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TETRAHEDRON

Synthesis of Angular-substituted Tetracyclic Azepino-indole Derivatives *via* *N*-Acyliminium Ion Cyclization

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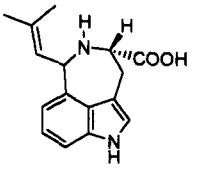
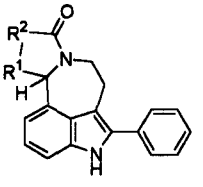
Abstract: A concise and efficient synthesis of tetracyclic azepino-indole derivatives **2** having a substituent at the angular position has been accomplished through an *N*-acyliminium ion cyclization. The coupling reaction of indol-3-yl-ethylamine **3** with 4- or 5-keto-acid **4** followed by cyclization reaction of the resulting tautomeric mixtures of keto-amide **5** and hydroxylactam **6** in refluxing formic acid provided **2**.

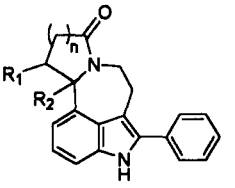
Azepino[5,4,3-*cd*]indole is an interesting heterocycle and forms the skeleton of clavicipitic acid, a derailment product of normal ergot metabolism.[1] Owing to the unique structure and potential biological activities of this ring system, several azepino-indole derivatives have been synthesized and some of them have found to possess α_2-adrenoceptor, 5-HT_{1A}, or dopamine D_2/D_4 receptor binding affinity.[2-4] However, there was no report on the synthesis of pyrrolidine or piperidine ring-fused azepino[5,4,3-*cd*]indoles. In this regard, we have recently reported the synthesis of new type of azepino[5,4,3-*cd*]indole system (**1**).[5] The strategy comprises three-step sequence: 1) condensation of tryptamine derivatives with dicarboxylic acids to produce cyclic imides; 2) regioselective reduction of cyclic imides to give hydroxy- or alkoxylactams; 3) formation of pyrrolidino- or piperidino-azepine rings through the capture of *N*-acyliminium ion intermediates by the 4-position of indole nucleus in acidic condition.



Clavivipitic acid



1



2, R_2 = alkyl or phenyl

In connection with our efforts on the syntheses of pharmacologically active compounds,[6] we describe

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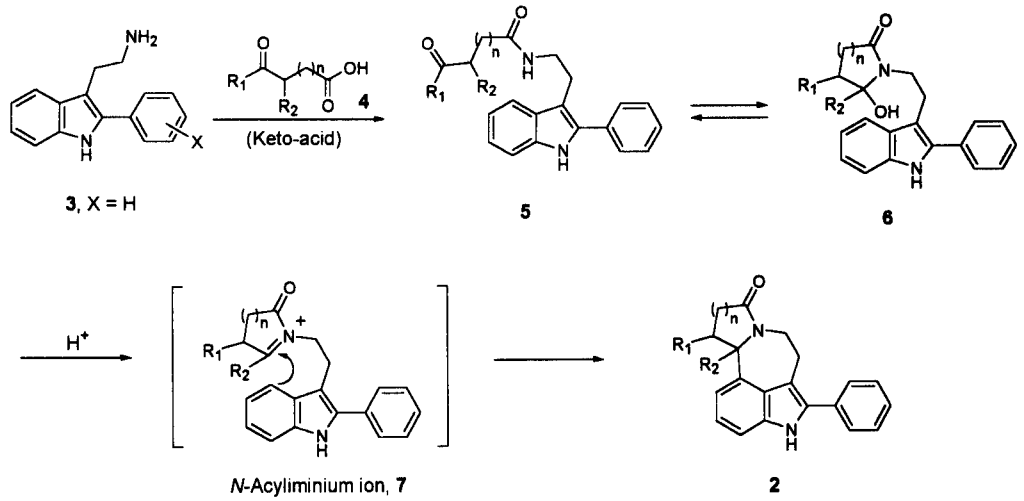
here a concise synthesis of pyrrolidino- or piperidino-azepino-indole derivatives (**2**) which has an alkyl or a phenyl substituent at the angular position by a two-step reaction sequence starting from commercially available 4- or 5-keto-acids **4**. Although some examples on the synthesis of angular-substituted indolizidine derivatives have been published from our laboratory[7] or by other groups[8], there is no report on the synthesis of pyrrolidino-azepine or piperidino-azepine derivatives bearing an angular-substituent.

