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3-cd]indoles and a New Finding on  
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# The Chemistry of Indoles. CVII.<sup>1)</sup> A Novel Synthesis of 3,4,5,6-Tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles and a New Finding on Pictet–Spengler Reaction

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Serotonins were found to produce 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles by simple heating with amines under an oxygen atmosphere. Serotonins also reacted with various aldehydes to provide 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles rather than  $\beta$ -carbolines under basic conditions. In these novel reactions, the presence of the 5-hydroxy group on the indole nucleus was suggested to be essential. Possible mechanisms are discussed.

**Key words** 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole; serotonin

Aurantioclabine (**1a**) and clavicipitic acid (**1b**) are members of ergot alkaloids (Fig. 1).<sup>2)</sup> *Na,Nb*-Dimethylserotonin (**2a**), serotonin (**2b**), and *Nb*-methylserotonin (**2c**) are well known biologically active amines.<sup>3)</sup> Combination of the former compounds with the latter ones results in a chimera skeleton such as 7-substituted 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole, as shown in a general formula (**3**). In our attempt to develop biologically active substances, we have identified **3** and its various derivatives to be possible promising compounds.

In 1988, we reported the preparation of 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivatives (**4**) starting from 4-cyanoindoles.<sup>4)</sup> However, the synthetic route is not applicable for the preparation of **3**, because suitably functionalized 4-cyanoindole derivatives are not readily available.<sup>5)</sup> On the other hand, we have established a simple method for serotonin congeners<sup>6a)</sup> (**2a–c**) utilizing our 1-hydroxyindole chemistry.<sup>7)</sup> Making use of **2a–c** as starting materials, we now wish to report our success in developing a novel synthetic method for 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles (**5**) as one of our targets (**3**).

**I. A Novel Reaction for Preparing 3,4,5,6-Tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles** Synthesis of 3,4,5,6-tetrahydro-7-hydroxy-1,5,6-trimethyl-1*H*-azepino[5,4,3-*cd*]indole (**5a**) was easily attained by refluxing the MeOH solution of *Na,Nb*-dimethylserotonin (**2a**) in the presence of ex-

cess Et<sub>3</sub>N under an oxygen atmosphere. The results of this novel reaction are summarized in Table 1. The desired **5a** and an unreacted **2a** were obtained in 26 and 74% yields, respectively, after refluxing for 20 h (entry 1). As can be seen from entries 1–3, the longer the reaction time, the better the yield of **5a**. It should be noted that the reaction was clean, and no tar formation was observed; thus, even after 68 h refluxing, only **5a** and **2a** were obtained in 49 and 50% yields, respectively (entry 3). Interestingly, the introduction of bubbling oxygen into the reaction medium did not improve the rate of formation or the yield of **5a**.

The compound (**5a**) was found to be identical by direct comparison with the sample prepared in 91% yield, alternatively, by reacting **2a** with acetaldehyde under similar reac-

Table 1.

Entry	Additive (mol eq)	Reaction time (h)	Yield (%) of	
			<b>5a</b>	Recovery
1	—	20	26	74
2	—	43	36	52
3	—	68	49	50
4	MeCHO (1.7)	2/3	91	0

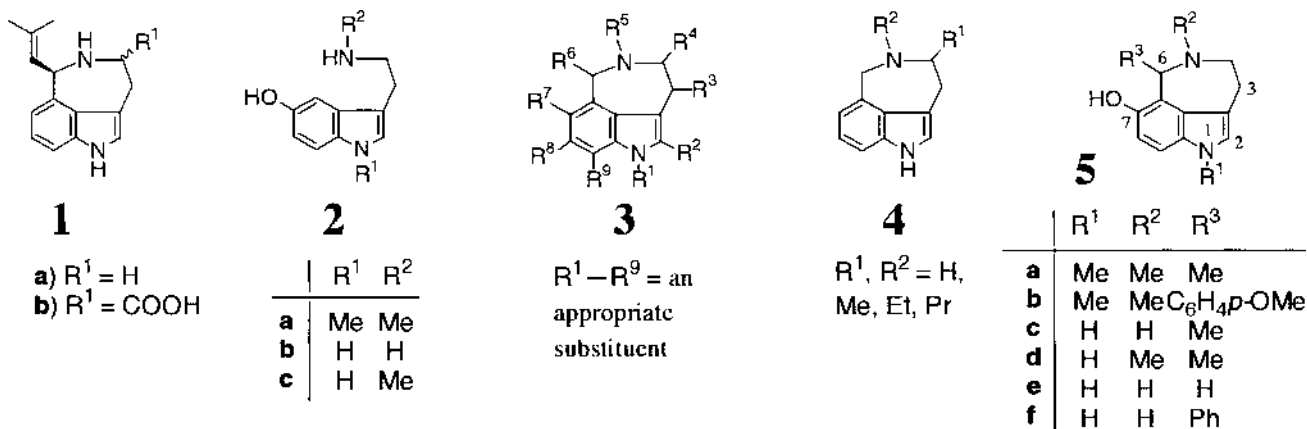


Fig. 1

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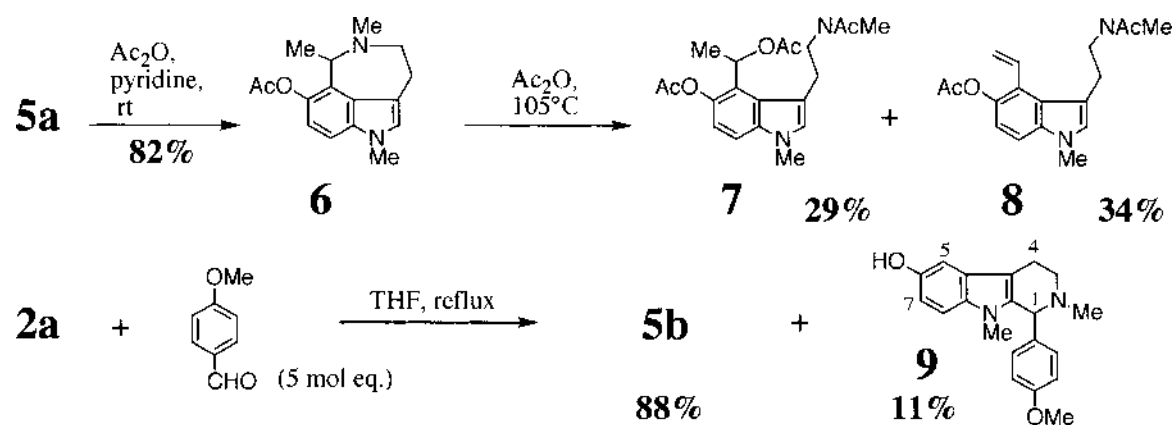
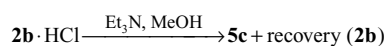


Chart 1

Table 2.



