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

The Chemistry of Indoles. CVII.[1] 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 β-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).[2] *Na*,*Nb*-Dimethylserotonin (**2a**), serotonin (**2b**), and *Nb*-methylserotonin (**2c**) are well known biologically active amines.[3] 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.[4] However, the synthetic route is not applicable for the preparation of **3**, because suitably functionalized 4-cyanoindole derivatives are not readily available.[5] On the other hand, we have established a simple method for serotonin congeners[6a] (**2a**—**c**) utilizing our 1-hydroxyindole chemistry.[7] 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 excess Et_3N 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.

2a $\xrightarrow{Et_3N,\ MeOH,\ O_2\ balloon,\ reflux}$ **5a** + recovery

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

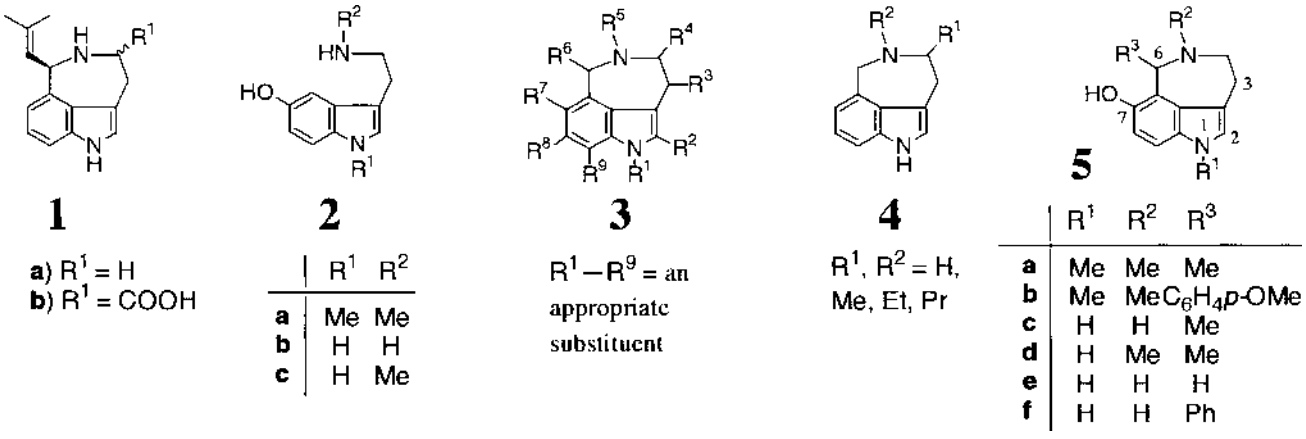

Fig. 1

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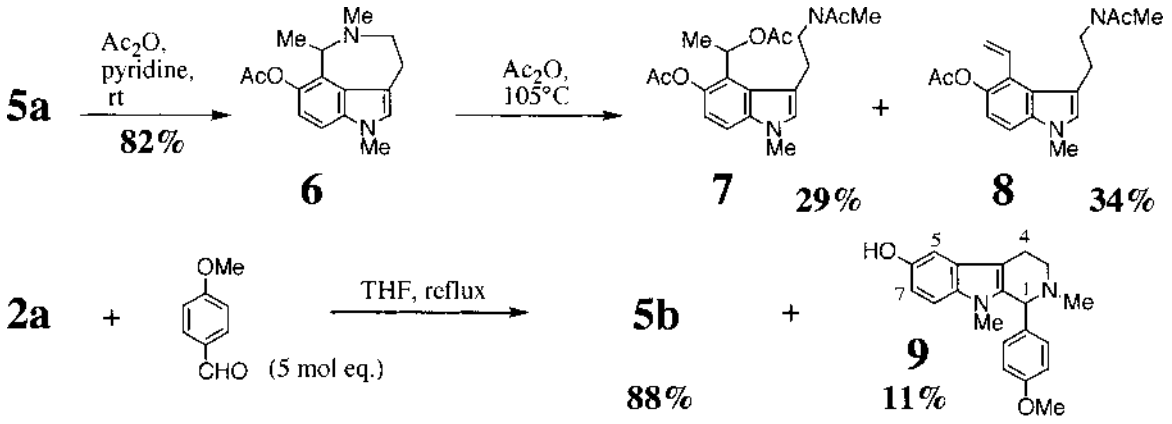


