Preparation of Hydrogenated Azepino[3,2,1-*hi*]indoles

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A general method for the preparation of 4,5-dihydro-, 1,2,4,5-tetrahydro-, 4,5,6,7-tetrahydro- and 1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indoles was established by using intramolecular Friedel-Crafts alkylation of chloromethylthioacetamide as a crucial step.

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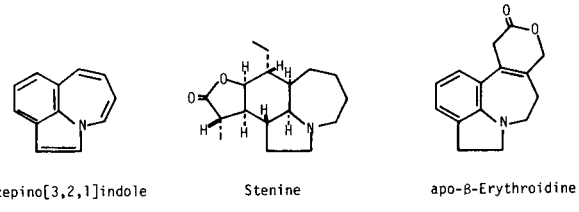
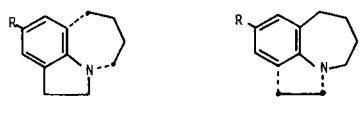
Azepino[3,2,1-*hi*]indole is a skeletal compound of the alkaloids such as stenine, tuberostemonine [1] and apo-β-erythroidine [2]. Its hydrogenated derivatives thus attracted the interest of some synthetic chemists [3] as well as a few medicinal chemists [4]. There are a few reports about the preparation of the title compounds [5], but all available methods are not satisfactory as a general method for the following reasons: (1) low total yield with multi-step reactions, (2) special structural requirements for the construction of molecule, and (3) drastic reaction conditions which are not applicable for the preparation of the authentic specimens for *N*-Claisen rearrangement, which we are studying currently [6]. Therefore we have started to look for a general method for the construction of hydrogenated azepino[3,2,1-*hi*]indoles that does not have these limitations.

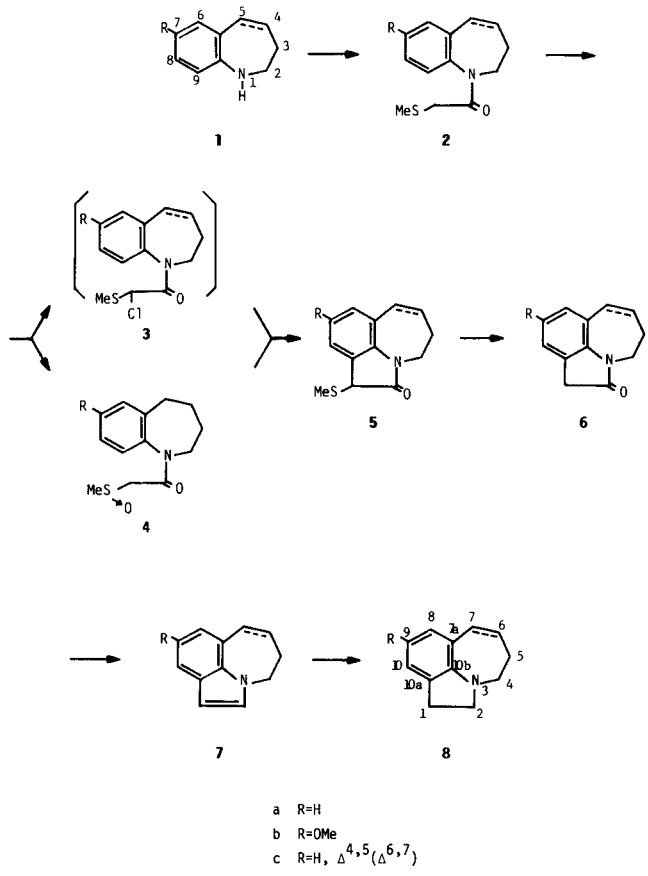
Preparation.

Initially two approaches were considered for our goal: A, construction of the seven-membered ring onto the indoline skeleton, and B, formation of the five-membered ring onto the hydrogenated 1-benzazepine framework (Scheme 1). However, approach A was concluded to be inappropriate in our investigation, because intramolecular Friedel-Crafts acylation leading to a seven-membered ring does not give acceptable yields [3b], and although Dieckmann condensation is effective to construct a seven-membered ring [3b,7], it requires the introduction of reactive carbon unit at a *peri* position to nitrogen prior condensation. Therefore approach B was adopted in this report. Starting materials, 2,3,4,5-tetrahydro-1-benzazepines, **1a** and **1b** [8] were prepared by the reduction of the corresponding tetralone oximes with diisobutylaluminum hydride (DIBAL) [9] and 2,3-dihydro-1-benzazepine **1c** was obtained by the known methods [10]. As noted in the construction of a five-membered ring onto tetrahydro-1,4-benzdiazepines [11], our preliminary experiments to fuse the five-membered