Entry	Atmosphere	Additive (mol eq)	Reaction conditions		Yield (%) of		Note
			Temp. (°C)	Time (h)	5c	Recovery	
1	O <sub>2</sub>	—	Reflux	20	20	59	Clean
2	O <sub>2</sub>	MeCHO (3)	21.5	4	0	51	Tar
3	O <sub>2</sub>	MeCHO (6)	21.5	24	0	18	Tar
4	Ar	MeCHO (3)	24	4	8	44	Tar

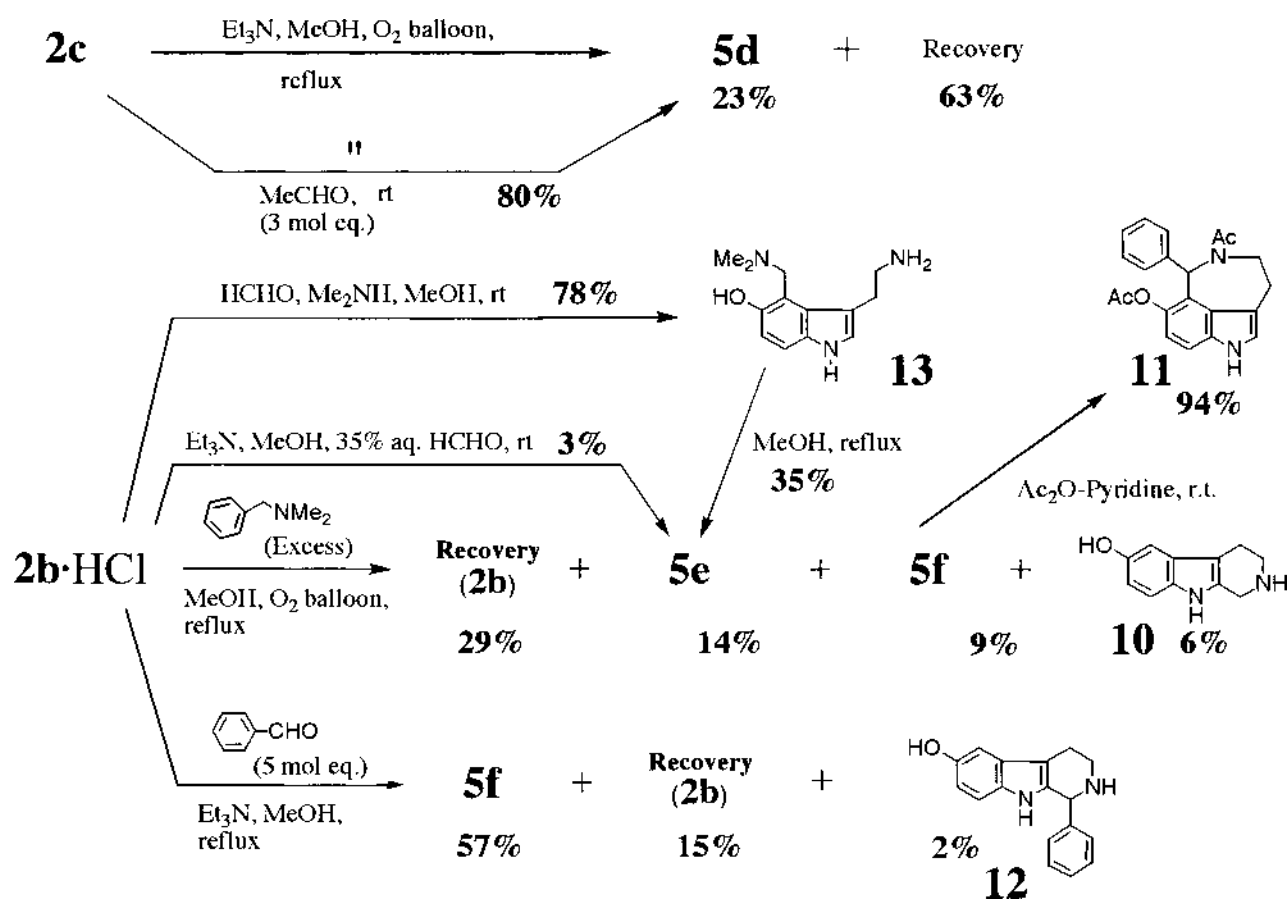
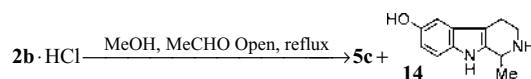


Chart 2

Table 3.



Entry	pH	MeCHO (mol eq)	Concentration of $2b \cdot HCl$ ( $10^{-2}$ mol/l)	Time (h)	Yield (%) of			Note
					5c	14	Recovery (2b)	
1	4	50	11.9	1	0	26	0	Tar
2	4	50	2.4	20	0	13	0	Tar
3	5	50	2.5	20	27	53	0	Clean
4	5	10	2.4	20	28	30	40	Clean

tion conditions (entry 4). With an aim to prove its structure, the acetylation of **5a** was carried out with  $Ac_2O$ -pyridine to give **6** in 82% yield (Chart 1). Further treatment of **6** with refluxing  $Ac_2O$  cleaved the seven-membered ring to afford **7** and **8** in 29 and 34% yields, respectively. In the  $^1H$ -NMR spectra of these compounds (**5a**, **6**–**8**), two *ortho*-coupled protons and a singlet proton were observed in the aromatic region, suggesting that **5a** and **6** have a *1H*-azepino[5,4,3-*cd*]indole skeleton. To obtain further proof, the reaction of **2a** with *p*-methoxybenzaldehyde in refluxing tetrahydrofuran (THF) was carried out. In this case, luckily, a set of isomers, **5b** and **9**, were produced in 88 and 11% yields, respectively. Although the pattern of proton signals of **5b** is quite similar to those of **5a**, **6**–**8**, the spectrum of **9** is different and it clearly exhibits *meta*-coupled signals assignable to the 5- and 7-positions of the  $\beta$ -carboline nucleus.

The above results suggested that  $Et_3N$  worked as an acetaldehyde equivalent. To confirm this view, the reaction was applied to serotonin (**2b**). Using serotonin hydrochloride ( $2b \cdot HCl$ ), the reaction with excess  $Et_3N$  for 20 h under an oxygen atmosphere was expectedly successful and clean, and the corresponding **5c** and unreacted **2b** were obtained in 20 and 59% yields, respectively (Table 2, entry 1). In order to confirm the structure of **5c**, an attempt was made to react **2b** with acetaldehyde, but the reaction afforded tar matter, even at room temperature, and the desired **5c** was not formed under the reaction conditions described in entries 2 and 3. Considering the intrinsically sensitive nature of **2b** to oxygen, the reaction was next examined under Ar atmosphere. Monitoring with thin layer chromatography, the reaction time for maximizing **5c** was found to be 4 h, at which an 8% yield of **5c** was obtained, together with a significant amount of tar (entry 4).

As in the cases of **2a**, **b**, the reaction of **2c** with excess  $Et_3N$  under an oxygen atmosphere was also clean giving **5d** in 23% yield after 20 h refluxing (Chart 2). The authentic sample of **5d** was prepared in 80% yield by reacting **2c** with acetaldehyde.

