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The Chemistry of Indoles. XLIV.[1] Synthetic Study Directed toward 3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles

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A simple synthetic method which can provide 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivatives having a carbon side chain at any desired position of the nucleus was developed. The method was applied to the preparation of 4- and 5-alkyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles.

Keywords——4-cyano-3-(2-nitroethyl)indole; 4-cyano-3-(2-aminoethyl)indole; 4-cyano-3-(2-nitrovinyl)indole; 4-cyano-3-indolecarboxaldehyde; 3-acetyl-4-cyanoindole; cyclization; 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole

Aurantioclavine[2] (**1a**) and clavicipitic acid[3] (**1b**) form one group of ergot alkaloids, which have a 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole skeleton. Although some synthetic studies on 1*H*-azepino[5,4,3-*cd*]indoles have been reported,[4] they are available only through long and laborious multi-step syntheses, so that no systematic study of their pharmacological activities[4] has yet been carried out.

In our continuing synthetic studies on 4-substituted indoles, we have attempted to synthesize various 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivatives (A), with the aim of developing new pharmacologically active compounds. To obtain compounds (A), we selected the following common synthetic strategy (Chart 1) to introduce a carbon side chain into any desired position of the skeleton at the appropriate reaction step as shown by arrows.

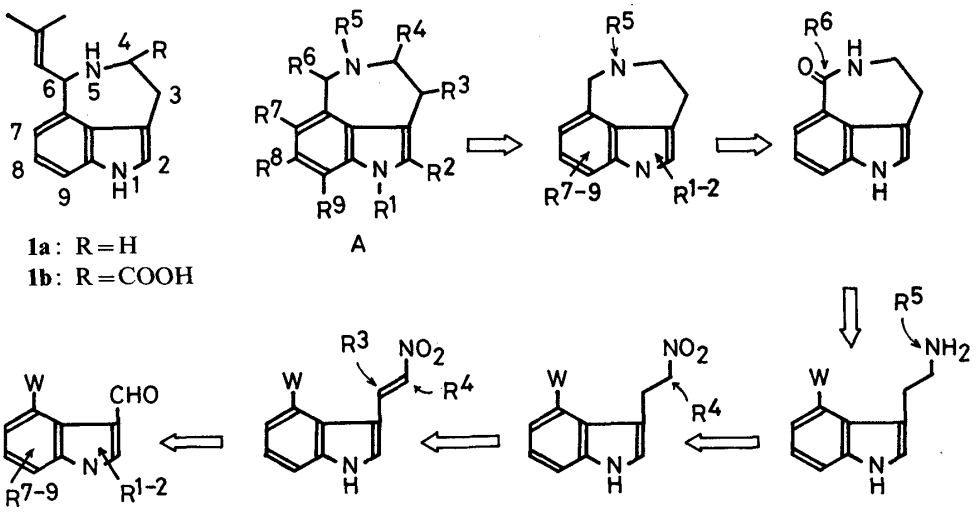


Chart 1. Common Synthetic Strategy for 3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles (A)

In this report, we describe the syntheses of 4- and 5-substituted 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivatives based on the above strategy.

5-Substituted 3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles

Although 3,4,5,6-tetrahydro-1*H*-azepino [5,4,3-*cd*]indole (**8a**) is available by Bowman's procedure[4c] using Uhre's ketone,[5] we attempted to develop a shorter synthesis. Since we have already established a simple one-pot synthetic method[6] for 4-cyano-3-indolecarboxaldehyde[7] (**3**) from 3-indolecarboxaldehyde, we first chose **3** as a starting material among various candidates satisfying the general formula (B) in Chart 1. Compound **3** was prepared readily by the cyanation of 4-iodo-3-indolecarboxaldehyde[8] (**2**) with cuprous cyanide in *N*,*N*-dimethylformamide (DMF) in 70% yield. Aldol condensation of **3** with nitromethane (CH_3NO_2) in the presence of ammonium acetate (NH_4OAc) gave 4-cyano-3-(2-nitrovinyl)indole (**4a**) in 85% yield. Reduction of the vinyl moiety of **4a** with sodium borohydride ($NaBH_4$) cleanly produced 4-cyano-3-nitroethylindole (**5a**) in 87% yield. Compound **5a**, upon reduction with zinc in refluxing methanolic hydrochloric acid (HCl), afforded 3-aminoethyl-4-cyanoindole (**6a**) in 72% yield.