Chart 1

Table 2.

$$\mathbf{2b}\cdot HCl \xrightarrow{Et_3N,\ MeOH} \mathbf{5c} + \text{recovery } (\mathbf{2b})$$

Entry	Atmosphere	Additive (mol eq)	Reaction conditions		Yield (%) of		Note
			Temp. (°C)	Time (h)	**5c**	Recovery	
1	O_2	—	Reflux	20	20	59	Clean
2	O_2	MeCHO (3)	21.5	4	0	51	Tar
3	O_2	MeCHO (6)	21.5	24	0	18	Tar
4	Ar	MeCHO (3)	24	4	8	44	Tar

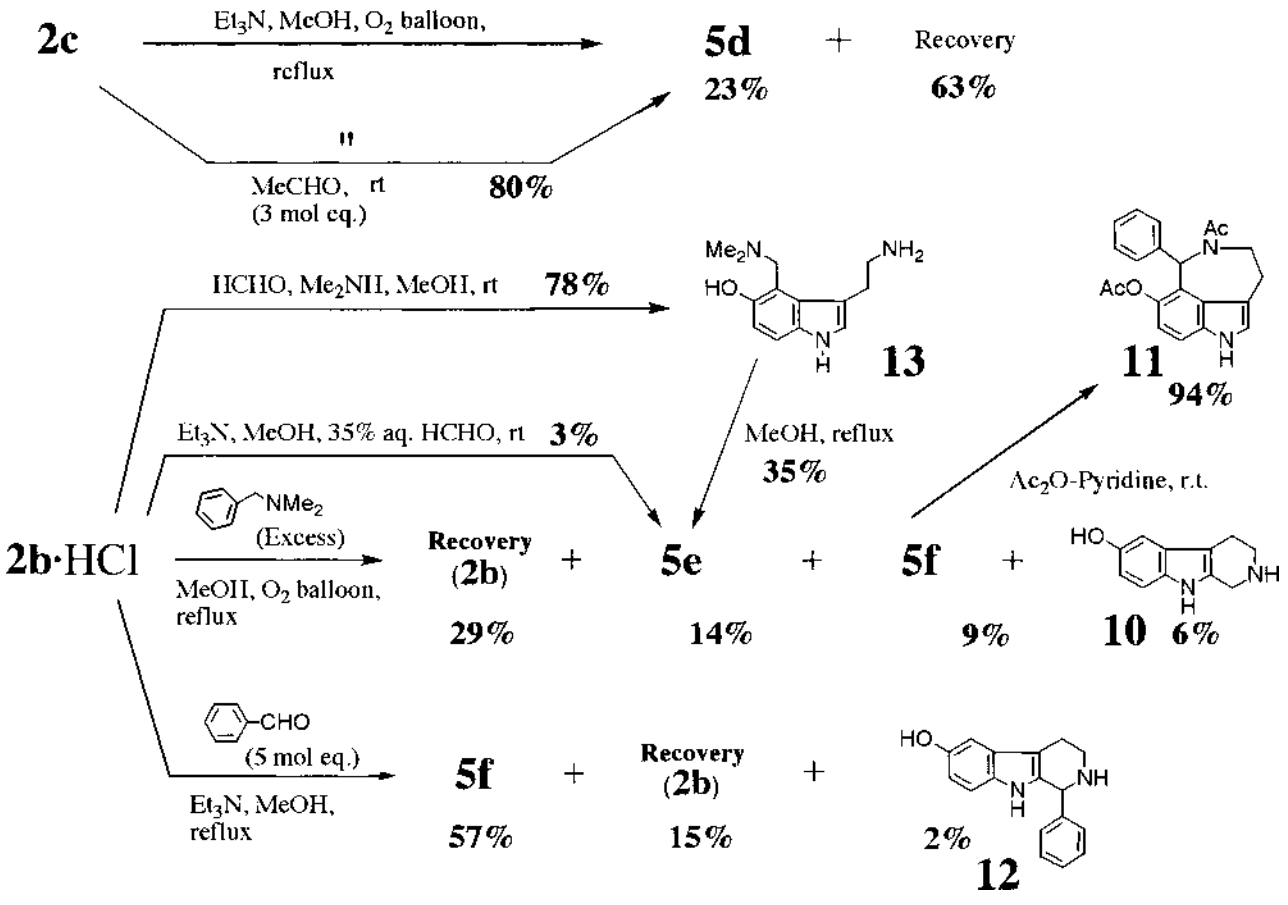
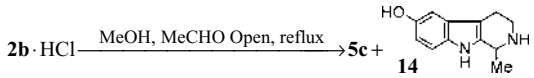


Chart 2

Table 3.