Since  $Et_3N$  was found to function as a good substitute for acetaldehyde, we next tried to extend this novel reaction to other amines such as *N,N*-dimethylbenzylamine. A methanol solution of  $2b \cdot HCl$  and an excess amount of *N,N*-dimethylbenzylamine was refluxed for 6 h under an oxygen atmosphere. The reaction was again clear, and 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indole (**5e**), its 6-phenyl derivative (**5f**), and 1,2,3,4-tetrahydro-6-hydroxy- $\beta$ -carboline (**10**) were obtained in 14, 9, and 6% yields, respectively, in addition to a 29% yield of unreacted **2b**. Treatment of **5f** with  $Ac_2O$  and pyridine afforded a diacetyl compound (**11**) in

94% yield. Although comparison of the spectroscopic data of **5f** and **11** suggested their structures to be as shown, further proof was obtained by direct comparison with authentic **5f**. Thus, it was prepared by the reaction of  $2b \cdot HCl$  with benzaldehyde in MeOH at reflux in 57% yield, in addition to unreacted **2b** and 1,2,3,4-tetrahydro-6-hydroxy-1-phenyl- $\beta$ -carboline (**12**) in the respective yields of 15 and 2%.

The attempt to obtain an authentic sample of **5e** resulted in poor yields. Thus, the reaction of  $2b \cdot HCl$  directly with formaldehyde in methanolic  $Et_3N$  formed a lot of tar, together with the desired **5e** in only 3% yield. A better yield of **5e** was attained by employing the following two-step route. Thus, **2b** was converted to compound (**13**) by Mannich reaction with HCHO in the presence of dimethylamine in 78% yield. Subsequent heating of its methanol solution at reflux afforded a 35% yield of **5e**.

**II. Pictet–Spengler Type Reaction for Serotonin Congeners under Basic Conditions** The reaction of tryptamines with aldehydes under acidic or neutral conditions is well known as the Pictet–Spengler reaction for preparing  $\beta$ -carbolines.<sup>8)</sup> Under basic reaction conditions, as described in the section I, our results upon reactions of serotonins (**2a**–**c**) with amines or aldehydes are quite different from the Pictet–Spengler reaction, giving 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles rather than  $\beta$ -carbolines.

Therefore, under careful pH control, we next examined the reaction of  $2b \cdot HCl$  with acetaldehyde. A summary of typical results is shown in Table 3. Adjusting the pH of the reaction media to 4 by adding aq. HCl, the reactions of  $2b \cdot HCl$  with an excess amount (50 mol eq) of acetaldehyde provided  $\beta$ -carboline (**14**) as the sole product in 26% yield, together with tar matter (entry 1). When the concentration of  $2b \cdot HCl$  was diluted with an aim to reduce the formation of tar, the yield of **14** dropped to 13% (entry 2). Interestingly, under similar reaction conditions, except for pH 5, the more basic conditions, 7-hydroxy-5-methyl-1*H*-azepino[5,4,3-*cd*]indole (**5c**) was obtained in 27% yield, together with 53% yield of **14** (entry 3). Use of less acetaldehyde (10 mol eq) decreased the yield of **5c** and **14** into 28 and 30% yields, respectively, in addition to unreacted **2b** (entry 4).

Since pH was suggested to be an important factor in determining products, further trials were carried out to confirm this. The reaction of *Na,Nb*-dimethylserotonin (**2a**) with acetaldehyde at pH 5 produced **15** and **5a** in 27 and 58% yields, respectively (Chart 3). In the same reaction, except for the presence of excess  $Et_3N$  (the more basic conditions), the formation of **15** was completely excluded and **5a** was obtained in 91% yield. In contrary, when the reaction of **16**,<sup>6)</sup> prepared in 94% yield by a  $LiAlH_4$  reduction of 5-methoxy-