Scheme 1



Scheme 2

ring onto the seven-membered ring of **1a** by Fischer indolization did not give acceptable yields [12], so the Tamura's method was used, which constitutes the intramolecular Friedel-Crafts alkylation of α-chloro-α-methylthioacetamide [13]. Thus, 2,3,4,5-tetrahydro-1-benzazepines **1** were treated with α-methylthioacetylchloride [14] in the presence of tertiary amines and amides **2** were obtained in good yield. The cyclization of **2** into **5** was carried out by intramolecular Friedel-Crafts alkylation. Thus compounds **2** were chlorinated with *N*-chlorosuccimide (NCS) at 0°, and the resulting solution, after removal of succimide, was treated with stannous chloride to effect intramolecular alkylation of **3** into **5**. It proceeded in good yield. As described in the original report, **5a** was also obtained in moderate yield by the oxidation of **2a** with 30% hydrogen peroxide and the subsequent Pummerer reaction of sulfoxide **4a**. From the standpoint of yield and simplicity, the Friedel-Crafts alkylation was used for the remaining cyclizations. The methylthio group of **5** was removed by W-2 Raney nickel. For desulfurization of **5c**, the deteriorated reducing agent was used because freshly prepared Raney nickel was able to saturate the olefinic bond of **5c**. Since the reduction of **6a** and **6b** with lithium aluminum hydride in tetrahydrofuran (THF) gave a mixture of indole and indoline derivatives and the yield was poor, lactam **6** was transformed first into indole derivatives **7** by the reduction with DIBAL, then **7** was reduced with sodium cyanoborohydride in acidic media

Table 1

^{1}H-NMR Spectra of Hydrogenated Azepino[3,2,1-*hi*]indoles

	Protons δ [ppm]										
Compound	1	2	4	5	6	7	8	9	10	SCH_3	OCH_3
5a	4.21 s	—	3.95 t, J = 5.5 Hz	2.01 m		2.95 t, J = 5.2 Hz	7.01 d, J = 7.5 Hz	6.95 dd, J = 6.5, 7.5 Hz	7.19 d, J = 6.5 Hz	2.03 s	—
5b	4.19 s	—	3.91 t, J = 5.6 Hz	1.99 m		2.91 t, J = 5.7 Hz	6.56 d, J = 2.4 Hz	—	6.82 d, J = 2.4 Hz	2.02 s	3.77 s
5c	4.25 s	—	3.94 m	2.55 m	6.05 td, J = 6.1, 11.4 Hz	6.41 d, J = 11.4 Hz	7.10 dd, J = 1.9, 7.8 Hz	7.04 dd, J = 6.6, 7.8 Hz	7.26 br d, J = 6.6 Hz	2.06 s	—
6a	3.89 s	—	4.36 t, J = 5.5 Hz	2.43 m		3.36 t, J = 5.8 Hz	7.39 d, J = 7.5 Hz	7.30 dd, J = 7.1, 7.5 Hz	7.46 d, J = 7.1 Hz	—	—
6b	3.48 s	—	3.90 t, J = 5.4 Hz	1.99 m		2.91 t, J = 5.7 Hz	6.53 d, J = 2.4 Hz	—	6.68 d, J = 2.4 Hz	—	3.76 s
6c	3.54 s		3.93 t, J = 4.6 Hz	2.54 m	6.04 td, J = 6.1, 11.2 Hz	6.40 d, J = 11.2 Hz	7.07 d, J = 8.0 Hz	6.97 dd, J = 6.8, 8.0 Hz	7.09 d, J = 6.8 Hz	—	—
7a	6.45 d, J = 2.9 Hz	6.97 d, J = 2.9 Hz	4.11 t, J = 5.4 Hz	2.07 m		3.11 t, J = 5.7 Hz	6.92 dd, J = 1.9, 6.8 Hz	6.98 dd, J = 6.8, 7.1 Hz	7.44 dd, J = 1.9, 7.1 Hz	—	—
7b	6.37 d, J = 2.9 Hz	6.95 d, J = 2.9 Hz	4.06 t, J = 5.4 Hz	2.04 m		3.04 t, J = 5.7 Hz	6.62 d, J = 2.4 Hz	—	6.90 d, J = 2.4 Hz	—	3.81 s
7c	6.47 d, J = 3.2 Hz	6.95 d, J = 3.2 Hz	4.21 t, J = 4.9 Hz	2.73 m	5.98 td, J = 6.1, 11.4 Hz	6.60 d, J = 11.4 Hz	7.01 dd, J = 2.4, 7.1 Hz	7.05 dd, J = 6.6, 7.1 Hz	7.49 dd, J = 2.4, 6.6 Hz	—	—
8a	2.95 t, J = 8.3 Hz	3.32 t, J = 8.3 Hz	2.90 t, J = 5.5 Hz	1.84 m	1.73 m	2.74 t, J = 5.6 Hz	6.87 dd, J = 1.4, 7.3 Hz	6.66 t, J = 7.3 Hz	6.96 dd, J = 1.4, 7.3 Hz	—	—
8b	2.93 t, J = 8.4 Hz	3.29 t, J = 8.4 Hz	2.83 t, J = 5.3 Hz	1.86 m	1.70 m	2.70 t, J = 5.4 Hz	6.46 d, J = 2.4 Hz	—	6.59 d, J = 2.4 Hz	—	3.73
8c	2.93 t, J = 8.3 Hz	3.37 t, J = 8.3 Hz	3.16 t, J = 4.9 Hz	2.61 m	5.76 td, J = 5.1, 11.9 Hz	6.25 br d, J = 11.9 Hz	6.81 d, J = 7.8 Hz	6.64 dd, J = 7.1, 7.8 Hz	6.92 d, J = 7.1 Hz		