Entry	pH	MeCHO (mol eq)	Concentration of **2b**·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 ^{1}H-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 1*H*-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 β-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**·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**·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-β-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**·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-β-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**·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 β-carbolines.[8] 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 β-carbolines.

Therefore, under careful pH control, we next examined the reaction of **2b**·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**·HCl with an excess amount (50 mol eq) of acetaldehyde provided β-carboline (**14**) as the sole product in 26% yield, together with tar matter (entry 1). When the concentration of **2b**·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**,[6] prepared in 94% yield by a $LiAlH_4$ reduction of 5-methoxy-

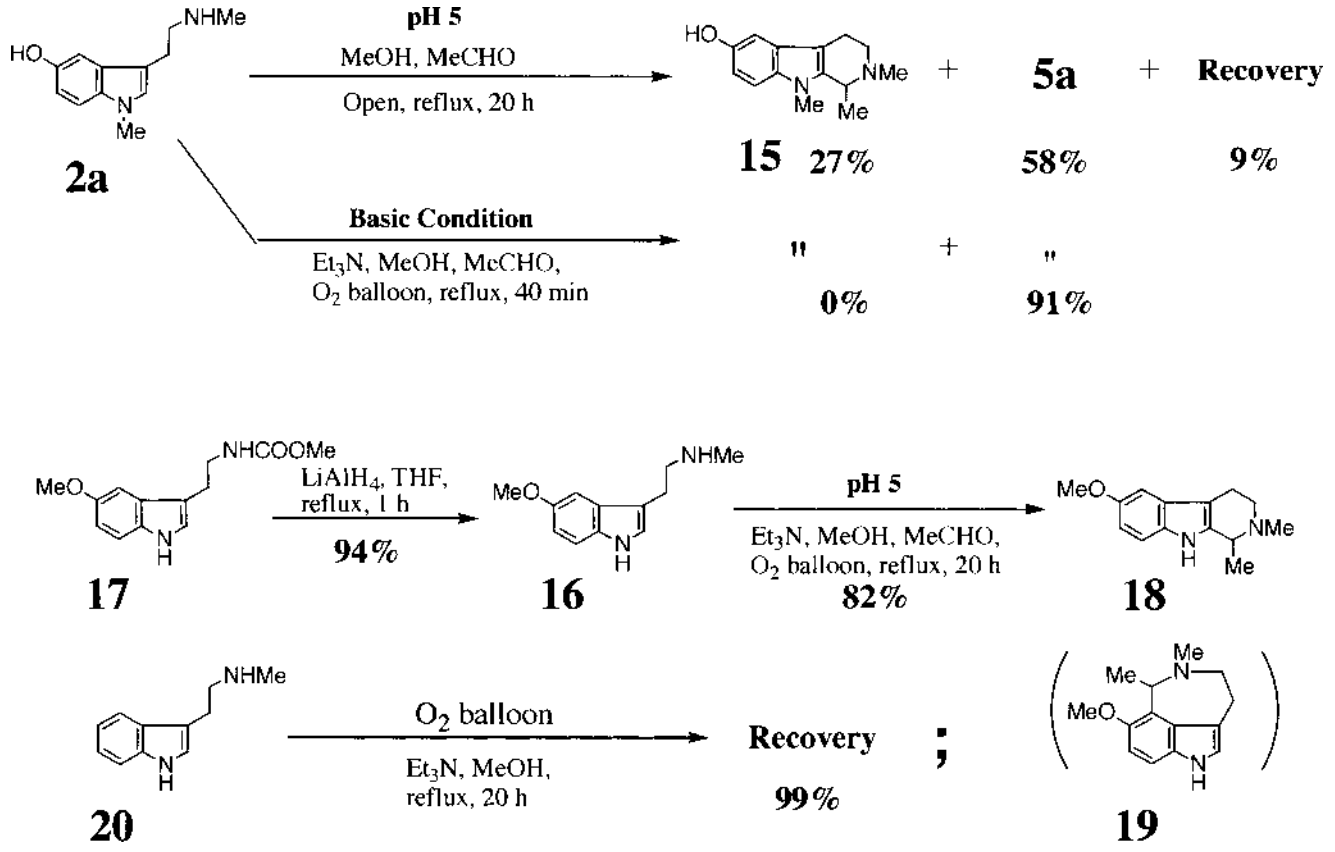


Chart 3

