bromosuccinimide (NBS) or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO) gave the 5-bromo- (**8**) and the 5,7-dibromo (**9**) derivatives. On the other hand, the 5-bromo derivative (**11**) was the major product of the bromination of the *N*-acetyl cyclic tautomer (**6**) even with 2 mol of NBS. The 5-nitro derivative (**17**) was obtained in excellent yield by the nitration of **6** with ammonium nitrate in trifluoroacetic anhydride (TFAA). Reduction of **17** followed by bromination gave the 4,6-dibromo derivative (**19**), which gave the tribromide (**20**) in the Sandmeyer reaction. The 4,5,6-tribromo-3-indoleacetamide (**7**), which is the indole moiety of a marine indole alkaloid, chartelline A, was obtained by the ring opening of **20**. Furthermore, the oxidation of **5** with lead tetraacetate followed by acetylation gave the 5-acetoxy derivative (**22**). The selective hydrolysis and bromination of **22** gave the 4,6-dibromo-5-hydroxy derivative (**24**).

Keywords cyclic tautomer; 3-indoleacetamide; nitration; bromination; 4,5,6-tribromoindole; chartelline; *N*-bromosuccinimide; ammonium nitrate

We have previously reported that the cyclic tautomer (**2**, X=H) could readily be obtained from *N*_b-acyltryptophans (**1**), and its electrophilic substitution reaction provided a convenient method for the preparation of the 5- and 6-substituted tryptophans (**3**) from tryptophan *via* **2**.²⁾

In this paper we describe the preparation and reactions of the cyclic tautomers (**5** and **6**) of the 3-indoleacetamide (**4**) and the synthesis of *N*_b-methyl-4,5,6-tribromo-3-indoleacetamide (**7**), which is the indole moiety of chartelline A, a unique indole alkaloid isolated from marine Bryozoa.³⁾ Regioselective synthesis of 4,5,6-tribromo-3-indolecarbaldehyde and other tri- and tetrabromoindoles related to marine natural products has recently been reported by Ohta and Somei by different approaches.⁴⁾

When the indoleacetamide (**4**) was dissolved in 85% phosphoric acid at room temperature as in the case of **1**, the corresponding cyclic tautomer (**5**), mp 149–150 °C, was obtained in 56% yield. Acetylation of **5** with acetic anhydride–pyridine readily gave the 8-acetyl derivative (**6**). The ultraviolet (UV) spectrum of **5** showed an indoline chromophore ($\lambda_{\max}$ 243 and 296 nm) and its ¹H-nuclear magnetic resonance (¹H-NMR) spectrum showed a

multiplet at 4.03 ppm due to the 3a proton and a doublet at 5.33 ppm due to the 8a proton. The NMR spectrum of the acetyl derivative (**6**) showed the presence of rotamers due to slow rotation of the C–N bond of the *N*-acetyl group; *i.e.*, two small peaks appeared at 4.07 (3a-H) and 5.90 (8a-H) ppm besides a broad peak at 3.95 ppm due to the 3a proton and a broad doublet at 6.33 ppm due to the 8a proton.^{2d)}

The cyclic tautomer (**5**) was stable in acetic acid, compared with the cyclic tautomer (**2**, X, R²=H, R¹=CO₂Me), which readily reverted to **1** in acetic acid.^{2d)} However, the cyclic tautomers (**5** and **6**) reverted to the indole (**4**) on treatment with 10% sulfuric acid (H₂SO₄)–methanol (MeOH) at room temperature.

The bromination of **5** with *N*-bromosuccinimide (NBS)^{2f)} (1 mol eq) in methylene chloride (CH₂Cl₂) at room temperature gave the 5-bromo derivative (**8**) in 90% yield along with the 5,7-dibromo derivative (**9**, 8%). The reaction with 2 mol eq of NBS gave **9** in 89% yield. The bromination of **5** with NBS (1 mol eq) in acetic acid (AcOH) at room temperature gave **8** (63%) and **9** (16%), while **9** (47%) and the 5,7-dibromo-3-indoleacetamide (**10**, 43%) were ob-

Chart 1

tained with 2 mol eq of NBS. The latter compound (**10**) was probably formed from **9** under these reaction conditions. The bromination of **8** with NBS (1 mol eq) in AcOH gave **9** (94%). The bromination of **5** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO)⁵ in

CH₂Cl₂ gave similar results (see Experimental). The bromination of **9** with NBS (1 mol eq) in AcOH did not give the tribromo derivative, and **9** was recovered.

On the other hand, the bromination of the *N*-acetyl cyclic tautomer (**6**) with NBS or TABCO did not proceed at room

Chart 2

Chart 3

temperature in CH_2Cl_2 or AcOH. However, the bromination of **6** with NBS in AcOH at refluxing temperature gave the 5-bromo derivative (**11**) in 91% yield. The reaction of **6** using 2 mol eq of NBS in boiling AcOH gave only **11** and not the 5,7-dibromo derivative. The bromination of **6** with TABCO gave poorer results (see Experimental). It is interesting to note that the bromination of **2** (R^1 , $\text{X}=\text{H}$, $\text{R}^2=\text{Ac}$) with NBS in AcOH and the chlorination of **2** ($\text{X}=\text{H}$, $\text{R}^1=\text{CO}_2\text{Me}$, $\text{R}^2=\text{Ac}$) with *N*-chlorosuccinimide (NCS) proceeded at room temperature to give the 5-substituted derivative in excellent yield,^{2b,f)} whereas **6** required the refluxing temperature of AcOH. The above result indicated that 4,5,6-tribromoindole could not be obtained by direct bromination of **8** or **11**.