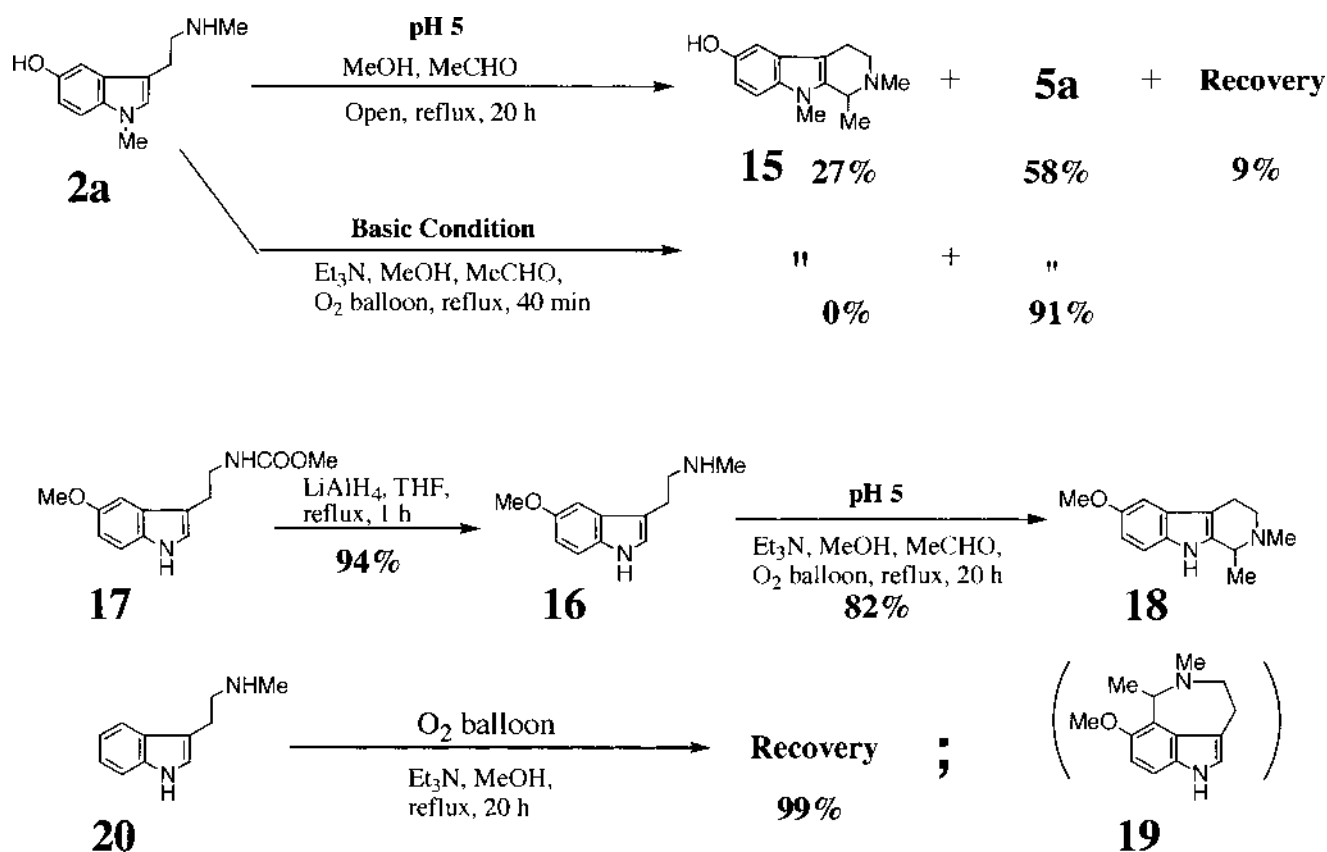


Chart 3

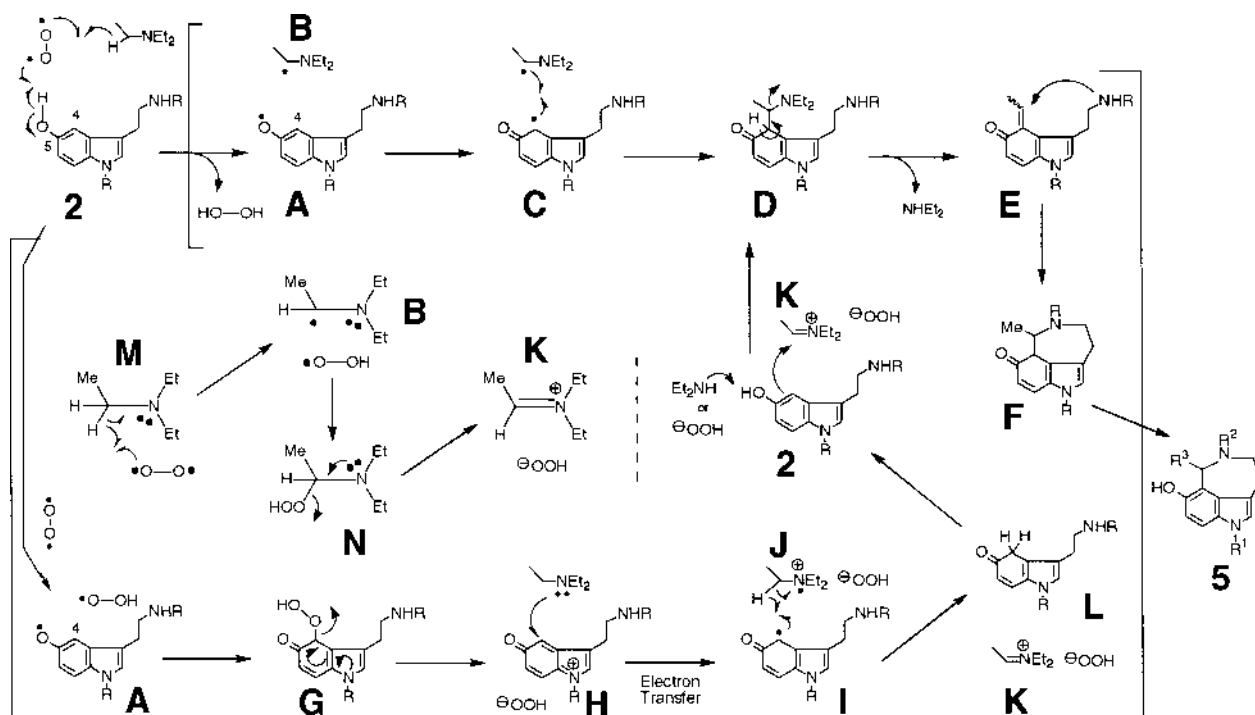


Chart 4. Possible Mechanism

*Nb*-methoxycarbonylindole<sup>9</sup> (**17**), with acetaldehyde was carried out at pH 5,  $\beta$ -carboline (**18**) was obtained in 82% yield as a sole product, while the formation of **19** was not detected at all.

These results clearly suggest that the 5-hydroxy group is essential for the formation of 1*H*-azepino[5,4,3-*cd*]indole. Under basic conditions, the 5-hydroxy group loses a proton to give a phenoxide ion which is responsible for activating

the nucleophilic reactivity of the 4-position of the indole nucleus toward aldehydes.

**III. Possible Mechanism for the Reaction of Amines with Serotonins** In section I, we found a novel reaction in which Et<sub>3</sub>N and *N,N*-dimethylbenzylamine worked as acetaldehyde, benzaldehyde, and formaldehyde equivalents in reactions with serotonins (**2**). A possible reaction mechanism is shown in Chart 4, employing Et<sub>3</sub>N as a representative. Initially, an oxygen molecule interacts with both triethylamine and **2** generating a phenoxy radical (A) and diethylaminoethyl radical (B). The radical (A) tautomerizes to radical (C) and it combines with B to produce D. Liberation of diethylamine from D affords *o*-quinomethane (E). Subsequent intramolecular cyclization of *Nb*-nitrogen to the  $\beta$ -carbon of the  $\alpha,\beta$ -unsaturated carbonyl part in E completes the process to **5** through the intermediate ketone (F).

The other possibility is the interaction of molecular oxygen with **2**, culminating in phenoxy (A) and hydroperoxy radicals. Their recombination to hydroperoxide (G), followed by elimination of the hydroperoxide anion from G generates a *p*-quinoneimine type cation (H). Subsequent single electron transfer from Et<sub>3</sub>N to H produces a radical (I) and cation radical (J). J is then converted to imminium species (K) by the abstraction of  $\alpha$ -hydrogen by I, as it transforms to L. L then enolizes to the starting phenol (**2**), and it can react with K to provide D.

The interaction of amine with molecular oxygen, as shown in M providing radical (B) and a hydroperoxide radical, is another possible pathway for the formation of K. Subsequent recombination of the radicals generates hydroperoxide (N). Elimination of the hydroperoxide anion from N affords K. If this mechanism is working, substrates would not be limited to serotonin congeners. Therefore, we examined the reaction using *N*-methyltryptamine (**20**, Chart 3). Refluxing of a MeOH solution of **20** with excess Et<sub>3</sub>N for 20 h under an oxygen atmosphere resulted in the complete recovery of unreacted **20** without a trace amount of  $\beta$ -carboline or 1*H*-azepino[5,4,3-*cd*]indoles.

To determine the reaction mechanism and extend the scope of the present novel reaction, we are now examining various amines in their reactions with serotonins, considering that any amines can become substitutes for aldehydes or ketones. We believe that this type of reaction would be working in our living body and associated with the function of serotonins.

#### 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 <sup>1</sup>H-NMR spectra with a JEOL GSX-500 spectrometer, with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102 A spectrometer. Column chromatography was performed on silica gel (SiO<sub>2</sub>, 100–200 mesh, from Kanto Chemical Co., Inc.). Preparative thin layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF<sub>254</sub> (type 60) (SiO<sub>2</sub>).

**3,4,5,6-Tetrahydro-7-hydroxy-1,5,6-trimethyl-1*H*-azepino[5,4,3-*cd*]indole (**5a**) from *Na,Nb*-Dimethylserotonin (**2a**)** Method 1: [Entry 1] Et<sub>3</sub>N (2 ml) was added to a solution of **2a** (20.3 mg, 0.10 mmol) in MeOH (2 ml) at 0 °C, and the mixture was refluxed for 20 h with stirring under O<sub>2</sub> atmosphere (O<sub>2</sub> balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:3:0.3, then 46:5:0.5, v/v) to give **5a** (6.0 mg, 26%) and unreacted **2a** (15.0 mg, 74%) in the order of elution. **5a**: mp 162.0–163.5 °C (pale yellow powder, recrystallized from CHCl<sub>3</sub>-hexane). IR (KBr): 1577, 1457, 1242, 787 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.49 (3H, d,

*J*=7.0 Hz), 2.61 (3H, s), 2.91 (1H, ddd, *J*=16.4, 3.4, 2.4 Hz), 3.08 (1H, ddd, *J*=14.3, 4.9, 2.4 Hz), 3.25 (1H, dddd, *J*=16.4, 13.1, 4.9, 1.2 Hz), 3.65 (1H, ddd, *J*=14.3, 13.1, 3.4 Hz), 3.68 (3H, s), 4.67 (1H, q, *J*=7.0 Hz), 6.69 (1H, d, *J*=8.5 Hz), 6.79 (1H, s), 6.97 (1H, d, *J*=8.5 Hz). High-resolution MS *m/z*: Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O: 230.1419. Found: 230.1417. Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O · 1/4H<sub>2</sub>O: C, 71.61; H, 7.94; N, 11.93. Found: C, 71.58; H, 7.78; N, 11.88.