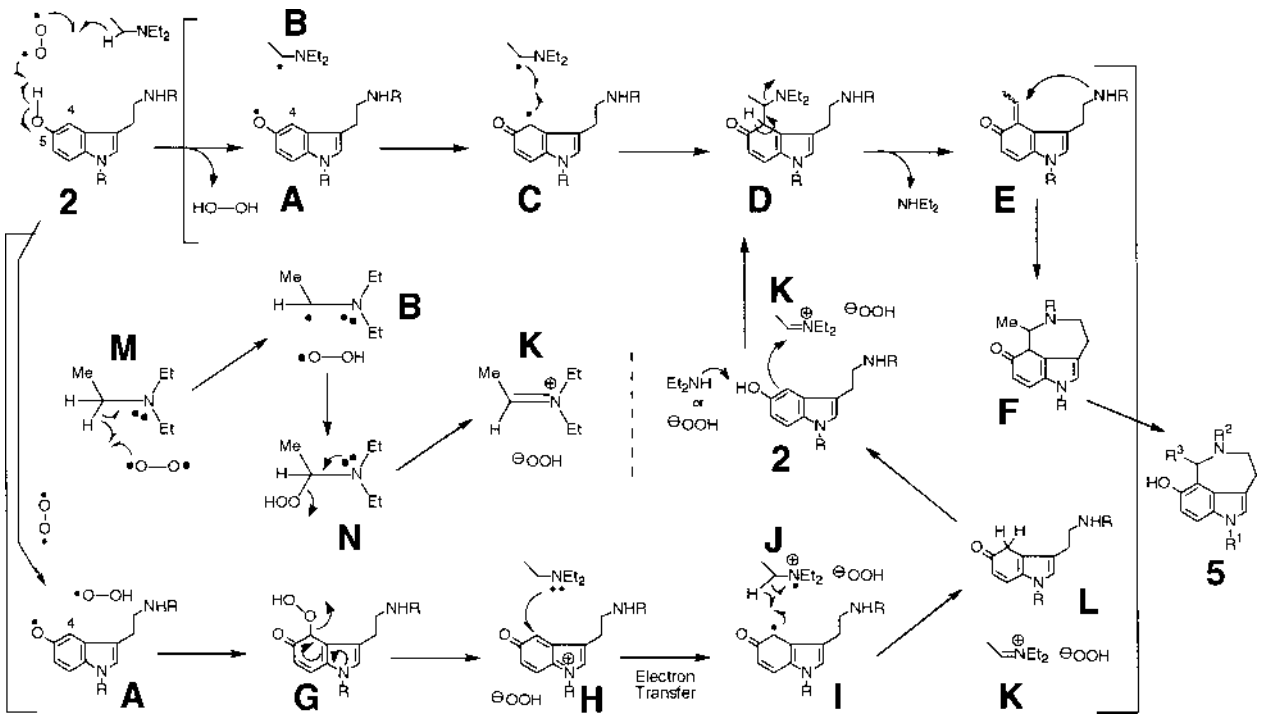


Chart 4. Possible Mechanism

Nb-methoxycarbonylindole[9] (**17**), with acetaldehyde was carried out at pH 5, β-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_3N 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_3N as a representative. Initially, an oxygen molecule interacts with both triethylamine and **2** generating a phenoxyl 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 β-carbon of the α,β-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 phenoxyl (A) and hydropeoxy 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 tranfer from Et_3N to H produces a radical (I) and cation radical (J). J is then converted to imminium species (K) by the abstraction of α-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_3N for 20 h under an oxygen atmosphere resulted in the complete recovery of unreacted **20** without a trace amount of β-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 belive 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 ^{1}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_2, 100—200 mesh, from Kanto Chemical Co., Inc.). Preparative thin layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (type 60) (SiO_2).