We next examined the nitration of **5** with ammonium nitrate (NH_4NO_3) in trifluoroacetic anhydride (TFAA).⁶⁾ The reaction at 0°C gave the 5-nitro-8-trifluoroacetyl derivative (**13**), which was converted to the 5-nitro derivative (**14**) by refluxing in MeOH. The reaction probably proceeded first to give **12**, which was isolated from the reaction at -60°C, and **12** was nitrated to give **13**. On the other hand, the nitration of **5** with fuming nitric acid (HNO_3) in acetic anhydride at -10°C gave the 8-nitro derivative (**15**, 21%), mp 130–131°C, along with **6**. The structure of **15** was fully supported by spectral data and elemental analysis. Furthermore, **14** was obtained in 20% yield along with **5** (13%) and the 7-nitro derivative (**16**, 19%), when **15** was refluxed in MeOH. The nitration of **6** with fuming HNO_3 at -10°C^{2f)} or with NH_4NO_3 in TFAA at room temperature gave the 5-nitro derivative (**17**) in 91% yield or 89% yield, and the 7-nitro derivative could not be obtained.

The catalytic hydrogenation of **13** and **14** in the presence of Pd-C in MeOH smoothly gave the corresponding amino derivatives, which were not stable and readily discolored in air. Similar catalytic hydrogenation of **17** gave the corresponding amine (**18**) which gave the 4,6-dibromo derivative (**19**) in 45% yield from **17** on bromination with NBS (2 mol eq) in AcOH. Sandmeyer reaction of **19** gave the tribromo derivative (**20**) in 86% yield. Ring opening of **20** with 10% H_2SO_4 in MeOH readily gave *N*-methyl-4,5,6-tribromo-3-indoleacetamide (**7**). On the other hand, the tetrabromide (**21**, 89%) was obtained by the Sandmeyer reaction for 5d at room temperature.

Oxidation of **5** with lead tetraacetate in trifluoroacetic acid (TFA) followed by reduction of the resulting quinoneimine with zinc^{2b,g)} and acetylation gave the 5-acetoxy-8-acetyl derivative (**22**) in 44% yield. The 6-acetoxy and other isomers could not be isolated. Selective hydrolysis of **22** with potassium carbonate (K_2CO_3) in MeOH smoothly gave the 5-hydroxy derivative (**23**). The bromination of **23** with NBS (2 mol eq) in CH_2Cl_2 gave the 4,6-dibromo derivative (**24**) in 70% yield along with the monobromo derivatives (**25**, 17%), which gave **24** (82%) on further bromination.

In conclusion, the cyclic tautomers (**5** and **6**) were found to be useful intermediates for the preparation of substituted 3-indoleacetamides.

Experimental

Melting points were measured with a Yamato MR-1 apparatus and are not corrected. The UV spectra were taken with Hitachi 323 and 340 spectrometers, and the infrared (IR) spectra with Hitachi 260-10 and 295

spectrometers. The mass spectra (MS) were recorded on Hitachi M-60 and 7M spectrometers, and the NMR spectra in CDCl_3 solution on JEOL JNM-GX-270, GSX-400, and GSX-500 apparatus using tetramethylsilane as an internal standard. Kieselgel (Merck, 300 mesh) was used for flash columns. Kieselgel 60 (Merck, 70–230 mesh) or Silica gel BW-820MH (Fuji-Davison) was used for open columns. Kieselgel GF₂₅₄ type 60 (Merck) DCI Fertigplatten SILG-50 UV₂₅₄ was used for preparative thin layer chromatography (TLC).

***N*-Methyl-3-indoleacetamide (4)** Methylamine (40% aqueous solution, 150 ml) was added to a solution of methyl 3-indoleacetate (106 g, 0.56 mol) in MeOH (350 ml) at room temperature, and the mixture was stirred for 15 h, then evaporated to leave a residue, which was recrystallized from AcOEt-hexane to give **4** (102 g, 97%). Recrystallization from AcOEt-hexane gave pale brown needles, mp 101–102°C. UV λ_{max} (EtOH) nm (ϵ): 222 (25300), 273 (5480), 280 (6000), 289 (5100). IR ν_{max} (KBr) cm^{-1} : 3300 (NH), 1630 (CO). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.12; H, 6.44; N, 14.86.

1-Methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (5) **4** (10.0 g, 53.2 mmol) was dissolved in 85% phosphoric acid (70 ml) at room temperature. The solution was stirred for 17 h at room temperature, and then poured into chilled 20% Na_2CO_3 solution (300 ml). The mixture was extracted with CH_2Cl_2 and the extract was washed with saturated NaCl solution, and then dried. Evaporation of the solvent gave a residue (9.96 g), which was chromatographed on a silica gel column (500 g, AcOEt-hexane-MeOH, 40:1:1–60:1:2) to give **5** (5.64 g, 56%), **4** (1.6 g, 16%), and more polar products. Recrystallization of **5** from acetone-hexane gave colorless needles, mp 149–150°C. UV λ_{max} (MeOH) nm (ϵ): 243 (6600), 296 (2500). IR ν_{max} (KBr) cm^{-1} : 1650 (CO). MS m/z (rel. intensity): 188 (M^+ , 100), 130 (85). ¹H-NMR (270 MHz) δ : 2.62 (1H, dd, $J=17.1$, 2.4 Hz, 3-Ha), 2.85 (3H, s, NCH_3), 2.93 (1H, dd, $J=17.1$, 10.4 Hz, 3-Hb), 4.03 (1H, m, 3a-H), 4.56 (1H, br, 8-H), 5.33 (1H, d, $J=7.6$ Hz, 8a-H), 6.66–7.12 (4H, m, arom. H). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.51; N, 14.81.