[Entry 2] Et<sub>3</sub>N (3 ml) was added to a solution of **2a** (22.5 mg, 0.11 mmol) in MeOH (3 ml) at 0 °C and the mixture was refluxed for 43 h with stirring under O<sub>2</sub> atmosphere (O<sub>2</sub> balloon). After the same work-up and separation described in entry 1, **5a** (9.2 mg, 36%) and unreacted **2a** (11.7 mg, 52%) were obtained.

[Entry 3] Et<sub>3</sub>N (4 ml) was added to a solution of **2a** (22.1 mg, 0.11 mmol) in MeOH (4 ml) at 0 °C, and the mixture was refluxed for 68 h with stirring under O<sub>2</sub> atmosphere (O<sub>2</sub> balloon). After the same work-up and separation described in entry 1, **5a** (12.3 mg, 49%) and unreacted **2a** (11.0 mg, 50%) were obtained.

Method 2: Acetaldehyde (0.04 ml, 0.72 mmol) was added to a solution of **2a** (84.5 mg, 0.41 mmol) in MeOH (4 ml) and Et<sub>3</sub>N (4 ml) at 0 °C and the mixture was refluxed for 40 min with stirring under O<sub>2</sub> atmosphere (O<sub>2</sub> balloon). After evaporation of the solvent, H<sub>2</sub>O was added to the residue. The whole was extracted with CHCl<sub>3</sub>. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:3:0.3, v/v) to give **5a** (87.9 mg, 91%).

**3,4,5,6-Tetrahydro-7-hydroxy-6-(4-methoxyphenyl)-1,5-dimethyl-1*H*-azepino[5,4,3-*cd*]indole (**5b**) and 1,2,3,4-Tetrahydro-6-hydroxy-1-(4-methoxyphenyl)-2,9-dimethyl- $\beta$ -carboline (**9**) from **2a**** *p*-Methoxybenzaldehyde (0.062 ml, 0.51 mmol) in anhydrous THF (0.5 ml) was added to a solution of **2a** (21.6 mg, 0.11 mmol) in anhydrous THF (2.5 ml) at 0 °C, and the mixture was refluxed for 22 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO<sub>2</sub>, successively, with CHCl<sub>3</sub>, CHCl<sub>3</sub>-MeOH (97:3, v/v), and CHCl<sub>3</sub>-MeOH (95:5, v/v) to give **9** (3.8 mg, 11%) and **5b** (30.1 mg, 88%) in the order of elution. **5b**: Colorless oil. IR (film): 2914, 1510, 1456, 1246, 756 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.72 (3H, s), 2.81–2.88 (2H, m), 3.21–3.28 (2H, m), 3.73 (6H, s), 5.70 (1H, s), 6.75 (2H, d, *J*=8.8 Hz), 6.77 (1H, d, *J*=8.6 Hz), 6.83 (1H, s), 7.05 (2H, d, *J*=8.5 Hz), 7.08 (1H, d, *J*=8.6 Hz). High-resolution MS *m/z*: Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: 322.1681. Found: 322.1694. **9**: mp 177–181 °C (colorless needles, recrystallized from CHCl<sub>3</sub>-hexane). IR (KBr): 2920, 1603, 1508, 1224, 1032, 755 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 2.43 (3H, s), 2.74 (1H, dt, *J*=11.8, 5.4 Hz), 2.79–2.89 (2H, m), 2.98–3.04 (1H, m), 3.16 (3H, s), 3.79 (3H, s), 4.59 (1H, s), 6.73 (1H, dd, *J*=8.6, 2.4 Hz), 6.83 (2H, d, *J*=8.8 Hz), 6.94 (1H, d, *J*=2.4 Hz), 7.04 (1H, d, *J*=8.6 Hz), 7.08 (2H, d, *J*=8.8 Hz). MS *m/z*: 322 (M<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.35; H, 6.87; N, 8.65.

**3,4,5,6-Tetrahydro-7-acetoxy-1,5,6-trimethyl-1*H*-azepino[5,4,3-*cd*]indole (**6**) from **5a**** Ac<sub>2</sub>O (2.5 ml) was added to a solution of **5a** (55.8 mg, 0.24 mmol) in pyridine (5 ml) under ice cooling and the mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH (97:3, v/v) to give **6** (53.9 mg, 82%). **6**: Colorless oil. IR (film): 1755, 1365, 1215, 1193 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.50 (3H, d, *J*=7.0 Hz), 2.35 (3H, s), 2.61 (3H, s), 3.01 (1H, br d, *J*=15.4 Hz), 3.18–3.30 (2H, m), 3.68 (1H, dt, *J*=3.6, 13.7 Hz), 3.73 (3H, s), 4.51 (1H, br q, *J*=7.0 Hz), 6.87 (1H, d, *J*=8.8 Hz), 6.88 (1H, s), 7.15 (1H, d, *J*=8.8 Hz). High-resolution MS *m/z*: Calcd for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 272.1525. Found: 272.1526.

**5-Acetoxy-4-(1'-acetoxyethyl)-*Nb*-acetyl-*Na,Nb*-dimethyltryptamine (**7**) and 5-Acetoxy-*Nb*-acetyl-*Na,Nb*-dimethyl-4-vinyltryptamine (**8**) from **6**** A solution of **6** (53.9 mg, 0.20 mmol) in Ac<sub>2</sub>O (8 ml) was heated for 4 h at 105 °C with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with AcOEt and CHCl<sub>3</sub> to give **8** (21.3 mg, 34%) and **7** (21.8 mg, 29%) in the order of elution. **7**: Colorless oil. IR (film): 1758, 1738, 1635, 1568, 1245, 1200 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>, 110 °C)  $\delta$ : 1.63 (3H, d, *J*=6.7 Hz), 1.91 (6H, s), 2.27 (3H, s), 2.92 (3H, br s), 2.98–3.17 (2H, m), 3.60 (2H, t, *J*=7.6 Hz), 3.70 (3H, s), 6.54 (1H, br q, *J*=6.7 Hz), 6.81 (1H, d, *J*=8.7 Hz), 7.14 (1H, s), 7.28 (1H, d, *J*=8.7 Hz). High-resolution MS *m/z*: Calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>: 374.1841. Found: 374.1830. **8**: mp 118–119 °C (colorless needles). IR (film): 1759, 1644, 1206 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>, 120 °C)  $\delta$ : 1.89 (3H, br s), 2.19 (3H, s), 2.81–2.92 (3H, s), 2.96 (2H, br t, *J*=7.3 Hz), 3.45 (2H, br t, *J*=7.3 Hz), 3.71 (3H, s), 5.45 (1H, d, *J*=18.3 Hz), 5.55 (1H,

$d, J=12.0$  Hz), 6.84 (1H,  $d, J=8.7$  Hz), 7.04 (1H, dd,  $J=18.3, 12.0$  Hz), 7.12 (1H, s), 7.26 (1H,  $d, J=8.7$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{18}H_{22}N_2O_3$ ; 314.1630. Found: 314.1630.