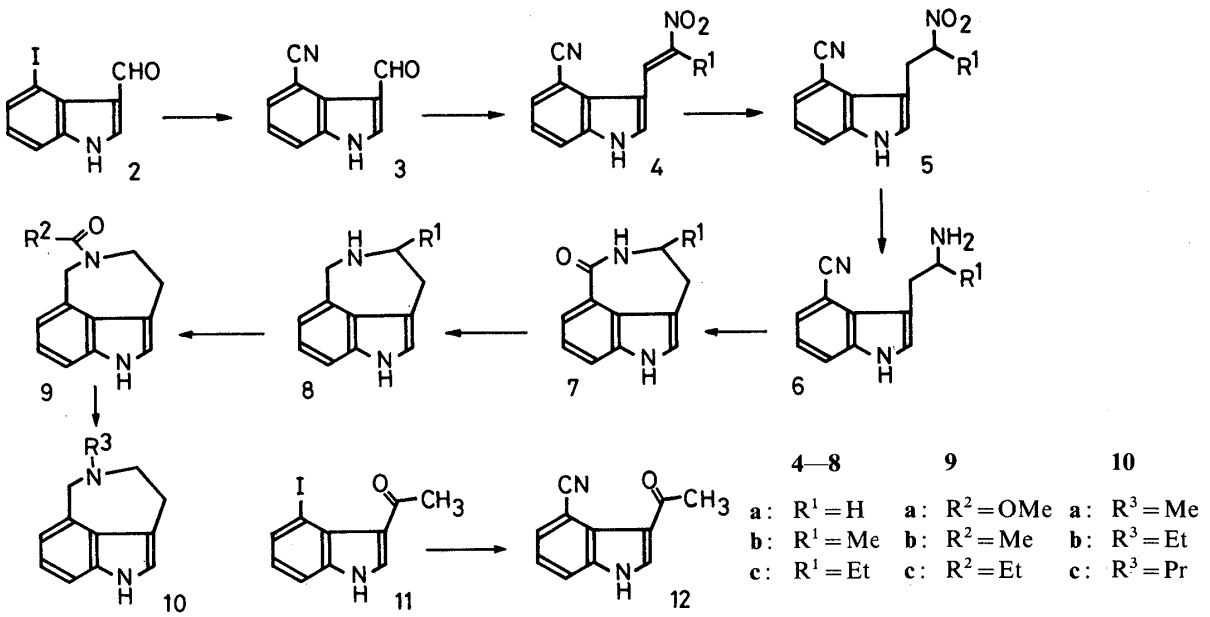
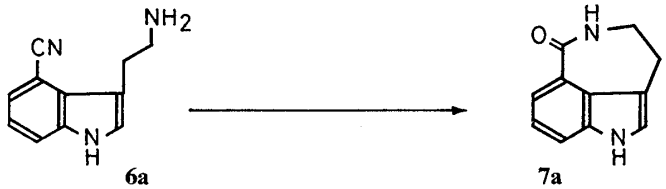


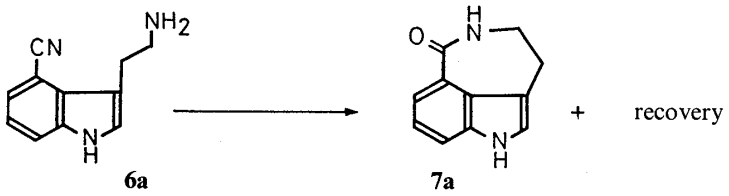
Chart 2

TABLE I. Pyrolytic Cyclization of 3-(2-Aminoethyl)-4-cyanoindole



Run	Starting material (mg)	Al_2O_3 (g)	SiO_2 (g)	Powdered KOH (mg)	Reaction conditions Temperature (°C)	Time (min)	Yield (%) of **7a**
1	34.6	—	1.00	—	248—252	5	12
2	31.1	—	1.00	—	231—237	20	29
3	35.0	—	1.00	104.6	235—239	20	19
4	32.9	1.02	—	93.0	230—232	20	11

TABLE II. Base-Catalyzed Cyclization of 3-(2-Aminoethyl)-4-cyanoindole



6a **7a**

Run	Reaction conditions				Yield (%) of	
	Base	Solvent	Temperature (°C)	Time (h)	**7a**	**6a**
1	*tert*-BuOK	*tert*-BuOH	Reflux	27	7	18
2	LiOH	DMSO	115	3	0	68
3	40% KOH	MeOH	Reflux	1.5	4	75
4	20% KOH	MeOH	Reflux	5	16	74
5	40% Triton B in H_2O	MeOH	Reflux	36	71	6
6	40% Triton B in MeOH	H_2O	Reflux	36	61	11