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_3N (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_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 : 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 $CHCl_3$–hexane). IR (KBr): 1577, 1457, 1242, 787 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1417. *Anal.* Calcd for $C_{14}H_{18}N_2O \cdot 1/4H_2O$: C, 71.61; H, 7.94; N, 11.93. Found: C, 71.58; H, 7.78; N, 11.88.

[Entry 2] Et_3N (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_2 atmosphere (O_2 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_3N (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_2 atmosphere (O_2 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_3N (4 ml) at 0 °C and the mixture was refluxed for 40 min with stirring under O_2 atmosphere (O_2 balloon). After evaporation of the solvent, H_2O was added to the residue. 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 **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-β-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_2, successively, with $CHCl_3$, $CHCl_3$–MeOH (97 : 3, v/v), and $CHCl_3$–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^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{20}H_{22}N_2O_2$: 322.1681. Found: 322.1694. **9**: mp 177—181 °C (colorless needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 2920, 1603, 1508, 1224, 1032, 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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^+). *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: 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_2O (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_2 with $CHCl_3$–MeOH (97 : 3, v/v) to give **6** (53.9 mg, 82%). **6**: Colorless oil. IR (film): 1755, 1365, 1215, 1193 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{16}H_{20}N_2O_2$: 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_2O (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_2 with AcOEt and $CHCl_3$ 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^{-1}. ^{1}H-NMR (DMSO-d_6, 110 °C) δ: 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 $C_{20}H_{26}N_2O_5$: 374.1841. Found: 374.1830. **8**: mp 118—119 °C (colorless needles). IR (film): 1759, 1644, 1206 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 120 °C) δ: 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-1*H*-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}. ^{1}H-NMR (CD_3OD) δ: 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-1*H*-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}. ^{1}H-NMR (CD_3OD) δ: 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-1*H*-azepino[5,4,3-*cd*]indole (5f), and 1,2,3,4-Tetrahydro-6-hydroxy-β-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}. ^{1}H-NMR (CD_3OD) δ: 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}. ^{1}H-NMR (CD_3OD) δ: 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}. ^{1}H-NMR (CD_3OD) δ: 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-1*H*-azepino[5,4,3-*cd*]indole (5f) and 1,2,3,4-Tetrahydro-6-hydroxy-1-phenyl-β-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}. ^{1}H-NMR (CD_3OD) δ: 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-1*H*-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}. ^{1}H-NMR (DMSO-d_6, 140 °C) δ: 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}. ^{1}H-NMR (CD_3OD) δ: 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-1*H*-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[6] (16) from 5-Methoxy-*Nb*-methoxycarbonyltryptamine[9] (17) $LiAlH_4$ (184.7 mg, 4.87 mmol) was added to a solution of **17**[5] (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**[6a] (93.0 mg, 94%).

1,2,3,4-Tetrahydro-6-methoxy-1,2-dimethyl-β-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 *Rf* 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}. ^{1}H-NMR ($CDCl_3$) δ: 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 $C_{14}H_{18}N_2O$·1/4H_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_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 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-1*H*-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_3 under ice cooling, and was then 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 : 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^{-1}. ^{1}H-NMR (CD_3OD) 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^+). *Anal.* Calcd for $C_{12}H_{14}N_2O$: 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_2 with $CHCl_3$–MeOH–28% aq. NH_3 (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-1*H*-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_2 with $CHCl_3$–MeOH–28% aq. NH_3 (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 $CHCl_3$–hexane). IR (KBr): 1627, 1583, 1471, 1419, 1163 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=6.7 Hz), 1.60 (1H, br s, disappeared on addition of D_2O), 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^+). *Anal.* Calcd for $C_{14}H_{18}N_2O \cdot 1/2H_2O$: C, 70.26; H, 8.00; N, 11.70. Found: C, 70.46; H, 7.70; N, 11.38.

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