**3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-*cd*]indole (5c) from Serotonin Hydrochloride (2b·HCl)** [Entry 1]  $Et_3N$  (2 ml) was added to a solution of **2b·HCl** (20.9 mg, 0.10 mmol) in MeOH (2 ml) at 0 °C, and the mixture was refluxed for 20 h with stirring under  $O_2$  atmosphere ( $O_2$  balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:5:0.5, then 46:10:1, v/v) to give **5c** (4.0 mg, 20%) and unreacted **2b** (10.2 mg, 59%) in the order of elution. **5c**: Pale yellow oil. IR (KBr): 3400, 3300, 1579, 1417, 794  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 1.49 (3H,  $d, J=6.8$  Hz), 2.93–3.01 (1H, m), 3.10–3.15 (2H, m), 3.35–3.41 (1H, m), 4.91 (1H, q,  $J=6.8$  Hz), 6.63 (1H,  $d, J=8.6$  Hz), 6.95 (1H, s), 7.03 (1H,  $d, J=8.6$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{12}H_{14}N_2O$ ; 202.1107. Found: 202.1110.

[Entry 2] Acetaldehyde (0.016 ml, 0.29 mmol) was added to a solution of **2b·HCl** (20.5 mg, 0.10 mmol) in MeOH (2 ml) and  $Et_3N$  (2 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h under  $O_2$  atmosphere ( $O_2$  balloon). After the same work-up and separation as described in entry 1, unreacted **2b** (8.6 mg, 51%) was obtained.

[Entry 3] Acetaldehyde (0.16 ml, 2.86 mmol) was added to a solution of **2b·HCl** (98.1 mg, 0.46 mmol) in MeOH (4 ml) and  $Et_3N$  (4 ml) at 0 °C, and the mixture was stirred at room temperature for 24 h under  $O_2$  atmosphere ( $O_2$  balloon). After the same work-up and separation as described in entry 1, an unidentified product (10.1 mg) and unreacted **2b** (14.9 mg, 18%) were obtained.

[Entry 4] Acetaldehyde (0.016 ml, 0.29 mmol) was added to a solution of **2b·HCl** (20.5 mg, 0.10 mmol) in MeOH (2 ml) and  $Et_3N$  (2 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h under Ar atmosphere. After the same work-up and separation as described in entry 1, **5c** (1.5 mg, 8%) and unreacted **2b** (7.5 mg, 44%) were obtained.

**3,4,5,6-Tetrahydro-7-hydroxy-5,6-dimethyl-1H-azepino[5,4,3-*cd*]indole (5d) from *Nb*-Methylserotonin (2c)** Method 1:  $Et_3N$  (2 ml) was added to a solution of **2c** (21.4 mg, 0.11 mmol) in MeOH (2 ml) at 0 °C, and the mixture was refluxed for 20 h with stirring under  $O_2$  atmosphere ( $O_2$  balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$ , successively, with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:5:0.5, then 46:10:1, v/v) to give **5d** (5.6 mg, 23%) and unreacted **2c** (13.4 mg, 63%) in the order of elution. **5d**: Pale yellow oil. IR (KBr): 3400, 1579, 1435, 790  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 1.44 (3H,  $d, J=6.8$  Hz), 2.59 (3H, s), 2.97–3.04 (2H, m), 3.19–3.27 (1H, m), 3.60–3.68 (1H, m), 4.73 (1H, q,  $J=6.8$  Hz), 6.65 (1H,  $d, J=8.6$  Hz), 6.95 (1H, s), 7.03 (1H,  $d, J=8.6$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{13}H_{16}N_2O$ ; 216.1262. Found: 216.1266.

Method 2: Acetaldehyde (0.018 ml, 0.32 mmol) was added to a solution of **2c** (20.3 mg, 0.11 mmol) in MeOH (2 ml) and  $Et_3N$  (2 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h under  $O_2$  atmosphere ( $O_2$  balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:5:0.5, v/v) to give **5d** (18.5 mg, 80%).

**3,4,5,6-Tetrahydro-7-hydroxy- (5e), -6-Phenyl-1H-azepino[5,4,3-*cd*]indole (5f), and 1,2,3,4-Tetrahydro-6-hydroxy- $\beta$ -carboline (10) from 2b·HCl** *N,N*-Dimethylbenzylamine (2 ml) was added to a solution of **2b·HCl** (20.5 mg, 0.10 mmol) in MeOH (2 ml) at 0 °C, and the mixture was refluxed for 6 h with stirring under  $O_2$  atmosphere ( $O_2$  balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  successively with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, then 46:5:0.5, v/v) to give **5f** (2.3 mg, 9%), **5e** (2.5 mg, 14%), **10** (1.0 mg, 6%), and unreacted **2b** (4.9 mg, 29%) in the order of elution. **5e**: Pale beige viscous oil. IR (KBr): 3305, 1581, 1433, 795  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 3.08 (2H, t,  $J=5.4$  Hz), 3.20 (2H, t,  $J=5.4$  Hz), 4.31 (2H, s), 6.65 (1H,  $d, J=8.5$  Hz), 6.99 (1H, s), 7.05 (1H,  $d, J=8.5$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{11}H_{12}N_2O$ ; 188.0950. Found: 188.0949. **5f**: mp 122.5–124.0 °C (colorless prisms, recrystallized from  $CHCl_3$ -MeOH). IR (KBr): 3290, 1577, 1425, 1298, 1242, 1011, 796, 756, 704  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.79 (1H, ddd,  $J=13.4, 4.6, 3.7$  Hz), 2.87 (1H, ddd,  $J=13.4, 11.0, 4.2$  Hz), 2.94–3.04 (2H, m), 5.92 (1H, s), 6.63 (1H,  $d, J=8.6$  Hz), 6.98 (1H, s), 7.03 (2H, br  $d, J=7.3$  Hz), 7.13 (1H,  $d, J=8.6$  Hz), 7.11–7.20 (3H, m). MS  $m/z$ : 264 ( $M^+$ ). Anal. Calcd for  $C_{17}H_{16}N_2O$ ·MeOH: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.19; H, 6.78; N, 9.40. **10**: mp 285 °C (dec., colorless powder). IR (KBr): 3398, 3265, 1589, 1565, 1454, 1200  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.71 (2H, t,  $J=5.9$  Hz), 3.13 (2H, t,  $J=5.9$  Hz), 3.96 (2H, s), 6.60 (1H, dd,  $J=8.5, 2.3$  Hz), 6.77 (1H,  $d, J=2.3$  Hz), 7.08 (1H,  $d,$

$J=8.5$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{11}H_{12}N_2O$ ; 188.0950. Found: 188.0946.