Cyclization of **6a** to 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-one (**7a**) is the key step of our synthetic strategy. Firstly, we examined the pyrolytic ring closure reaction using silica gel or alumina. As can be seen in Table I, the yield of **7a** was low and could not be increased above 30% under various reaction conditions. Therefore, we next tried to use a base to promote the ring closure reaction, and the results are summarized in Table II. Potassium *tert*-butoxide (run 1) resulted in polymer formation and consequently the yield of **7a** was quite low. Lithium hydroxide (run 2) did not produce **7a**. Differences in the concentration of potassium hydroxide (runs 3 and 4) had a significant effect on the yield of **7a**. Finally, benzyltrimethylammonium hydroxide (Triton B) was found to be the reagent of choice and the desired **7a** became obtainable in 61—71% yield (runs 5 and 6), though a longer reaction time caused the ring opening of **7a** and a shorter reaction time was not sufficient for cyclization.

Reduction of **7a** with lithium aluminum hydride ($LiAlH_4$) in anhydrous tetrahydrofuran (THF) smoothly proceeded to give 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole[4c] (**8a**) in 94% yield. 5-Methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**10a**) was easily obtained from **8a** *via* 5-methoxycarbonyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**9a**) in good yield according to Bowman *et al.*[4c] Similarly, 5-acetyl- (**9b**) and 5-propionyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**9c**) were obtained by the reaction of **8a** with acetic anhydride and pyridine or propionyl chloride in 89% or 68% yield, respectively. Subsequent reduction of **9b** and **9c** with $LiAlH_4$ in anhydrous THF produced the desired 5-ethyl- (**10b**) and 5-propyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**10c**) in 74% and 50% yields, respectively.

4-Substituted 3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles

Nitroaldol reaction of **3** either with nitroethane or nitropropane in the presence of NH_4OAc afforded (*E*)-4-cyano-3-(2-nitro-1-propenyl-(**4b**) or -(2-nitro-1-butenyl)indole (**4c**) as a single isomer in 94% or 71% yield, respectively. Reduction of **4b** and **4c** with $NaBH_4$ in MeOH gave the corresponding saturated compounds (**5b**) and (**5c**) in 46% and 57% yields, respectively. Subsequent reduction of **5b** and **5c** with zinc in methanolic HCl produced the corresponding amines (**6b**) and (**6c**) in 86% and 69% yields, respectively. Cyclization of **6b** and **6c** with Triton B afforded 4-methyl- (**7b**) and 4-ethyl-3,4,5,6-tetrahydro-1*H*-azepino–[5,4,3-*cd*]indol-6-one (**7c**) in 28% and 41% yields, respectively. Decreases in the cyclization yields compared with that of **6a** might be explained by the steric hindrance of the 4-alkyl substituent.

Further reduction of **7b** and **7c** with $LiAlH_4$ in anhydrous THF produced 4-methyl- (**8b**) and 4-ethyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**8c**) in 75% and 71% yields, respectively.

3-Acetyl-4-iodoindole (**11**), prepared from 3-acetylindole by means of the thallation-iodination method[9] in 31% yield, was also found to give 3-acetyl-4-cyanoindole (**12**) in 81% yield. Further studies aimed at obtaining 3-methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles by utilizing **12** are in progress.

In conclusion, we have now succeeded in the syntheses of 4- and 5-substituted 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles by a simple method. We are using the same approach in attempts to obtain compounds having substituents at other positions. Biological evaluations of the new compounds described in this report are in progress.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL JNM-PMX60 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-003 spectrometer. Preparative thin-layer chromatography (p-TLC) was performed on Merck Kiesel-gel GF_{254} (Type 60) (SiO_2). Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co., Inc.) throughout the present study.

4-Cyano-3-indolecarboxaldehyde (3) from 4-Iodo-3-indolecarboxaldehyde (2)——A mixture of cuprous cyanide (1.43 g) and **2** (1.35 g) in DMF (40.0 ml) was heated at 110 °C for 4 h with stirring. After cooling of the reaction mixture, CH_2Cl_2–MeOH (9 : 1, v/v, 200 ml) was added and the whole was filtered through SiO_2 to remove precipitates. The filtrate was concentrated under reduced pressure to give an oil, which was purified by column chromatography with CH_2Cl_2–MeOH (95 : 5, v/v) as an eluent to give **3** (583.0 mg, 70%). mp 225—228 °C (lit.[7] mp 224—226 °C, colorless prisms, recrystallized from MeOH). IR (KBr): 3210, 2205, 1659 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.30 (1H, t, J=7.0 Hz), 7.62 (1H, dd, J=7.0, 1.2 Hz), 7.82 (1H, dd, J=7.0, 1.2 Hz), 8.38 (1H, s), 10.16 (1H, s). MS m/z: 170 (M^+). *Anal.* Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.86; H, 3.43; N, 16.54.