8-Acetyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (6) **5** (1.53 g, 8.1 mmol) was dissolved in acetic anhydride (15 ml) and pyridine (50 ml), and the mixture was stirred overnight. Usual work up gave **6** (1.89 g, 100%). Recrystallization from acetone-hexane gave colorless needles, mp 184–186°C. UV λ_{max} (EtOH) nm (ϵ): 205 (25600), 243 (12900), 276 (2300). IR ν_{max} (KBr) cm^{-1} : 1700, 1655 (CO). ¹H-NMR (270 MHz) δ : 2.47 (3H, s, CH_3CO), 2.63 (1H, d-like, 3-Ha), 2.90 (3H, s, NCH_3), 2.95 (1H, m, 3-Hb), 3.95 (4/5H, br, 3a-H), 4.07 (1/5H, br, 3a-H), 5.90 (1/4H, br, 8a-H), 6.33 (3/4H, brd, 8a-H), 7.10–7.30 (4H, m, arom. H). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.18; N, 12.17. Found: C, 67.58; H, 6.11; N, 12.07.

Bromination of 5 1) NBS in CH_2Cl_2 : NBS (104 mg, 1.1 eq) was added to a solution of **5** (100 mg, 0.532 mmol) in CH_2Cl_2 (6 ml) at room temperature, and the mixture was stirred for 5 min. The mixture was evaporated to leave a residue (216 mg), which was separated by flash column chromatography (SiO_2 , 15 g, AcOEt-hexane-MeOH, 3:1:10–15:0:1) to give **8** (128 mg, 90%) and **9** (14.6 mg, 8%). Recrystallization of **8** from acetone-hexane gave colorless prisms, mp 187.5–188°C. UV λ_{max} (MeOH) nm (ϵ): 253 (10400), 309 (2500). IR ν_{max} (KBr) cm^{-1} : 3300 (NH), 1660 (CO). MS m/z (rel. intensity): 268 (M^+ , 100), 266 (M^+ , 100). ¹H-NMR (270 MHz) δ : 2.59 (1H, dd, $J=16.9$, 2.2 Hz, 3-Ha), 2.84 (3H, s, NCH_3), 2.91 (1H, dd, $J=16.9$, 9.9 Hz, 3-Hb), 4.02 (1H, m, 3a-H), 4.62 (1H, br, NH), 5.34 (1H, d, $J=8.1$ Hz, 8a-H), 6.54 (1H, d, $J=8.1$ Hz, 7-H), 7.19 (1H, d, $J=8.1$ Hz, 6-H), 7.20 (1H, s, 4-H). Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{BrN}_2\text{O}$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.37; H, 4.04; N, 10.59. Recrystallization of **9** from acetone-hexane gave colorless needles, mp 240–243°C. UV λ_{max} (EtOH) nm (ϵ): 212 (27900), 254 (10600), 315 (3200). IR ν_{max} (KBr) cm^{-1} : 3320 (NH), 1685 (CO). MS m/z (rel. intensity): 348 (M^+ , 36), 346 (M^+ , 70), 344 (M^+ , 36), 42 (100). ¹H-NMR (270 MHz) δ : 2.58 (1H, dd, $J=17.1$, 2.8 Hz, 3-Ha), 2.88 (3H, s, NCH_3), 2.93 (1H, m, 3-Hb), 4.11 (1H, m, 3a-H), 4.80 (1H, s, NH), 5.40 (1H, dd, $J=7.6$, 2.4 Hz, 8a-H), 7.14 (1H, d, $J=1.8$ Hz, 6-H), 7.37 (1H, d, $J=1.8$ Hz, 4-H). The presence of the 4-H was supported by a difference nuclear Overhauser effect (NOE) experiment, which showed enhancements between 3a-H and 3-Ha (6.2%), 3a-H and 4-H (1.0%), and 3a-H and 8a-H (6.3%). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{Br}_2\text{N}_2\text{O}$: C, 38.18; H, 2.91; N, 8.10. Found: C, 37.92; H, 2.88; N, 7.98.

Bromination of **8** (52 mg) with NBS (38 mg, 1.1 eq) in AcOH (2 ml) gave **9** (63 mg, 94%). Bromination of **5** (300 mg, 1.57 mmol) with NBS (597 mg, 2.0 eq) in CH_2Cl_2 (10 ml) at room temperature gave **9** (493 mg, 89%).

2) TABCO- CH_2Cl_2 : TABCO (120 mg, 1.1 eq) was added to a solution

of **5** (50 mg, 0.266 mmol) in CH_2Cl_2 (5 ml) at room temperature. The mixture was stirred for 10 min, and worked up as above to give **8** (59 mg, 84%) and **9** (11 mg, 12%). The reaction of **5** (50 mg) with TABCO (229 mg, 2.1 eq) in CH_2Cl_2 (5 ml) gave **9** (91 mg, 99%).