into **8**. According to above methods, hydrogenated azepino[3,2,1-*hi*]indoles, **7** and **8** were prepared in practical total yields.

NMR Spectra.

Concerning the methylene protons of the seven-membered ring in hydrogenated azepino[3,2,1-*hi*]indoles, positions 5-H and 6-H overlapped when a carbonyl or a double bond was present in the five-membered ring (Table 1). When these functional groups were absent in five-membered ring, these methylene protons appeared at different positions, and were readily recognized by irradiation experiments. Irradiation at 5-H resulted in the decoupling of 4-H and the irradiation at 6-H decoupled 7-H, both into singlets. After 5-H and 6-H were correctly assigned, selective experiments in the ^{13}C nmr spectrum allowed the assignments of 5-C and 6-C (Table 2). This experiment was not applicable when 5-H and 6-H appeared at the same position. In this case, 6-C was positioned at higher field than 5-C as observed in the above series of compounds.

Chemical shifts of the aromatic protons and carbons of the hydrogenated azepino[3,2,1-*hi*]indoles were assigned by comparison with chemical shifts of 2,3,4,5-tetrahydro-1-benzazepines, indolines and indoles as the reference compounds. The conclusions for the assignments of the aromatic framework of hydrogenated azepino[3,2,1-*hi*]indoles were obtained by combining tetrahydrobenzazepines with indolines or indoles, and are as follows: (1) 8-H appears at higher field than 10-H, (2) 8-C resonates at lower field than 10-C, and (3) 7a-C is at lower field than 10a-C in the series of compounds with a saturated seven-membered ring. These conclusions were exactly what was observed. Support for the above assumptions were also available from nuclear Overhauser experiments (nOe). Weak irradiation at 7-H of **6b** increased the integration of 8-H by 3.4% (8-H:3.4%) and irradiation at 1-H the integration of 10-H by 4.8% (10-H:4.8%). Other nOe results were as follows: **8a** 10-H:14%; **8b** 8-H:6.1%, 10-H:11.1%; **5c** 8-H:12.8%, 10-H:4.2%. Splittings of the aromatic protons were not sharp and exact coupling constants were only available by decoupling experiments. Irradiation at 7-H or 1-H sharpened aromatic proton signals and permitted us to determine the coupling constants. The values obtained for **5a** are as follows: $J_{8,9}$ = 7.56 Hz, $J_{9,10}$ = 6.59 Hz, $J_{8,10}$ = 1.95 Hz, $J_{8,1}$ = 0.49 Hz, $J_{10,1}$ = 0.98 Hz.

Based upon the above assignments of the aromatic protons, selective experiments in the ^{13}C nmr spectra were conducted and aromatic carbons were assigned. Results are in good accord with the above conclusions. Support for the assignments of the 7a-C and the 10a-C in **6a** was collected also by irradiation experiments. Weak irradiation at 7-H during acquisition of the ^{13}C nmr spectrum led to the increase of the peak height of 7a-C and irradiation at 1-H heightened 10a-C. In the series of compound with a double bond in the seven-membered ring, it was assumed that 10a-C would be affected only slightly by the C-6, C-7 double bond, therefore the chemical shift values that were similar to the values for the 10a-C of the saturated compound with the same substituents were assigned for 10a-C, and the others for 7a-C. Upfield shifts of 7a-C by 5-9 ppm were observed for **6c**, **7c**, and **8c**. A similar shift was also observed in **1c** (5a-C: δ 123.0). These shifts were probably due to the more effective resonance participation of the lone pair on nitrogen, compared to its saturated analogue,