(*E*)-4-Cyano-3-(2-nitrovinyl)indole (4a) from 3——A mixture of NH_4OAc (400.0 mg) and **3** (400.0 mg) in CH_3NO_2 (25.0 ml) was heated at 110 °C for 2 h with stirring. The reaction mixture was concentrated under reduced pressure to leave crystals, which were collected by filtration, washed with MeOH–H_2O (1 : 1, v/v), and dried to give **4a** (331.0 mg) as red prisms. The combined filtrate and washings were concentrated, H_2O was added and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with H_2O, dried over Na_2SO_4, and evaporated under reduced pressure to give an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–*n*-hexane (7 : 3, v/v) as a developing solvent to afford a further crop of **4a** (87.4 mg). The total yield of **4a** was 418.4 mg (83%). mp 247—248 °C (reddish brown prisms, recrystallized from MeOH). IR (KBr): 3240, 2195, 1613 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.28 (1H, t, J=7.5 Hz), 7.59 (1H, dd, J=7.5, 1.5 Hz), 7.80 (1H, dd, J=7.5, 1.5 Hz), 8.02 (1H, d, J=13.5 Hz), 8.46 (1H, s), 8.72 (1H, d, J=13.5 Hz). MS m/z: 213 (M^+). *Anal.* Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.85; H, 3.43; N, 19.55.

(*E*)-4-Cyano-3-(2-nitro-1-propenyl)indole (4b) from 3——In the same procedure as described for **4a**, 1.320 g of NH_4OAc, 1.221 g of **3**, and 100.0 ml of nitroethane were used. The total yield of **4b** was 1.535 g (94%). mp 268—270 °C (reddish brown prisms, recrystallized from MeOH). IR (KBr): 3230, 2200, 1629, 1476 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.44 (3H, s), 7.14 (1H, t, J=7.5 Hz), 7.47 (1H, dd, J=7.5, 1.6 Hz), 7.63 (1H, dd, J=7.5, 1.6 Hz), 7.91 (1H, s), 8.49 (1H, s). MS m/z: 227 (M^+). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.91; H, 4.02; N, 17.99.

(*E*)-4-Cyano-3-(2-nitro-1-butenyl)indole (4c) from 3——In the same procedure as described for **4a**, 303.0 mg of NH_4OAc, 317.0 mg of **3**, and 25.0 ml of nitropropane were used. The total yield of **4c** was 317.7 mg (71%). mp 243—244 °C (reddish brown prisms, recrystallized from MeOH). IR (KBr): 3240, 2215, 1629, 1264 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.0 Hz), 2.92 (2H, q, J= 7.0 Hz), 7.25 (1H, t, J=7.2 Hz), 7.57 (1H, br d, J=7.2 Hz), 7.77 (1H, br d, J=7.2 Hz), 8.01 (1H, s), 8.76 (1H, s). MS m/z: 241 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O_2 \cdot 1/4H_2O$: C, 63.53; H, 4.71; N, 17.10. Found: C, 63.94; H, 4.39; N, 17.15.

4-Cyano-3-(2-nitroethyl)indole (5a) from 4a——$NaBH_4$ (2.180 g) was added to a solution of **4a** (1.080 g) in DMF (40.0 ml) and MeOH (40.0 ml) and stirring was continued at room temperature for 1.5 h. After addition of brine to the reaction mixture, the whole was made neutral (pH 7) by the addition of 2 N HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with CH_2Cl_2 as an eluent to give **5a** (953.2 mg, 87%). mp 163—164 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3345, 2205, 1546 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 3.61 (2H, t,

J=6.5 Hz), 4.74 (2H, t, J=6.5 Hz), 7.12 (1H, t, J=7.5 Hz), 7.25 (1H, s), 7.38 (1H, dd, J=7.5, 1.5 Hz), 7.58 (1H, dd, J=7.5, 1.5 Hz). MS m/z: 215 (M^+). *Anal.* Calcd for $C_{12}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.55; H, 4.17; N, 19.65.