3) NBS–AcOH: NBS (298 mg, 2.1 eq) was added to a solution of **5** (150 mg, 0.798 mmol) in AcOH (4 ml) at room temperature. The mixture was stirred for 30 min at room temperature and the solvent was evaporated off to leave a residue. The residue (522 mg) was chromatographed on a silica gel column (40 g, AcOEt–hexane (2:1)–AcOEt) to give **10** (118 mg, 43%) and **9** (129 mg, 47%). Recrystallization of **10** from acetone–hexane gave colorless powder, mp 170–172°C. UV λ_{max} (EtOH) nm: 231, 284, 296, 307. IR ν_{max} (KBr) cm^{-1} : 3290 (NH), 1640 (CO). MS m/z (rel. intensity): 348 (M^+ , 17), 346 (M^+ , 33), 344 (M^+ , 18), 288 (100). $^1\text{H-NMR}$ (400 MHz, in CD_3OD) δ : 2.71 (3H, s, NCH_3), 3.59 (2H, s, CH_2), 7.29 (1H, s, 2-H), 7.40 (1H, d, $J=1.7$ Hz, 4-H), 7.70 (1H, d, $J=1.7$ Hz, 6-H).

The reaction of **5** with NBS (1 eq) in AcOH gave **8** (63%) and **9** (16%).

Bromination of 6 1) NBS–AcOH: NBS (426 mg, 1.1 eq) was added to a solution of **6** (500 mg, 2.17 mmol) in AcOH (8 ml) and the mixture was refluxed for 1 h, and allowed to cool. Then 20% K_2CO_3 solution (30 ml) was added, and the whole was extracted with CH_2Cl_2 . The CH_2Cl_2 solution was washed with saturated NaCl solution and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (35 g, AcOEt–hexane (3:1)–5:1) to give **11** (610 mg, 91%). Recrystallization of **11** from acetone–hexane gave a colorless powder, mp 198–201°C. UV λ_{max} (EtOH) nm (ϵ): 206 (19200), 252 (18100), 285 (2600), 293 (2300). IR ν_{max} (KBr) cm^{-1} : 1695, 1670 (CO). MS m/z (rel. intensity): 310 (M^+ , 84), 308 (M^+ , 85), 268 (100), 266 (99). $^1\text{H-NMR}$ (270 MHz) δ : 2.44 (3H, s, CH_3CO), 2.61 (1H, d-like, 3-Ha), 2.89 (3H, s, NCH_3), 2.94 (1H, m, 3-Hb), 3.94 (2/3H, br t, 3a-H), 4.05 (1/3H, br, 3a-H), 5.87 (1/3H, br, 8a-H), 6.31 (2/3H, br d, 8a-H), 7.38 (1H, d, $J=1.8$ Hz, 4-H), 7.40 (1H, dd, $J=7.6$, 1.8 Hz, 6-H), 7.02 (2/3H, br d, 7-H), 7.93 (1/3H, br s, 7-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_2$: C, 50.51; H, 4.24; N, 9.06. Found: C, 50.34; H, 4.21; N, 8.99.

The same compound was obtained by acetylation of **8** with acetic anhydride–pyridine. The reaction of **6** with NBS (2 eq) in boiling AcOH gave **11** (80%) and the dibromide was not obtained.

2) TABCO– CH_2Cl_2 : TABCO (98 mg, 1.1 eq) was added to a solution of **6** (50 mg, 0.217 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred overnight at room temperature to give **6**, and the mixture was refluxed for 16 h. The solvent was evaporated off to leave a residue, which was subjected to flash column chromatography (SiO_2 , 10 g, AcOEt) to give **11** (37 mg, 56%), and **6** (15 mg, 31%).

Nitration of 5 1) NH_4NO_3 –TFAA at -10°C : NH_4NO_3 (22 mg, 1.05 eq) was added to a solution of **5** (50 mg, 0.266 mmol) in TFAA (3 ml) at -60°C . The mixture was stirred for 6.5 h at -10°C , then was poured into ice-water and extracted with CH_2Cl_2 . The extract was washed with H_2O and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (5 g, AcOEt–hexane (2:1)–1:0) to give **13** (67 mg, 88%). Recrystallization from acetone–hexane gave a colorless powder, mp 233–236°C. UV λ_{max} (EtOH) nm: 225, 306; (EtOH–NaOH) nm: 225, 315, 365. IR ν_{max} (KBr) cm^{-1} : 1720, 1680 (CO). MS m/z (rel. intensity): 329 (M^+ , 100), 260 (57). $^1\text{H-NMR}$ (270 MHz) δ : 2.80 (1H, br d, $J=17.4$ Hz, 3-Ha), 2.88 (3H, s, NCH_3), 3.03 (1H, dd, $J=17.1$, 8.6 Hz, 3-Hb), 4.20 (1H, t-like, $J=7.3$ Hz, 3a-H), 6.26 (1H, br, 8a-H), 7.70–8.45 (1H, br, 7-H), 8.19 (1H, dd, $J=2.4$, 1.2 Hz, 4-H), 8.29 (1H, dd, $J=8.9$, 2.2 Hz, 6-H); at 50°C : 2.78 (1H, br d, $J=17.1$ Hz, 3-Ha), 2.87 (3H, s, NCH_3), 3.00 (1H, dd, $J=17.1$, 8.5 Hz, 3-Hb), 4.16 (1H, dd, $J=8.2$, 7.0 Hz, 3a-H), 6.24 (1H, d, $J=7.0$ Hz, 8a-H), 8.02 (1H, br d, 7-H), 8.17 (1H, dd, $J=2.4$, 1.2 Hz, 4-H), 8.28 (1H, dd, $J=8.9$, 2.4 Hz, 6-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_4$: C, 47.43; H, 3.06; N, 12.76. Found: C, 47.38; H, 3.07; N, 12.79.