Table 2

^{13}C-NMR Spectra of Hydrogenated Azepino[3,2,1-*hi*]indoles

Compound	Carbons δ [ppm]													
	1	2	4	5	6	7	7a	8	9	10	10a	10b	SMe	OMe
5a	40.4	175.4	41.1	26.3	26.3	30.6	125.9	130.3	122.7	125.2	125.2	142.9	12.3	—
5b	46.5	175.2	41.1	26.4	26.4	31.1	127.2	115.7	155.9	109.0	126.2	136.3	12.3	55.7
5c	45.6	174.5	42.1	28.9	131.1	129.0	121.0	131.0	122.6	123.5	125.9	141.7	12.3	
6a	36.0	175.3	40.7	26.4	26.2	30.7	125.2	129.1	122.0	122.0	124.6	144.0	—	—
6b	36.6	175.1	41.1	26.5	26.3	31.2	126.0	114.1	155.4	108.8	126.0	127.4	—	55.7
6c	35.7	174.3	41.9	28.9	130.9	129.2	120.9	130.0	122.0	122.8	124.7	142.9	—	—
7a	101.7	129.8	50.3	29.2	27.5	34.3	130.2	122.0	119.4	118.5	126.7	136.8	—	—
7b	101.5	130.4	50.4	29.2	27.4	34.4	130.6	112.2	153.8	99.9	127.8	132.2	—	55.7
7c	101.3	128.8	49.2	30.6	128.5	131.0	122.5	123.9	119.5	120.1	129.9	134.2	—	—
8a	29.2	56.7	55.6	30.4	27.6	36.0	131.6	128.8	119.2	122.0	126.7	152.6	—	—
8b	29.7	57.1	56.3	30.6	27.5	36.1	133.1	114.1	153.7	108.5	127.9	146.5	—	55.7
8c	29.0	56.0	49.3	31.9	128.5	129.1	120.0	129.9	118.6	122.8	120.8	151.2	—	—

All signals have the corresponding multiplicities.

which was induced by the introduction of a double bond in the seven-membered ring.

EXPERIMENTAL

Melting points were measured on Yanako MP-3 hot stage apparatus and are uncorrected. Infrared (ir) spectra were measured with Hitachi 215 instrument and nuclear magnetic resonance (nmr) spectra were taken in deuteirochloroform with JEOL JNM-PMX-60 and JNM-FT-200 spectrometers using tetramethylsilane as an internal standard. High resolution mass spectra (ms) were obtained with a Hitachi RMU-7MG double focus spectrometer. Ultraviolet (uv) spectra were recorded with a Shimadzu UV-200 spectrometer.

1-Methylthioacetyl-2,3,4,5-tetrahydro-1-benzazepine **2a**.

α-Methylthioacetyl chloride [14] (3.02 g, 24.2 mmoles) was added to a solution of 2,3,4,5-tetrahydro-1-benzazepine **1a** [8c] (2.48 g, 16.8 mmoles) and dry pyridine (2.0 ml) in anhydrous dichloromethane (35 ml) at 0° and the resulting solution was stirred at room temperature for 2 hours. The reaction mixture was washed with 1*M* sodium carbonate, brine, 1*M* hydrochloric acid and brine successively then dried over anhydrous magnesium sulfate. The crude product was purified by column chromatography on silica gel (100 g) with dichloromethane-ethyl acetate (97:3). Crystalline **5a** (3.8 g, 95%) was recrystallized from methanol and a pure specimen (2.03 g, 51%) was obtained, mp 71.0-71.5° (hexane); ir (potassium bromide): 2855, 1642, 1401, 1141, 773 cm^{-1}; ^{1}H-nmr: δ 1.27-1.49 (m, 1H), 1.80-2.06 (m, 3H), 2.12 and 2.18 (each s, 3H, S-CH_3), 2.62 (m, 1H), 2.71 (m, 1H), 2.94 (ddd, J = 1.9, 12.2, 14.2 Hz, 1H), 3.03 (AB type, J = 13.6 Hz, 1H), 3.12 (AB type, J = 13.6 Hz, 1H), 4.70 (d with splittings, J = 13.1 Hz, 1H), 7.20-7.25 (m, 4H, Ar-H); ^{13}C-nmr: δ 16.2 (SMe), 26.5 (4), 29.1 (3), 34.6 (5), 35.5 (SCH_2CO), 47.6 (2), 127.3 (8), 127.5 (6), 128.1 (7), 130.3 (9), 141.1 (5a), 143.0 (9a), 168.1 (CO); signals for isomer: δ 20.1, 29.3, 30.3, 38.4, 47.8, 126.3, 128.4, 129.2, 136.6, 137.6.

Anal. Calcd. for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.31; N, 5.87.

1-Methylthioacetyl-7-methoxy-2,3,4,5-tetrahydro-1-benzazepine **2b**.