4-Cyano-3-(2-nitropropyl)indole (5b) from 4b——In the same procedure as described for **5a**, 1.900 g of $NaBH_4$, 1.024 g of **4b**, 40.0 ml of DMF, and 40.0 ml of MeOH were used. The yield of **5b** was 475.4 mg (46%). mp 115—118 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3320, 2204, 1553 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.60 (3H, d, J=7.0 Hz), 3.45 (2H, d, J=7.0 Hz), 4.93 (1H, sext, J=7.0 Hz), 7.10 (1H, t, J=7.5 Hz), 7.15 (1H, br s), 7.35 (1H, dd, J=7.5, 1.5 Hz), 7.56 (1H, dd, J=7.5, 1.5 Hz). MS m/z: 229 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.60; H, 4.86; N, 18.12.

4-Cyano-3-(2-nitrobutyl)indole (5c) from 4c——In the same procedure as described for **5a**, 120.0 mg of $NaBH_4$, 122.0 mg of **4c**, 5.0 ml of DMF, and 5.0 ml of MeOH were used. The yield of **5c** was 70.0 mg (57%). mp 128—130 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3390, 2215, 1539 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.0 Hz), 1.99 (2H, q, J=7.0 Hz), 3.51 (1H, dd, J=14.4, 8.8 Hz), 3.61 (1H, dd, J=14.4, 4.0 Hz), 4.55—5.15 (1H, m), 6.97—7.63 (4H, m), 8.03—8.81 (1H, br s). MS m/z: 243 (M^+). *Anal.* Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 63.96; H, 5.35; N, 16.82.

3-(2-Aminoethyl)-4-cyanoindole (6a) from 5a——A solution of **5a** (1.428 g) in MeOH (200 ml) was added to a mixture of zinc powder (10.301 g) and 2 N HCl (200 ml) and the whole was heated under reflux for 2.5 h with stirring. After removal of the precipitates by filtration, the filtrate was made alkaline (pH 11) by the addition of 20% aqueous NaOH solution and extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a crystalline solid. Recrystallization from MeOH afforded **6a** (808.3 mg). Evaporation of the mother liquor under reduced pressure afforded an oil, which was purified by p-TLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH (46 : 5 : 0.5, v/v) as a developing solvent to give a further crop of **6a** (61.0 mg). The total yield of **6a** was 869.3 mg (72%). mp 133—134 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3030, 2200, 1595, 1427 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (2H, br s, NH_2), 3.06 (4H, br s), 6.99 (1H, t, J=7.0 Hz), 7.02 (1H, s), 7.28 (1H, dd, J=7.0, 1.2 Hz), 7.40 (1H, dd, J=7.0, 1.2 Hz), 8.60—9.87 (1H, br s). MS m/z: 185 (M^+). *Anal.* Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.68. Found: C, 71.21; H, 5.89; N, 22.72.

3-(2-Aminopropyl)-4-cyanoindole (6b) from 5b——In the same procedure as described for **6a**, 101.0 mg of **5b**, 15.0 ml of MeOH, 1.050 g of zinc, and 15.0 ml of 2 N HCl were used. Since the product was an oil, the recrystallization step of the above procedure was omitted. The yield of **6b** was 75.0 mg (86%). Colorless oil. IR (film): 2210, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d, J=7.0 Hz), 1.68—3.52 (5H, m), 6.95 (1H, t, J=7.2 Hz), 7.00 (1H, br s), 7.24 (1H, dd, J=7.2, 1.5 Hz), 7.38 (1H, dd, J=7.2, 1.5 Hz). High resolution MS m/z: Calcd for $C_{12}H_{13}N_3$: 199.1108. Found: 199.1129.

3-(2-Aminobutyl)-4-cyanoindole (6c) from 5c——In the same procedure as described for **6a**, 30.9 mg of **5c**, 3.0 ml of MeOH, 322.7 mg of zinc, and 3.0 ml of 2 N HCl were used. Since the product was an oil, the recrystallization step of the above procedure was omitted. The yield of **6c** was 18.6 mg (69%). Colorless oil. IR (film): 3340—3125, 2210, 1582 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=6.0 Hz), 1.23—2.33 (4H, br m), 2.40—3.56 (3H, br m), 7.01 (1H, t, J=7.2 Hz), 7.03 (1H, br s), 7.30 (1H, dd, J=7.2, 1.5 Hz), 7.42 (1H, dd, J=7.2, 1.2 Hz), 9.45 (1H, br s). High-resolution MS m/z: Calcd for $C_{13}H_{15}N_3$: 213.1268. Found: 213.1276.