When the reaction was quenched after 30 min at -60°C under the above conditions, **12**, mp 117–118°C (MeOH), was obtained in 99% yield. UV λ_{max} (EtOH) nm: 250, 275, 283. IR ν_{max} (KBr) cm^{-1} : 1700, 1670 (CO). MS m/z (rel. intensity): 284 (M^+ , 100), 215 (70). $^1\text{H-NMR}$ (270 MHz) δ : 2.72 (1H, br d, 3-Ha), 2.86 (3H, s, NCH_3), 2.95 (1H, dd, $J=17.1$, 8.5 Hz, 3-Hb), 4.07 (1H, br, 3a-H), 6.15 (1H, br, 8a-H), 7.24–7.96 (3H, m, 4,5,6-H), 8.03 (1H, br, 7-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 54.79; H, 3.90; N, 9.89.

2) NH_4NO_3 –TFAA at 0°C : NH_4NO_3 (223 mg, 1.05 eq) was added to a solution of **5** (500 mg, 2.66 mmol) in TFAA (8 ml) at 0°C . The mixture was stirred for 6.5 h at 0°C , and poured into ice-water (50 ml). This mixture was extracted with CH_2Cl_2 and the extract was washed with H_2O and dried. Evaporation of the solvent gave a residue (crude **13**, 865 mg), which was dissolved in MeOH (50 ml). The solution was refluxed for 1.5 h and

evaporated to leave a residue, which was chromatographed on a silica gel column (35 g, AcOEt–acetone (1:0–1:1–0:1)) to give **14** (610 mg, 98%). Recrystallization from MeOH gave a yellow powder, mp 234–237°C. UV λ_{max} (EtOH) nm (ϵ): 201 (22300), 230 (5600), 243 (4700), 304 (2400), 314 (3400), 369 (14500). IR ν_{max} (KBr) cm^{-1} : 3300 (NH), 1685 (CO). MS m/z (rel. intensity): 233 (M^+ , 100), 175 (70). $^1\text{H-NMR}$ (270 MHz) δ : 2.66 (1H, dd, $J=17.7$, 2.5 Hz, 3-Ha), 2.88 (3H, s, NCH_3), 3.04 (1H, dd, $J=17.1$, 9.8 Hz, 3-Hb), 4.09 (1H, m, 3a-H), 5.33 (1H, br, NH), 5.50 (1H, d, $J=7.9$ Hz, 8a-H), 6.60 (1H, d, $J=8.9$ Hz, 7-H), 8.01 (1H, br, 4-H), 8.07 (1H, dd, $J=8.9$, 0.6 Hz, 6-H). *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.71; H, 4.74; N, 17.96.

3) HNO_3 –Ac₂O: **5** (50 mg, 0.266 mmol) was added to a chilled solution of fuming HNO_3 ($d=1.50$, 0.014 ml) in acetic anhydride (1.4 ml) at -10°C , and the mixture was stirred for 1 h at the same temperature. Work-up as above gave **15** (13 mg, 21%) and **6** (39 mg, 64%). Recrystallization of **15** from AcOEt–hexane gave pale yellow needles, mp 130–131°C. UV λ_{max} (EtOH) nm (ϵ): 271 (6400), 282 (7400), 291 (7700). IR ν_{max} (KBr) cm^{-1} : 1710 (CO), 1535, 1475 (NO_2). $^1\text{H-NMR}$ (500 MHz) δ : 2.59 (1H, dd, $J=17.3$, 2.8 Hz, 3-Ha), 3.02 (1H, dd, $J=17.3$, 10.2 Hz, 3-Hb), 3.07 (3H, s, NCH_3), 4.25 (1H, t-like, 3a-H), 6.51 (1H, d, $J=8.0$ Hz, 8a-H), 7.27 (1H, d, $J=8.3$ Hz, 4-H), 7.31 (1H, t, $J=8.3$ Hz, 6-H), 7.41 (1H, m, 5-H), 7.86 (1H, d, $J=8.3$ Hz, 7-H). *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.78; H, 4.84; N, 17.84.

Reaction of 15 in Boiling MeOH A solution of **15** (100 mg, 0.429 mmol) in MeOH (8 ml) was refluxed for 23 h. Evaporation of the solvent gave a residue, which was separated by flash column chromatography (SiO_2 , 8 g, AcOEt–hexane (5:1)–1:0) to give **14** (20 mg, 20%), **15** (10 mg, 10%), **16** (19 mg, 19%), and **5** (10 mg, 13%). Recrystallization of **16** from AcOEt–hexane gave pale yellow needles, mp 214–216°C. UV λ_{max} (EtOH) nm: 238, 277, 398. IR ν_{max} (KBr) cm^{-1} : 3420 (NH), 1685 (CO), 1510, 1450 (NO_2). $^1\text{H-NMR}$ (500 MHz) δ : 2.65 (1H, dd, $J=17.3$, 2.2 Hz, 3-Ha), 2.92 (3H, s, NCH_3), 3.01 (1H, dd, $J=17.3$, 9.9 Hz, 3-Hb), 4.09 (1H, ddd, $J=9.9$, 8.8, 2.2 Hz, 3a-H), 5.56 (1H, d, $J=8.8$ Hz, 8a-H), 6.76 (1H, dd, $J=8.5$, 7.2 Hz, 5-H), 7.31 (1H, d, $J=7.2$ Hz, 4-H), 7.37 (1H, br, NH), 7.90 (1H, d, $J=8.8$ Hz, 6-H).