7-Methoxy-2,3,4,5-tetrahydro-1-benzazepine **1b** [8d] (2.76 g, 15.6 mmoles), which was prepared from 6-methoxytetralone oxime by the treatment with DIBAL [9], was similarly treated with methylthioacetyl chloride (2.16 g, 17.3 mmoles) and triethylamine (2.40 ml, 17.2 mmoles) in dry dichloromethane (59 ml). The purification of the crude product (4.40 g) by column chromatography (silica gel 80 g, dichloromethane:ethyl acetate = 9:1) gave **2b** (4.00 g, 97%) which was recrystallized from cyclohexane to afford crystalline **2b** (1.78 g, 43%), mp 63-64°; ir (potassium bromide): 1661 (shoulder), 1642, 1600 (sh), 1506, 1315, 1245 cm^{-1}; H-nmr: δ 1.27-1.47 (m, 1H), 1.80-2.32 (m, 3H), 2.19 (s, 3H, SCH_3), 2.52-2.66 (m, 2H), 2.90 (t, J = 13 Hz, 1H), 3.02 (AB type, J = 13.6 Hz, 1H), 3.12 (AB type, J = 13.6 Hz, 1H), 3.81 (s, 3H, OCH_3), 4.67 (d with small couplings, J = 13.2 Hz, 1H), 6.72 (dd, J = 2.9, 8.3 Hz, 1H), 6.77 (d, J = 2.9 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H); ^{13}C-nmr: δ 16.2 (SMe), 26.6 (4), 29.1 (3), 34.8 (5), 35.4 (SCH_2CO), 47.7 (2), 55.4 (OMe), 111.8 (8), 115.5 (6), 128.3 (9), 135.8 (5a), 142.4 (9a), 158.9 (7), 168.4 (CO).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.15; H, 7.19; N, 5.11.

1-Methylthio-2,3-dihydro-1-benzazepine **2c**.

2,3-Dihydro-1-benzazepine [10] **1c** (2.11 g, 14.5 mmoles) was dissolved in dry dichloromethane (30 ml) and reacted with methylthioacetyl chloride (2.70 g, 21.6 mmoles) in the presence of pyridine (2.5 ml) as described above. The crude product (4.03 g) was purified by column chromatography (silica gel 100 g, dichloromethane:ethyl acetate = 98:2) and recrystallization from methanol gave crystalline **2c** (2.69 g, 79%), mp 78-78.5°; ir (potassium bromide): 1642, 1497, 1398, 1118, 785 cm^{-1}; ^{1}H-nmr: δ 2.12 (s, 3H, SCH_3), 2.41 (m, 1H), 2.76-3.07 (m, 2H), 3.16 (AB type, J = 13.9 Hz, 1H), 3.20 (AB type, J = 13.9 Hz, 1H), 4.69 (m, 1H), 5.97 (d with many splittings, J = 12.2 Hz, 1H), 6.39 (dd, J = 2.2, 12.2 Hz, 1H), 7.21-7.30 (m, 4H, Ar-H); ^{13}C-nmr: δ 16.1 (SMe), 30.7 (3), 35.4 (SCH_2CO), 45.7 (2), 126.6 (9), 126.8 (5), 127.2 (7.8), 131.8 (6), 132.3 (4), 133.1 (5a), 144.8 (9a), 168.1 (CO).

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.75; H, 6.47; N, 6.05.

1-Methylthio-2-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole **5a**.

A solution of **5a** (1.298 g, 5.5 mmoles) in dry dichloromethane (25 ml) was cooled in an ice bath and kept under an atmosphere of dry nitrogen. Under vigorous stirring, NCS (98%, 0.828 g, 6.0 mmoles) was added, and the resulting solution was stirred for 1 hour. The white precipitate was removed by filtration under a positive pressure of dry nitrogen and washed with dry dichloromethane (5 ml). Into a mixture of the filtrate and washings, anhydrous stannous chloride (1.30 g, 11.1 mmoles) was introduced for 7 minutes and the resulting green solution was stirred for 50 minutes. Excess reagent was quenched with water (30 ml) and the mixture was stirred for 0.5 hour. The isolated organic layer was washed with 1*N* hydrochloric acid, water and brine successively. The crystallization of the crude product (1.14 g) from methanol gave **5a** (0.93 g, 72%). An analytical specimen was prepared by recrystallization from hexane, mp 69.5-70.0°; ms: m/z 233 (M^+, 32), 187 (86), 186 (100); ir (potassium bromide): 1705, 1475, 1360, 1206, 1163, 777, 747 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.98; H, 6.49; N, 6.03.

9-Methoxy-1-methylthio-2-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole **5b**.