3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-one (7a) from 6a——A solution of **6a** (50.1 mg) in MeOH (1.5 ml) and Triton B (40% solution in H_2O, 1.5 ml) was heated under reflux for 36 h with stirring. After addition of H_2O, the whole was extracted with EtOAc–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 purified by p-TLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH (20 : 5 : 0.5, v/v) as a developing solvent to afford **7a** (35.6 mg, 71%). mp 240—242 °C (lit.[4c] mp 237—239 °C, colorless prisms, recrystallized from MeOH). IR (KBr): 3185, 1630, 1608 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.88—3.14 (2H, m), 3.38—3.78 (2H, m), 5.30 (1H, br s), 7.16 (1H, br s), 7.23 (1H, t, J=7.5, 1.2 Hz), 7.60 (1H, dd, J=7.5, 1.2 Hz), 8.33 (1H, dd, J=7.5, 1.2 Hz). MS m/z: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.78; H, 5.34; N, 15.12.

4-Methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-one (7b) from 6b——In the same procedure as described for **7a**, 46.8 mg of **6b**, 2.0 ml of H_2O, and 2.0 ml of Triton B (40% solution in MeOH) were used, and the refluxing time was 18 h. In the purification by p-TLC, two bands were detected under ultraviolet (UV) light. Extraction from the upper band with CH_2Cl_2–MeOH (95 : 5, v/v) afforded **7b** (13.0 mg, 28%). Extraction from the lower band with $CHCl_3$–MeOH–NH_4OH (20 : 5 : 1, v/v) afforded unreacted **6b** (17.6 mg, 38%). **7b**: mp 125—126 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3240, 1633, 1605 cm^{-1} ^{1}H-NMR (pyridine-d_5) δ: 1.32 (3H, d, J=6.5 Hz), 2.86—3.12 (2H, m), 3.56—4.22 (1H, m), 7.19 (1H, t, J=8.0 Hz), 7.22 (1H, s), 7.55 (1H, dd, J=8.0, 1.2 Hz), 8.32 (1H, dd, J=8.0, 1.2 Hz). MS m/z: 200 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.97; H, 6.05; N, 14.05.

4-Ethyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indol-6-one (7c) from 6c——In the same procedure as described for **7a**, 92.1 mg of **6c**, 2.0 ml of H_2O, and 2.0 ml of Triton B (40% solution in MeOH were used, and the refluxing time was 24 h. Purification was carried out following the same procedure as described for **7b**. Yields of **7c** and the unreacted **6c** were 38.2 mg (41%) and 20.3 mg (22%), respectively. **7c**: mp 259—260 °C (colorless prisms, recrystallized

from MeOH). IR (KBr): 3220, 1623, 1603 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 0.93 (3H, t, J=7.0 Hz), 1.34—1.88 (2H, m), 2.99 (2H, d, J=7.0 Hz), 3.33—3.84 (1H, m), 7.09 (1H, br s), 7.22 (1H, t, J=7.2 Hz), 7.56 (1H, dd, J=7.2, 1.5 Hz), 8.05 (1H, br s), 8.31 (1H, dd, J=7.2, 1.5 Hz). MS m/z: 214 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.77; H, 6.63; N, 12.90.

3,4,5,6-Tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (8a) from 7a——$LiAlH_4$ (250.5 mg) was added to a solution of **7a** (160.4 mg) in anhydrous THF (10.0 ml) and the mixture was heated under reflux for 6 h with stirring. After excess $LiAlH_4$ had been destroyed by the addition of MeOH, aqueous Rochelle salt was added and the whole was extracted with EtOAc–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 purified by column chromatography on SiO_2 with $CHCl_3$–MeOH–NH_4OH (46 : 5 : 0.5, v/v) as an eluent to give **8a** (139.2 mg, 94%). mp 227—229 °C (lit.[4c] mp 226—228 °C, colorless prisms, recrystallized from MeOH). IR (KBr): 3290, 1617, 1429, 1355 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.93—3.21 (4H, m), 4.21 (2H, s), 6.69 (1H, dq, J=7.2, 1.0 Hz), 6.93 (1H, dd, J= 8.0, 7.2 Hz), 6.96 (1H, br s), 7.14 (1H, dt, J=8.0, 0.7 Hz). MS m/z: 172 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O \cdot 1/12H_2O$: C, 76.05, H, 7.06; N, 16.12. Found: C, 76.06; H, 7.11; N, 16.06.