**3,4,5,6-Tetrahydro-7-hydroxy-6-phenyl-1H-azepino[5,4,3-*cd*]indole (5f) and 1,2,3,4-Tetrahydro-6-hydroxy-1-phenyl- $\beta$ -carboline (12) from 2b·HCl** Benzaldehyde (0.48 ml, 4.72 mmol) was added to a solution of **2b·HCl** (201.4 mg, 0.95 mmol) in MeOH (5 ml) and  $Et_3N$  (5 ml) at 0 °C, and the mixture was refluxed for 20 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, 46:5:0.5, then 46:10:1, v/v) to give **12** (3.9 mg, 2%), **5f** (141.8 mg, 57%), and unreacted **2b** (25.5 mg, 15%) in the order of elution. **12**: Pale yellow viscous oil. IR (KBr): 3400, 3290, 1625, 1593, 1454, 1201, 702  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.71–2.77 (1H, m), 2.82–2.88 (1H, m), 3.03 (1H, ddd,  $J=12.5, 7.8, 5.1$  Hz), 3.25 (1H, dt,  $J=12.5, 5.1$  Hz), 5.13 (1H, s), 6.60 (1H, dd,  $J=8.5, 2.2$  Hz), 6.84 (1H,  $d, J=2.2$  Hz), 7.03 (1H,  $d, J=8.5$  Hz), 7.27–7.36 (5H, m). High-resolution MS  $m/z$ : Calcd for  $C_{17}H_{16}N_2O$ ; 264.1263. Found: 264.1259.

**7-Acetoxy-5-acetyl-3,4,5,6-tetrahydro-6-phenyl-1H-azepino[5,4,3-*cd*]indole (11) from 5f**  $Ac_2O$  (1 ml) was added to a solution of **5f** (4.7 mg, 0.02 mmol) in pyridine (2 ml) under ice cooling, and the mixture was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH (99:1, v/v) to give **11** (18.7 mg, 94%). **11**: Colorless oil. IR (film): 3276, 1757, 1628, 1423, 1198, 750  $cm^{-1}$ .  $^1H$ -NMR ( $DMSO-d_6, 140$  °C)  $\delta$ : 1.85 (3H, br s), 2.17 (3H, s), 2.79–4.02 (4H, m), 6.55 (1/3H, br s), 6.82 (1H,  $d, J=8.6$  Hz), 6.92–6.97 (2H, m), 7.11 (1H, br s), 7.17–7.23 (3H, m), 7.31 (1H, br  $d, J=8.6$  Hz), 7.60 (2/3H, br s), 10.65 (1H, br s, disappeared on addition of  $D_2O$ ). High-resolution MS  $m/z$ : Calcd for  $C_{21}H_{20}N_2O_3$ ; 348.1474. Found: 348.1474.

**5-Hydroxy-4-(*N,N*-dimethylaminomethyl)tryptamine (13) from 2b·HCl** 50%  $Me_2NH$  (2 ml) and HCHO (35%, 0.20 ml, 2.46 mmol) were added to a solution of **2b·HCl** (104.5 mg, 0.49 mmol) in MeOH (2 ml) at 0 °C. The mixture was stirred at room temperature for 4 h. After the addition of  $H_2O$  under ice cooling, the whole was extracted with  $CHCl_3$ -MeOH (95:5, v/v). The extract was washed with brine, dried over  $Na_2SO_4$ , and evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, v/v) to give **13** (89.5 mg, 78%). **13**: mp 127–128 °C (dec., unstable colorless solid). IR (KBr): 3342, 1583, 1469, 1417, 1232, 991, 796  $cm^{-1}$ .  $^1H$ -NMR ( $CD_3OD$ )  $\delta$ : 2.38 (6H, s), 2.90 (2H, t,  $J=6.6$  Hz), 2.97 (2H, t,  $J=6.6$  Hz), 4.05 (2H, s), 6.61 (1H,  $d, J=8.5$  Hz), 6.99 (1H, s), 7.12 (1H,  $d, J=8.5$  Hz). High-resolution MS  $m/z$ : Calcd for  $C_{13}H_{19}N_3O$ ; 233.1528. Found: 233.1525.

**3,4,5,6-Tetrahydro-7-hydroxy-1H-azepino[5,4,3-*cd*]indole (5e) from 13** A solution of **13** (10.5 mg, 0.05 mmol) in MeOH (2 ml) was refluxed for 9 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, v/v) to give **5e** (3.0 mg, 35%).

**5-Methoxy-*Nb*-methyltryptamine<sup>9</sup> (16) from 5-Methoxy-*Nb*-methoxy-carbonyltryptamine<sup>9</sup> (17)**  $LiAlH_4$  (184.7 mg, 4.87 mmol) was added to a solution of **17<sup>9</sup>** (120.6 mg, 0.49 mmol) in anhydrous THF (20 ml) at 0 °C, and the mixture was refluxed for 1 h with stirring. After the addition of MeOH and saturated Rochelle salt under ice cooling, the whole was extracted with  $CHCl_3$ . The extract was washed with brine, dried over  $Na_2SO_4$ , and evaporated under reduced pressure to leave an oil, which was column-chromatographed on  $SiO_2$  with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, v/v) to give **16<sup>6a</sup>** (93.0 mg, 94%).

**1,2,3,4-Tetrahydro-6-methoxy-1,2-dimethyl- $\beta$ -carboline (18) from 16** A solution of **16** (49.4 mg, 0.24 mmol) in MeOH (3.5 ml) was made acidic (pH 5.0) by adding 1% HCl in MeOH (v/v). Acetaldehyde (0.67 ml, 12.0 mmol) in MeOH (0.5 ml) was added to the solution at 0 °C, and the mixture was refluxed for 20 h with stirring. The solvent was evaporated under reduced pressure to leave a solid, which was subjected to p-TLC on  $SiO_2$ , developed twice with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, v/v). Extraction of the band having an *R<sub>f</sub>* value of 0.43–0.27 with  $CHCl_3$ -MeOH-28% aq.  $NH_3$  (46:3:0.3, v/v) gave **18** (45.9 mg, 82%). **18**: mp 155–157 °C (colorless powder, recrystallized from  $CHCl_3$ -hexane). IR (KBr): 1629, 1602, 1489, 1217, 1157, 820  $cm^{-1}$ .  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.44 (3H,  $d, J=6.6$  Hz), 2.51 (3H, s), 2.70–2.75 (2H, m), 2.78–2.85 (1H, m), 3.11–3.15 (1H, m), 3.56 (1H, q,  $J=6.6$  Hz), 3.85 (3H, s), 6.79 (1H, dd,  $J=8.8, 2.4$  Hz), 6.94 (1H,  $d, J=2.4$  Hz), 7.19 (1H,  $d, J=8.8$  Hz), 7.56 (1H, br s, disappeared on addition of  $D_2O$ ). MS  $m/z$ : 230 ( $M^+$ ). Anal. Calcd for  $C_{14}H_{18}N_2O$ ·1/4 $H_2O$ : C, 71.61; H, 7.94; N, 11.93. Found: C, 71.37; H, 7.75; N, 11.88.

**Reaction of *Nb*-Methyltryptamine (20) with  $Et_3N$**   $Et_3N$  (2 ml) was

added to a solution of **20** (20.4 mg, 0.12 mmol) in MeOH (2 ml) at 0 °C, and the mixture was refluxed for 20 h with stirring under O<sub>2</sub> atmosphere (O<sub>2</sub> balloon). The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:5:0.5, v/v) to give unreacted **20** (20.2 mg, 99%).