Methylthioacetamide **2b** (9.53 g, 36 mmoles) and NCS (98%, 5.27 g, 40 mmoles) were reacted in dry dichloromethane (120 ml) as described above. After removing succinamide, the filtrate was treated with stannous chloride (13.86 g, 53 mmoles) and reacted for 2 hours. Purification of the crude product (9.5 g) was carried out by column chromatography (Florisil 70 g, benzene) and the isolated product (7.1 g, 75%) was recrystallized from cyclohexane to give pure **5b** (5.59 g, 59%), mp 109-109.5°; ir (potassium bromide): 1700, 1490, 1340, 1170, 1025, 865 cm^{-1}.

Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.58; N, 5.23.

1-Methylthio-2-oxo-1,2,4,5-tetrahydroazepino[3,2,1-*hi*]indole **5c**.

Amide **2c** (2.198 g, 9.4 mmoles) in dichloromethane (50 ml) was reacted with NCS (98%, 1.412 g, 10.3 mmoles), then with stannous chloride (2.1 ml, 17.8 mmoles) as described above. The crude product (2.4 g) was chromatographed on silica gel (18 g) with dichloromethane and the product (1.900 g, 87%) was recrystallized from methanol to give crystalline **5c** (1.691 g, 77%), mp 89.0-90.0°; ir (potassium bromide): 3030, 1700, 1597, 1465, 1357, 1183, 1030, 777, 725 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.57; H, 5.67; N, 6.06.

1-Methylsufinylacetyl-2,3,4,5-tetrahydro-1-benzazepine **4**.

A mixture of methylthioacetamide **2a** (238 mg, 1 mmole) and 30% hydrogen peroxide (1.72 ml) in methanol (5 ml) was stirred at room temperature for 14 hours. The reaction mixture was diluted with brine and extracted with dichloromethane three times. The crude product (259 mg) was recrystallized from benzene, giving sulfoxide **4** (141 mg, 55%), mp 124.5-125°; ms: m/z 251 (M^+, 8), 189 (25), 188 (100); ir (potassium bromide): 2860, 1642, 1408, 1040, 1030, 978, 790 cm^{-1}; ^{1}H-nmr: (a mixture of stereoisomers) δ 1.21-1.52 (m, 1H), 1.80-2.12 (m, 3H), 2.61-2.93 (m, 3H), 2.69 and 2.76 (s, 3H, $SOCH_3$), 3.35 and 3.83 (AB type, J = 13.9 Hz, 1H, SOC*H*HCON), 3.51 and 3.64 (d, J = 13.9 Hz, 1H, SOCH*H*CON), 4.67 (d, J = 12.9 Hz, 1H), 7.12-7.29 (m, 4H, Ar-H); ^{13}C-nmr: (a mixture of stereoisomers) δ 26.3 (t), 28.8 (t)*, 28.9 (t), 34.3 (t)*, 34.4 (t), 39.8 (q), 40.3 (q)*, 47.5 (t)*, 47.6 (t), 58.6 (t)*, 127.4 (d), 127.6 (d)*, 127.7 (d)*, 127.8 (d), 128.8 (d), 130.5 (d), 130.6 (d)*, 140.0 (s)*, 140.5 (s)*, 140.8 (s), 163.3 (s)* (Signals of major isomer are marked with *).

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 61.89; H, 6.84; N, 5.46.

Pummerer Reaction of Sulfoxide **4**.

From a solution of *p*-toluenesulfonic acid monohydrate (175 mg, 0.92 mmole) in benzene (24 ml) 14 ml of benzene was distilled off and sulfoxide **4** (98 mg, 0.39 mmole) was added into the remaining solution and the solution was refluxed for 0.5 hour. The reaction mixture was washed with aqueous sodium hydrogen carbonate and brine. The crude product (88 mg) was purified by column chromatography (silica gel 1.0 g, dichloromethane) and **5a** was obtained in 87% yield (79 mg).

2-Oxo-1,2,4,5,6,7-hexahydrozepino[3,2,1-*hi*]indole **6a**.

W-2 Raney nickel (13.5 ml, 18 g) was added to a solution of methylsulfide **5a** (2.761 g, 12 mmoles) in ethanol (110 ml), and the mixture was refluxed for 5 hours. The catalyst was removed, and the filtrate was evaporated. The crude product (2.1 g) was filtered through a silica gel column (12 g) with dichloromethane and crystalline **7a** was obtained in 73% yield, mp 85.0-85.5° (cyclohexane-benzene); ms: m/z 187 (M^+, 100), 158 (18), 141 (18), 130 (19); ir (potassium bromide): 1717, 1463, 1362, 770, 740 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.94; H, 6.97; N, 7.43.

9-Methoxy-2-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole **6b**.