4-Methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (8b) from 7b——In the same procedure as described for **8a**, 2.456 g of $LiAlH_4$, 681.0 mg of **7b**, and 30.0 ml of anhydrous THF were used, and the refluxing time was 21 h. The yield of **8b** was 474.2 mg (75%). mp 229—234 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3280, 2910 (br), 1615, 1428 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 1.29 (3H, d, J=7.0 Hz), 2.68—3.34 (3H, m), 4.34 (1H, d, J=16.5 Hz), 4.57 (1H, d, J=16.5 Hz), 6.88 (1H, br d, J=7.2 Hz), 7.14 (1H, t, J=7.2 Hz), 7.16 (1H, s), 7.40 (1H, br d, J=7.2 Hz). MS m/z: 186 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2 \cdot 1/4H_2O$: C, 75.55; H, 7.66; N, 14.69. Found: C, 75.53; H, 7.49; N, 14.63.

4-Ethyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (8c) from 7c——In the same procedure as described for **8a**, 823.0 mg of $LiAlH_4$, 492.3 mg of **7c**, and 120.0 ml of anhydrous THF were used, and the refluxing time was 24 h. The yield of **8c** was 348.0 mg (76%). mp 203—205 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3290, 2880 (br), 1614, 1430 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.04 (3H, t, J=6.5 Hz), 1.57 (2H, quint, J=6.5 Hz), 2.64—3.43 (3H, m), 4.30 (1H, d, J=16.0 Hz), 4.59 (1H, d, J=16.0 Hz), 6.86 (1H, br d, J=6.5 Hz), 7.15 (1H, s), 7.15 (1H, t, J =6.5 Hz), 7.38 (1H, br d, J=6.5 Hz). MS m/z: 200 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2 \cdot 1/6H_2O$: C, 76.81; H, 8.10; N, 13.78. Found: C, 76.98; H, 8.06; N, 13.65.

5-Methoxycarbonyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (9a) from 8a——A solution of methyl chloroformate (50.0 mg) in anhydrous THF (1.0 ml) was added to a solution of **8a** (31.0 mg) in anhydrous THF (4.0 ml) and Et_3N (0.15 ml), and stirring was continued at room temperature for 10 min. H_2O was added to the reaction mixture and the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to afford **9a** (33.7 mg, 81%). mp 210—211 °C (lit.[4c] mp 210—212 °C, colorless prisms, recrystallized from MeOH). IR (KBr): 3300, 1675, 1481 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.92—3.43 (2H, m), 3.50—3.95 (2H, m), 3.54 and 3.61 (total 3H, each s), 4.88 and 5.00 (total 2H, each s), 6.90 (1H, br dd, J=7.2, 1.5 Hz), 6.97—7.23 (2H, m), 7.34 (1H, br dd, J=7.2, 1.5 Hz). MS m/z: 230 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_2 \cdot 1/6H_2O$: C, 66.94; H, 6.19, N, 12.01. Found: C, 67.22; H, 6.03; N, 11.80.

5-Acetyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (9b) from 8a——Acetic anhydride (2.0 ml) was added to a solution of **8a** (76.0 mg) in anhydrous pyridine (4.0 ml) and the whole was stirred at room temperature for 4 h. After evaporation of the solvent under reduced pressure, H_2O was added to the residue. The whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v), and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give an oil, which was purified by p-TLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH (20 : 5 : 1, v/v) as a developing solvent to afford **9b** (78.6 mg, 89%) as a colorless oil. IR (film): 3260, 1620, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 and 2.18 (total 3H, each s), 3.14 (2H, t, J=6.0 Hz), 3.88 (2H, t, J=6.0 Hz), 4.78 and 4.99 (total 2H, each s), 6.69—7.32 (4H, m), 8.19—8.69 (1H, br s). High-resolution MS m/z: Calcd for $C_{13}H_{14}N_2O$: 214.1105. Found: 214.1118.

5-Propionyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (9c) from 8a——A solution of propionyl chloride (35.0 mg) in anhydrous THF (5.0 ml) was added to a solution of **8a** (50.6 mg) in anhydrous THF (10.0 ml) and Et_3N (1.0 ml), and stirring was continued at 40 °C for 4.5 h. After addition of brine to the reaction mixture, the whole was extracted with CH_2Cl_2–MeOH (95 : 5, v/v) and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give an oil, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to give **9c** (45.0 mg, 68%). mp 180—181 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3200, 1625, 1597, 1427 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 1.05 and 1.17 (total 3H, each t, J=7.0 Hz), 2.37 (2H, q, J=7.0 Hz), 3.06 and 3.29 (total 2H, each t, J=6.0 Hz), 3.70 and 3.94 (total 2H, each t, J=6.0 Hz), 4.79 and 5.16 (total 2H, each s), 6.84—7.44 (4H, m). MS m/z: 228 (M^+). *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.64; H, 7.30; N, 12.40.