**1,2,3,4-Tetrahydro-6-hydroxy-1-methyl-β-carboline (14) and 3,4,5,6-Tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-cd]indole (5c) from 2b·HCl** [Entry 1] A solution of **2b·HCl** (100.8 mg, 0.47 mmol) in MeOH (4 ml) was made acidic (pH 4) by adding 2 N HCl under ice cooling, then acetaldehyde (1.32 ml, 23.6 mmol) was added to the solution at 0 °C. The mixture was refluxed for 1 h with stirring. The whole was made basic (pH 8) by adding 14% aq. NH<sub>3</sub> under ice cooling, and was then extracted with CHCl<sub>3</sub>. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:5:0.5, v/v) to give **14** (24.7 mg, 26%). **14**: mp 257–258 °C (dec., colorless prisms, recrystallized from MeOH). IR (KBr): 3383, 3273, 1589, 1454, 852, 798 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.45 (3H, d, *J*=6.6 Hz), 2.61 (1H, dddd, *J*=15.3, 4.9, 3.3, 1.5 Hz), 2.73 (1H, dddd, *J*=15.3, 9.6, 5.5, 2.0 Hz), 2.95 (1H, ddd, *J*=12.7, 9.6, 4.9 Hz), 3.26–3.30 (1H, m), 4.09 (1H, q, *J*=6.6 Hz), 6.60 (1H, dd, *J*=8.6, 2.4 Hz), 6.76 (1H, d, *J*=2.4 Hz), 7.09 (1H, d, *J*=8.6 Hz). MS *m/z*: 202 (M<sup>+</sup>). Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.89; H, 7.01; N, 13.62.

[Entry 2] A solution of **2b·HCl** (20.2 mg, 0.10 mmol) in MeOH (3.5 ml) was made acidic (pH 4) by adding 2 N HCl under ice cooling. Then, acetaldehyde (0.27 ml, 4.83 mmol) in MeOH (0.5 ml) was added to the solution at 0 °C. The mixture was refluxed for 20 h with stirring. After the same work-up and separation as described in entry 1, **14** (2.4 mg, 13%) was obtained.

[Entry 3] Acetaldehyde (0.28 ml, 5.01 mmol) in MeOH (0.5 ml) was added to a solution of **2b·HCl** (21.2 mg, 0.100 mmol) in MeOH (3.5 ml) at 0 °C. The pH of the resulting solution was 5. Then, the mixture was refluxed for 20 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:5:0.5, v/v) to give **14** (10.7 mg, 53%) and **5c** (5.4 mg, 27%).

[Entry 4] Acetaldehyde (0.054 ml, 0.97 mmol) was added to a solution of **2b·HCl** (20.7 mg, 0.10 mmol) in MeOH (4 ml) at 0 °C. The pH of the resulting solution was 5. Then, the mixture was refluxed for 20 h with stirring. After the same work-up and separation as described in entry 3, **14** (5.8 mg, 30%), **5c** (5.6 mg, 28%) and unreacted **2b** (6.8 mg, 40%) were obtained in the order of elution.

**3,4,5,6-Tetrahydro-7-hydroxy-1,5,6-trimethyl-1H-azepino[5,4,3-cd]indole (5a) and 1,2,3,4-Tetrahydro-6-hydroxy-1,2,9-trimethyl-β-carboline (15) from 2a** A solution of **2a** (24.9 mg, 0.12 mmol) in MeOH (3.5 ml) was made acidic (pH 5) by adding 1% HCl in MeOH (v/v). Acetaldehyde (0.34 ml, 6.08 mmol) in MeOH (0.5 ml) was added to the solution at

0 °C, and the mixture was refluxed for 20 h with stirring. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed repeatedly on SiO<sub>2</sub> with CHCl<sub>3</sub>-MeOH-28% aq. NH<sub>3</sub> (46:1:0.1, 46:3:0.3, then 46:5:0.5, v/v) to give **15** (7.5 mg, 27%), **5a** (16.3 mg, 58%), and unreacted **2a** (2.3 mg, 9%) in the order of elution. **15**: mp 201–202 °C (colorless powder, recrystallized from CHCl<sub>3</sub>-hexane). IR (KBr): 1627, 1583, 1471, 1419, 1163 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40 (3H, d, *J*=6.7 Hz), 1.60 (1H, br s, disappeared on addition of D<sub>2</sub>O), 2.52 (3H, s), 2.53–2.57 (1H, m), 2.80–2.90 (2H, m), 3.11–3.17 (1H, m), 3.58 (3H, s), 3.83 (1H, q, *J*=6.7 Hz), 6.73 (1H, dd, *J*=8.8, 2.4 Hz), 6.88 (1H, d, *J*=2.4 Hz), 7.11 (1H, d, *J*=8.8 Hz). MS *m/z*: 230 (M<sup>+</sup>). Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O·1/2H<sub>2</sub>O: C, 70.26; H, 8.00; N, 11.70. Found: C, 70.46; H, 7.70; N, 11.38.

#### References and Notes

- 1) Part 106: Somei M., Noguchi K., Yamada F., *Heterocycles*, **55**, 1237–1240 (2001).
- 2) Somei M., Yokoyama Y., Murakami Y., Ninomiya I., Kiguchi T., Naito T., "The Alkaloids," Vol. 54, ed. by Cordell G. A., Academic Press, 2000, pp. 191–257 and references cited therein.
- 3) Rapport M. M., Green A. A., Page I. H., *Science*, **108**, 329–330 (1948); *Idem*, *J. Biol. Chem.*, **176**, 1237–1241 (1948); Rapport M. M., *Ibid.*, **180**, 961–969 (1949); Stoll A., Troxler F., Peyer J., Hofmann A., *Helv. Chim. Acta*, **38**, 1452–1472 (1955) and references cited therein.
- 4) Somei M., Wakida M., Ohta T., *Chem. Pharm. Bull.*, **36**, 1162–1168 (1988) and references cited therein.
- 5) Review on 4-substituted indoles: Somei M., *Yuki Gosei Kagaku Kyokai Shi*, **40**, 387–400 (1982); *Idem*, *Yakugaku Zasshi*, **108**, 361–380 (1988). See also ref. 2.
- 6) a) Somei M., Yamada F., Kurauchi T., Nagahama Y., Hasegawa M., Yamada K., Teranishi S., Sato H., Kaneko C., *Chem. Pharm. Bull.*, **49**, 87–96 (2001); b) Wilkinson S., *J. Chem. Soc.*, **1958**, 2079–2081; Glennon R. A., Dukat M., El-Bermawy M., Law H., Angeles J. D. L., Teitler M., King A., Herrick-Davis K., *J. Med. Chem.*, **37**, 1929–1935 (1994); Bascop S.-I., Sapi J., Laronze J.-Y., Levy J., *Heterocycles*, **38**, 725–732 (1994); Somei M., Yamada F., Morikawa H., *ibid.*, **46**, 91–94 (1997).
- 7) Somei M., Kawasaki T., *Heterocycles*, **29**, 1251–1254 (1989); Review: Somei M., *Yuki Gosei Kagaku Kyokai Shi*, **49**, 205–217 (1991); *Idem*, *Heterocycles*, **50**, 1157–1211 (1999) and references cited therein.
- 8) Review on Pictet-Spengler reaction: Cox E. D., Cook J. M., *Chem. Rev.*, **95**, 1797–1842 (1995) and references cited therein.
- 9) Somei M., Fukui Y., Hasegawa M., Oshikiri N., Hayashi T., *Heterocycles*, **53**, 1725–1736 (2000). See also ref. 6a.