Methylsulfide **5b** (12.0 g) was desulfurized with W-2 Raney nickel (65 ml) in ethanol (550 ml) for 4 hours. The crude product was filtered through a Florisil column (20 g) by dichloromethane and crystalline **6b** (9.2 g, 93% yield) was obtained. Recrystallization from cyclohexane gave pure **6b** in 62% yield, mp 86.5-87°; ms: m/z 217 (M^+, 95), 202 (100); Calcd. for $C_{13}H_{15}NO_2$: 217.1101. Found: 217.1091; ir (potassium bromide): 1697, 1615, 1492, 1142, 855 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.92; H, 7.11; N, 6.35.

2-Oxo-1,2,4,5-tetrahydroazepino[3,2,1-*hi*]indole **6c**.

Methylsulfide **5c** (3.95 g) was dissolved in ethanol (100 ml) and desulfurized with W-2 Raney nickel (50 ml) which was stored in a refrigerator for six months. The crude product (3.00 g) was purified by column chromatography (silica gel 30 g, dichloromethane:ethyl acetate = 97:3) and crystalline **6c** (2.20 g, 69%) was obtained, mp 110.5-111.5° (cyclohexane); ms: m/z 185 (M^+, 99), 184 (21), 170 (32), 156 (100), 142 (39), 129 (9); ir (potassium bromide): 1703, 1595, 1345, 1178, 1018, 721 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.62; H, 5.97; N, 7.54.

4,5,6,7-Tetrahydroazepino[3,2,1-*hi*]indole **7a**.

A solution of lactam **6a** (317 mg, 1.7 mmoles) in dry dichloromethane (20 ml) was cooled by ice-water and stirred vigorously. Into this solution 25% (w/w) DIBAL in toluene (1.8 ml) was slowly added and the resulting solution was stirred for 2 hours. After addition of another amount of reagent (0.1 ml, total amount 1.9 ml, 2.8 mmoles), the reaction was continued for 20 minutes. Dichloromethane (20 ml), sodium fluoride (0.87 g, 20.7 mmoles) and water (0.2 ml) were successively added into the reaction mixture and the resulting solution was stirred at room temperature for 1 hour. The precipitate was removed by suction-filtration and washed with dichloromethane. The filtrate and washings were combined and evaporated. The residual product was filtered through silica gel column (2.0 g) by dichloromethane and the filtrate (224 mg, 77%) was further purified by flash column chromatography (silica gel 20 g, hexane:ethyl acetate = 96:4) [15], giving pure **7a** (191 mg, 66%), mp 38.0-38.5° (methanol); ms: m/z 171 (M^+, 100), 170 (45), 143 (16); ir (potassium bromide): 1426, 1515, 1193, 783, 753, 722 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.87; H, 7.60; N, 8.16.

9-Methoxy-4,5,6,7-tetrahydroazepino[3,2,1-*hi*]indole **7b**.

A solution of **6b** (9.3 g, 0.043 mole) in dry dichloromethane (200 ml) was cooled in an ice bath and treated with 25% DIBAL in hexane (45 ml, 55 mmoles) in a similar manner as described above. After 2 hours reaction time, dichloromethane (150 ml), sodium fluoride (45 g, 2.07 moles), and water (4.5 ml, 0.25 mole) were added to the reaction mixture, and worked up. The crude product (7.7 g) was purified by column chromatography on silica gel (140 g) with dichloromethane, and crystalline **7b** (5.0 g, 58%) was obtained, mp 70.5-71.0° (methanol); ms: m/z 221 (M^+, 100), 186 (67), 158 (19), 130 (13); ir (potassium bromide): 3100, 1435, 1246, 1152, 1050, 836, 735 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.36; H, 7.52; N, 6.94.

4,5-Dihydroazepino[3,2,1-*hi*]indole **7c**.

Lactam **6c** (185 mg, 1 mmole) dissolved in dry dichloromethane (10 ml) was reduced witn 25% DIBAL in toluene (1 ml, 2.9 mmoles) at 0° for 2 hours. The reaction mixture was worked up as described above and the crude product (180 mg) was purified by column chromatography (silica gel 6 g, benzene:hexane = 8:2) to give **7c** (130 mg, 77%), mp 32.5-33.0° (methanol); ms: m/z 169 (M^+, 78), 168 (100), 167 (27), 154 (32); Calcd. for $C_{11}H_{11}N$: 169.0890. Found: 169.0863; ir (potassium bromide): 3050, 3020, 1340, 1178, 803, 723 cm^{-1}; uv (hexane): λ nm (ϵ) 215 (12070), 222 (11000), 228 (12100), 239 (7350), 246 (7570), 254 (7100), 297 (sh, 4900), 310 (6410), 324 (6640).

Anal. Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.53; N, 8.28. Found: C, 85.20; H, 6.52; N, 8.32.

Reduction of **6a** with Lithium Aluminum Hydride.