Nitration of 6 NH_4NO_3 (730 mg, 1.05 eq) was added gradually to a solution of **6** (2.00 g, 8.70 mmol) in TFAA (30 ml) under ice cooling. The mixture was stirred for 3 h at room temperature, then poured into ice-water (150 ml) and extracted with CH_2Cl_2 . The CH_2Cl_2 solution was washed with H_2O and dried. Evaporation of the solvent gave a residue (2.68 g), which was recrystallized from acetone–hexane to give **17** (2.13 g, 89%) as cotton-like crystals, mp 239.5–241.5°C. UV λ_{max} (EtOH) nm (ϵ): 205 (4300), 229 (9900), 318 (12400). IR ν_{max} (KBr) cm^{-1} : 1695 sh, 1670 (CO), 1515, 1480 (NO_2). MS m/z (rel. intensity): 275 (M^+ , 49), 233 (100). $^1\text{H-NMR}$ (270 MHz) δ : 2.52 (3H, s, CH_3CO), 2.73 (1H, d-like, 3-Ha), 2.92 (3H, s, NCH_3), 3.02 (1H, dd, $J=17.5$, 9.3 Hz, 3-Hb), 4.10 (1H, br, 3a-H), 6.30 (1H, br, 8a-H), 7.10–7.60 (1H, br, 7-H), 8.14 (1H, br, 4-H), 8.24 (1H, dd, $J=8.2$, 1.8 Hz, 6-H); at 50°C : 2.50 (3H, s, CH_3CO), 2.70 (1H, d-like, 3-Ha), 2.91 (3H, s, NCH_3), 3.00 (1H, dd, $J=17.4$, 9.2 Hz, 3-Hb), 4.06 (1H, t-like, 3a-H), 6.20 (1H, br, 8a-H), 7.62 (1H, br, 7-H), 8.11 (1H, d, $J=2.1$ Hz, 4-H), 8.21 (1H, dd, $J=8.9$, 2.1 Hz, 6-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.77; N, 15.16.

Compound **17** was also obtained by the acetylation of **14** with acetic anhydride–pyridine. The nitration of **6** with fuming HNO_3 ($d=1.5$) at -10°C gave **17** in 91% yield.

8-Acetyl-5-amino-4,6-dibromo-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-one (19) from 17 A mixture of **17** (1.96 g, 7.13 mmol), MeOH (50 ml), 10% Pd–C (300 mg), and concentrated HCl (2 drops) was hydrogenated for 4.5 h under an H_2 atmosphere and at atmospheric pressure. The mixture was filtered and the filtrate was evaporated to leave a residue, which was dissolved in H_2O (20 ml) and CH_2Cl_2 (50 ml). The aqueous layer was basified with 20% K_2CO_3 solution and extracted with CH_2Cl_2 . The combined CH_2Cl_2 solution was dried and evaporated to leave a crude amine (**18**, 1.91 g). UV λ_{max} (EtOH) nm: 268, 312. NBS (2.66 g, 2.1 eq) was added gradually to a solution of the above **18** in AcOH (20 ml), and the mixture was stirred overnight at room temperature. Then 20% K_2CO_3 solution was added to the solution to make it alkaline under ice-cooling. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 solution was washed with saturated NaCl solution and dried. Evaporation of the solvent gave a residue, which was subjected to silica gel flash column chromatography (120 g, AcOEt–hexane–MeOH (20:2:1–20:1:2)) to give **19** (1.30 g, 45%). Recrystallization from MeOH gave a colorless powder, mp 234–237°C. UV λ_{max} (EtOH) nm (ϵ): 212 (27800), 265 (14900), 324 (4700). IR ν_{max} (KBr) cm^{-1} : 3460, 3340

(NH), 1690 (CO). MS m/z (rel. intensity): 405 (M^+ , 53), 403 (M^+ , 100), 401 (M^+ , 50), 363 (39), 361 (78), 359 (40). $^1\text{H-NMR}$ (270 MHz) δ : 2.40 (3H, s, CH_3CO), 2.92 (3H, s, NCH_3), 2.8—3.1 (2H, m, 3- H_2), 3.93 (1H, br, 3a-H), 4.52 (2H, br, 5-NH₂, exchangeable), 5.90 (1/3, brs, 8a-H), 6.28 (2/3H, br, 8a-H), 7.21 (2/3H, br, 7-H), 8.19 (1/3H, br, 7-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{Br}_2\text{N}_3\text{O}_2$: C, 38.74; H, 3.25; N, 10.42. Found: C, 38.69; H, 3.27; N, 10.36.