5-Methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (10a) from 9a——$LiAlH_4$ (501.3 mg) was added to a solution of **9a** (332.5 mg) in anhydrous THF (30.0 ml) and the mixture was heated under reflux for 30 min with stirring. After excess $LiAlH_4$ had been destroyed adding saturated aqueous Na_2SO_4, EtOAc–MeOH (1 : 1, v/v, 300 ml) was

added and the whole was filtered. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline residue, which was recrystallized from MeOH to give **10a** (201.0 mg, 76%) as colorless prisms. mp 199—200 °C (lit.[4c] mp 195—197 °C). IR (KBr): 1616, 1357, 736 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.46 (3H, s), 3.08 (4H, s), 4.18 (2H, s), 6.72—7.53 (4H, m). MS *m/z*: 186 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2 \cdot 1/6H_2O$: C, 76.16; H, 7.61; N, 14.80. Found: C, 76.57; H, 7.62; N, 14.65.

5-Ethyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (10b) from 9b—— In the same procedure as described for **10a**, 52.0 mg of $LiAlH_4$, 37.1 mg of **9b**, and 10.0 ml of anhydrous THF were used, and the refluxing time was 40 min. After recrystallization, the mother liquor was concentrated under reduced pressure to afford an oil, which was purified by p-TLC on SiO_2 with $CHCl_3$–MeOH–NH_4OH (20 : 5 : 1, v/v) as a developing solvent to give a further crop of **10b**. Total yield of **10b** was 25.6 mg (74%). mp 169 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1617, 1437, 1357 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.16 (3H, t, J=7.5 Hz), 2.74 (2H, q, J=7.5 Hz), 2.94—3.28 (4H, br s), 4.16 (2H, s), 6.70 (1H, br d, J=7.5 Hz), 6.95 (1H, t, J=7.5 Hz), 6.96 (1H, br s), 7.15 (1H, br d, J=7.5 Hz). MS *m/z*: 200 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2 \cdot 1/6H_2O$: C, 76.81; H, 8.10; N, 13.78. Found: C, 77.06; H, 7.97; N, 13.85.

5-Propyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (10c) from 9c——In the same procedure as described for **10a**, 700.0 mg of $LiAlH_4$, 482.1 mg of **9c**, and 50.0 ml of anhydrous THF were used, and the refluxing time was 1 h. The yield of **10c** was 227.0 mg (50%). mp 154—155 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 1617, 1435, 1358 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.89 (3H, t, J=7.5 Hz), 1.40—1.86 (2H, m), 2.52—2.73 (2H, m), 2.96—3.22 (4H, m), 4.17 (2H, s), 6.70 (1H, br d, J=7.0 Hz), 6.95 (1H, t, J=7.0 Hz), 6.96 (1H, br s), 7.15 (1H, br d, J=7.0 Hz). MS *m/z*: 214 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2 \cdot 1/6H_2O$: C, 77.38; H, 8.49; N, 12.89. Found: C, 77.35; H, 8.62; N, 13.05.

3-Acetyl-4-cyanoindole (12) from 3-acetyl-4-iodoindole (11)——A mixture of cuprous cyanide (64.1 mg) and **11**[9] (57.8 mg) in DMF (3.0 ml) was heated at 100—107 °C for 1 h with stirring. After cooling of the reaction mixture, CH_2Cl_2–MeOH (9 : 1, v/v) was added and the whole was filtered through SiO_2 to remove precipitates. The filtrate was concentrated under reduced pressure to give a crystalline solid, which was purified by p-TLC on SiO_2 with CH_2Cl_2–MeOH (95 : 5, v/v) as a developing solvent to afford **12** (30.3 mg, 81%). mp 274 °C (colorless prisms, recrystallized from MeOH). IR (KBr): 3300 (br), 2210, 1636 (br), 1611 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s), 7.19 (1H, t, J=7.0 Hz), 7.50 (1H, dd, J=7.0, 1.5 Hz), 7.67 (1H, dd, J=7.0, 1.5 Hz), 8.32 (1H, s). MS *m/z*: 184 (M^+). *Anal.* Calcd for $C_{11}H_8N_2O \cdot 1/6H_2O$: C, 70.57; H, 4.47; N, 14.96. Found: C, 70.94; H, 4.24; N, 14.85.

References and Notes

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