Into a refluxing solution of lithium aluminum hydride (103 mg, 2.7 mmoles) dissolved in dry THF (10 ml) a solution of lactam **6a** (106 mg, 0.57 mmole) in dry THF (2 ml) was added dropwise over a period of 10 minutes and the reaction was continued for 2 hours. Excess reagent was destroyed by the addition of 10% potassium hydroxide (0.35 ml) and subsequent refluxing. Filtration and evaporation of the filtrate gave the crude product (66 mg) which was chromatographed on silica gel (2.0 g) with dichloromethane. The first eluate was **7a** (18 mg, 18% yield), then **8a** (32 mg, 33% yield) followed.

Reduction of **6b** with Lithium Aluminum Hydride.

Lactam **6b** (2.67 g, 12 mmoles) in THF (45 ml) was reacted with lithium aluminum hydride (1.60 g, 42 mmoles) in dry THF (80 ml) for 4 hours. Chromatography of the crude product separated **7b** (0.305 g, 12%) and **8b** (1.12 g, 45%).

1,2,4,5,6,7-Hexahydroazepino[3.2.1-*hi*]indole **8a**.

Into a solution of **7a** (40 mg) and sodium cyanoborohydride (61 mg) in methanol-THF (1:1, 4 ml) a solution of 2*N* hydrochloric acid in methanol was added at such rate to retain the red color of methyl orange. When the red color persisted, the reaction mixture was stirred overnight. Dilution of the reaction mixture with 1*M* sodium carbonate, evaporation of the resulting solution and extraction of the residual solution gave **8a** as a colorless oil (36 mg, 89%); ms: m/z 174 (M^+ + 1, 36), 173 (M^+, 100), 172 (98), 171 (30), 170 (24), 145 (28), 144 (32), 130 (126); ir (chloroform): 1594, 1480, 1438, 1275 cm^{-1}.

The hydrobromide had mp 239-241° (sealed tube) (methanol-acetone); ir (potassium bromide): 2400, 1620, 1458, 1447, 1408, 988, 815 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}BrN$: C, 56.70; H, 6.36; N, 5.51. Found: C, 56.66; H, 6.34; N, 5.52.

9-Methoxy-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole **8b**.

A solution of **7b** (2.5 g, 12 mmoles) and sodium cyanoborohydride (1.63 g, 26 mmoles) in a mixture of acetonitrile (40 ml) and methanol (20 ml) containing a few drops of methyl orange was treated with 2*N* hydrochloric acid as described above. The crude product (2.47 g) was purified on a Florisil column (20 g, dichloromethane:ethyl acetate = 97:3) and **8b** (2.4 g, 95%) was isolated as a colorless oil; ms: m/z 203 (M^+, 57), 188 (100), 160 (5); Calcd. for $C_{13}H_{17}NO$: 203.1309. Found: 203.1271; ir (film): 1615, 1487, 1260, 1142, 1047 cm^{-1}.

The hydrobromide had mp 192-192.5° (dichloromethane-acetone); ir (potassium bromide): 2440, 1597, 1487, 1323, 1203, 1180, 1036, 852 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}BrNO$: C, 54.94; H, 6.38; N, 4.93. Found: C, 54.94; H, 6.38; N, 4.93.

1,2,4,5-Tetrahydroazepino[3,2,1-*hi*]indole **8c**.

Unsaturated lactam **6c** contaminated with saturated lactam **6a** (2.03 g, 11 mmoles) was dissolved in dry dichloromethane (120 ml) and reduced with 1.2*M* DIBAL in hexane (14.7 ml) at 0° for 2 hours and worked up with dichloromethane (100 ml), sodium fluoride (12.5 g) and water (1.5 ml) as described above. The crude product (1.7 g) was briefly filtered through a silica gel column with dichloromethane and the product **7c** (1.57 g) which was contaminated with about 15% of **7a** was dissolved in a mixture of methanol (10 ml) and acetonitrile (15 ml) and treated with sodium cyanoborohydride (1.22 g) as described above. The crude product (1.58 g) was subjected to column chromatography (silica gel 100 g, dichloromethane) and **8c** (1.2 g, 75%) and **8a** (0.3 g, 9%) were isolated. Compound **8c** was an oil; ms: m/z 171 (M^+, 78), 170 (100), 169 (11), 168 (15), 156 (14), 154 (13); Calcd. for $C_{12}H_{13}N$: 171.1047. Found: 171.1001; ir (chloroform): 3048, 2845, 1642, 1483, 1278, 1075 cm^{-1}.

The hydrobromide had mp 201-205° (sealed tube) (chloroform-acetone); ir (potassium bromide): 2760, 2400, 1610, 1380, 1165, 808 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}BrN$: C, 57.16; H, 5.60; N, 5.55. Found: C, 56.95; H, 5.56; N, 5.53.

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