1-Acetyl-4,5,6-tribromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (20). Sandmeyer Reaction of **19** NaNO_2 (22 mg, 1.3 eq) was added gradually to a solution of **19** (100 mg, 0.248 mmol) in 48% HBr solution (3 ml) at 0 °C, and the mixture was stirred for 30 min. CuBr (75 mg, 2.1 eq) was added to the mixture at 0 °C, and the whole was stirred for 4.5 h at the same temperature. AcOEt and 20% K_2CO_3 solution (15 ml) were then added and the aqueous solution was extracted with AcOEt . The combined AcOEt solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave a residue, which was chromatographed on a silica gel column (7 g, CH_2Cl_2 – MeOH (100:1)) to give **20** (100 mg, 86%). Recrystallization from MeOH gave pale yellow needles, mp 214–215 °C. UV λ_{max} (EtOH) nm (ϵ): 224 (34400), 255 (13100), 294 (2000), 304 (1600). IR ν_{max} (KBr) cm^{-1} : 1720, 1680 (CO). MS m/z (rel. intensity): 470 (M^+ , 14), 468 (M^+ , 39), 466 (M^+ , 40), 464 (M^+ , 14), 428 (24), 426 (71), 424 (73), 422 (25), 42 (100). $^1\text{H-NMR}$ (270 MHz) δ : at 40 °C: 2.43 (3H, s, CH_3CO), 2.92 (5H, br, NCH_3 , 3H₂), 4.10 (1H, t-like, 3a-H), 6.15 (1H, br, 8a-H), 7.44 (1/3H, s, 7-H), 7.70 (2/3H, br, 7-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{Br}_3\text{N}_2\text{O}_2$: C, 33.44; H, 2.34; N, 6.00. Found: C, 33.69; H, 2.44; N, 6.14.

When the reaction mixture after the addition of CuBr (3 eq) was stirred for 5 d at room temperature, and treated as above, the tetrabromide (**21**), mp 228.5–229.5 °C (from CH_2Cl_2 –hexane), was obtained in 89% yield. UV λ_{max} (EtOH) nm: 228, 263, 305, 327. IR ν_{max} (KBr) cm^{-1} : 3280 (NH), 1660 (CO). MS m/z (rel. intensity): 508 (M^+ , 2), 506 (M^+ , 9), 504 (M^+ , 14), 502 (M^+ , 10), 500 (M^+ , 3), 450 (17), 448 (66), 446 (100), 444 (68), 442 (18). Exact MS Calcd for $\text{C}_{11}\text{H}_8^{79}\text{Br}_4\text{N}_2\text{O}$: 499.7369. Found: 499.7361; Calcd for $\text{C}_{11}\text{H}_8^{79}\text{Br}_3^{81}\text{BrN}_2\text{O}$: 501.7349. Found: 501.7333; Calcd for $\text{C}_{11}\text{H}_8^{79}\text{Br}_2^{81}\text{Br}_2\text{N}_2\text{O}$: 503.7329. Found: 503.7322; Calcd for $\text{C}_{11}\text{H}_8^{79}\text{Br}^{81}\text{Br}_3\text{N}_2\text{O}$: 505.7309. Found: 505.7305; Calcd for $\text{C}_{11}\text{H}_8^{81}\text{Br}_4\text{N}_2\text{O}$: 507.7289. Found: 507.7274. $^1\text{H-NMR}$ (270 MHz) at 55 °C δ : 2.71 (1H, dd, J = 18.0, 4.0 Hz, 3-Ha), 2.90 (3H, s, NCH_3), 2.98 (1H, dd, J = 18.0, 10.4 Hz, 3-Hb), 4.14 (1H, ddd, J = 10.2, 8.2, 4.2 Hz, 3a-H), 5.02 (1H, br, NH, exchangeable), 5.47 (1H, d, J = 8.2 Hz, 8a-H).

***N*₆-Methyl-4,5,6-tribromo-3-indoleacetamide (7)** A solution of **20** (310 mg, 0.664 mmol) in 10% H_2SO_4 – MeOH (8 ml) was stirred overnight at room temperature, then 20% K_2CO_3 solution (30 ml) was added under ice-cooling. The mixture was extracted with AcOEt . The AcOEt solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave crude **7** (272 mg, 96%). Recrystallization from AcOEt –hexane gave colorless needles, mp 207–210.5 °C. UV λ_{max} (EtOH) nm (ϵ): 204 (21200), 237 (48000), 283 (5600), 294 (6000), 306 (4900). IR ν_{max} (KBr) cm^{-1} : 3400 (NH), 1630 (CO). MS m/z (rel. intensity): 428 (M^+ , 6), 426 (M^+ , 16), 424 (M^+ , 17), 422 (M^+ , 6), 370 (33), 368 (99), 366 (100), 364 (35). $^1\text{H-NMR}$ (500 MHz, in CD_3OD) δ : 2.70 (3H, s, NCH_3), 3.84 (2H, s, CH_2), 7.31 (1H, s, 2-H), 7.74 (1H, s, 7-H). *Anal.* Calcd for $\text{C}_{11}\text{H}_5\text{Br}_3\text{N}_2\text{O}$: C, 31.09; H, 2.13; N, 6.59. Found: C, 31.16; H, 2.21; N, 6.68.

5-Acetoxy-8-acetyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (22) A solution of lead tetraacetate (9.43 g, 2.0 eq) in CH_2Cl_2 (60 ml) was added gradually to a solution of **5** (2.00 g, 10.6 mmol) in TFA (25 ml) under ice-cooling. The mixture was stirred for 20 min, then Zn powder (5.0 g) was added under ice-cooling. Stirring was continued for 30 min. Water (100 ml) was then added and the mixture was extracted with CH_2Cl_2 . The aqueous solution was made alkaline with K_2CO_3 and extracted with CH_2Cl_2 . The combined CH_2Cl_2 solution was washed with saturated NaCl solution and dried. The solvent was evaporated off to leave a residue (crude 5-hydroxy-1-methylhexahydropyrroloindol-2-one, 1.48 g), which was dissolved in Ac_2O (15 ml) and pyridine (50 ml). The solution was stirred overnight at room temperature. Work-up as usual gave **22** (1.35 g, 44%), mp 158.5–161.5 °C (from acetone–hexane), as colorless cotton like crystals. UV λ_{max} (EtOH) nm (ϵ): 205 (9600), 246 (11900), 281 (2000), 286 (1900); (EtOH–NaOH): 273, 312 nm. IR ν_{max} (KBr) cm^{-1} : 1757, 1705, 1670 (CO). MS m/z (rel. intensity): 288 (M^+ , 29), 204 (100). $^1\text{H-NMR}$ (270 MHz) at 50 °C δ : 2.28 (3H, s, CH_3CO), 2.43 (3H, s, CH_3CO), 2.60 (1H, d, J = 17.4 Hz, 3-Ha), 2.89 (3H, s, NCH_3), 2.90 (1H, m, 3-Hb), 3.96 (1H, br t, 3a-H), 6.23 (1H, br, 8a-H), 6.99 (2H, m, 4- and 6-H), 7.20 (1H, br, 7-H). *Anal.* Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: C, 62.49; H, 5.59;

N, 9.72. Found: C, 62.39; H, 5.56; N, 9.63.

8-Acetyl-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (23) A mixture of **22** (930 mg, 3.23 mmol) and K_2CO_3 (7.0 g, 15 eq) in MeOH (50 ml) was stirred for 2 h at room temperature. The solvent was evaporated off to leave a residue, which was placed on top of a silica gel column (30 g). Elution with CH_2Cl_2 – MeOH (10:1) gave **23** (740 mg, 93%). Recrystallization from aqueous MeOH gave colorless prisms, mp 279–283.5 °C. UV λ_{max} (EtOH) nm (ϵ): 202 (24200), 252 (13200), 295 (3400); (EtOH–10%NaOH): 273, 312 nm. IR ν_{max} (KBr) cm^{-1} : 3195 (OH), 1680 (CO). MS m/z (rel. intensity): 246 (M^+ , 100). $^1\text{H-NMR}$ (270 MHz, in CD_3OD) δ : 2.42 (3H, s, CH_3CO), 2.53 (1H, br t, 3-Ha), 2.84 (3H, s, NCH_3), 2.95 (1H, dd, J = 17.2, 9.0 Hz, 3-Hb), 3.94 (2/3H, br t, 3a-H), 4.05 (1/3H, br t, 3a-H), 6.11 (1/3H, d, J = 6.6 Hz, 8a-H), 6.29 (2/3H, d, J = 6.7 Hz, 8a-H), 6.73 (2H, m, 4- and 6-H), 7.14 (2/3H, d, J = 8.5 Hz, 7-H), 7.75 (1/3H, d, J = 8.2 Hz, 7-H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.13; H, 5.82; N, 11.30.

Bromination of 23. Formation of 8-Acetyl-4,6-dibromo-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (24) and 8-Acetoxy-6(4)-bromo-5-hydroxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-2-one (25) NBS (76 mg, 2.1 eq) was added to a solution of **23** (50 mg, 0.203 mmol) in CH_2Cl_2 (5 ml) at room temperature and the mixture was stirred for 24 h at the same temperature. The solvent was evaporated off to leave a residue, which was chromatographed on a silica gel column (8 g, AcOEt –hexane– MeOH (60:1:1)) to give **24** (57 mg, 70%) from the first eluent and **25** (11 mg, 17%) from the second eluent.

Recrystallization of **25** from MeOH gave a colorless powder, mp 235.5–238 °C. UV λ_{max} (EtOH) nm: 254, 304; (EtOH–NaOH): 275, 324. IR ν_{max} (KBr) cm^{-1} : 1670 (CO). MS m/z (rel. intensity): 326 (M^+ , 96), 324 (M^+ , 100). The NMR spectrum showed a mixture of the 4- and 6-bromo derivatives.

Recrystallization of **24** from MeOH gave a colorless powder, mp 219–220 °C. UV λ_{max} (EtOH) nm: 217, 254, 304; (EtOH–NaOH): 278, 332. IR ν_{max} (KBr) cm^{-1} : 3200 (OH), 1690 (CO). MS m/z (rel. intensity): 406 (M^+ , 42), 404 (M^+ , 84), 402 (M^+ , 43), 364 (49), 362 (100), 360 (54). Exact MS Calcd for $\text{C}_{13}\text{H}_{12}^{79}\text{Br}_2\text{N}_2\text{O}_3$: 401.9215. Found: 401.9198. Calcd for $\text{C}_{13}\text{H}_{12}^{79}\text{Br}^{81}\text{BrN}_2\text{O}_3$: 403.9195. Found: 403.9192. Calcd for $\text{C}_{13}\text{H}_{12}^{81}\text{Br}_2\text{N}_2\text{O}_3$: 405.9175. Found: 405.9170. $^1\text{H-NMR}$ (270 MHz, CD_3OD) at 40 °C δ : 2.42 (3H, s, COCH_3), 2.43 (1H, m, 3-Ha), 2.90 (3H, s, NMe), 2.99 (1H, dd, J = 16.9, 9.0 Hz, 3-Hb), 4.09 (1H, br t, 3a-H), 6.22 (1H, br d, 8a-H), 7.90 (1H, br, 7-H).

Bromination of **25** with NBS (1.1 eq) in CH_2Cl_2 at room temperature gave **24** in 82% yield.

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References and Notes

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