It was expected that pyrrolidine or piperidine ring-fused azepino[5,4,3-*cd*]indole ring would be formed by electrophilic attack of indole ring to *N*-acyliminium ion in **7** based on previous results (Scheme 1).[9,10] The requisite keto-amide **5** or hydroxylactam **6**, precursors for *N*-acyliminium ion **7**, would be prepared by the condensation of indol-3-yl-ethylamine **3** with 4- or 5-keto-acids **4**. The compounds **4**, if not commercially available, could be readily prepared by known methods.[11]



Scheme 1.

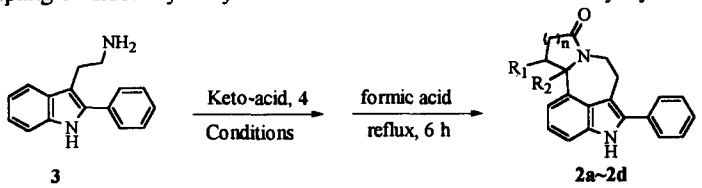
When **3** was heated at reflux with levulinic acid (**4a**) in toluene, tautomeric mixtures of keto-amide **5a** and hydroxylactam **6a** were obtained (Method A in Table 1). However, no separation of tautomers was tried since subsequent cyclization of both compounds leads to the same pyrrolidino- or piperidino-azepino-indole ring.[9,10] The crude mixture was directly subjected to the *N*-acyliminium ion cyclization condition (formic acid, reflux) to afford pyrrolidino-azepino-indole derivative **2a** in 61% yield. A better yield (71%) of **2a** was obtained when **3** was treated with **4a** in the presence of DCC and a catalytic amount of DMAP and then cyclized at the same condition (Method B) to indicate that the first coupling-step probably influences the overall yield in the synthesis of **2**. When 3-methyllevulinic acid (**4b**) was used as keto-acid, *cis*-dimethylated cyclization product **2b** was obtained in 45 – 64% yields as a single diastereomer based on the ^{1}H-NMR spectrum analysis.[5,6a]

For the synthesis of piperidino-azepino-indole derivative, **3** was coupled with 4-acetylbutyric acid (**4c**) and then cyclized to afford **2c** in 23 – 58% yields. When **3** was reacted with **4c** by DCC-coupling method,

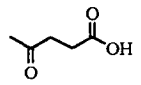
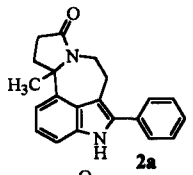
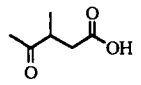
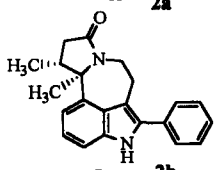
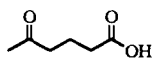
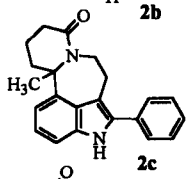
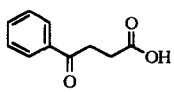
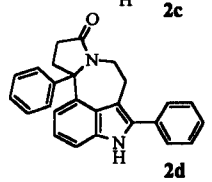
keto-amide **5c** was isolated as a major product (80% yield) instead of the tautomeric mixture of **5c** and hydroxylactam **6c**. The resulting keto-amide **5c** was cyclized cleanly in refluxing formic acid to provide **2c** in 72% yield.

In order to probe the possibility of the formation of sterically very congested structure, pyrrolidino-azepino-indole derivative which has a phenyl-substituent at the angular position, 3-benzoylpropionic acid was used in the cyclization reaction. Although the yield was not sufficient, cyclization reaction proceeded successfully to furnish **2d** in 16 – 26% yields. Since several 3-aryloylpropionic acids and 4-aryloylbutanoic acids could be readily prepared by Friedel-Craft acylations of succinic anhydrides or glutaric anhydrides with aromatic rings,[12] this strategy would open up to the synthesis of various pyrrolidino- or piperidino-azepino-indole derivatives which has an aryl-substituent at the angular position.

Table 1. Coupling of Indol-3-yl-ethylamine **3** with Keto-acids **4** followed by Cyclization Reaction.



3 **2a~2d**

Entry	Keto-acid	Conditions[a] / Yields[b]	Product
1	 **4a**	A / 61% B / 71%	 **2a**
2	 **4b**	A / 45% B / 64%	 **2b**
3	 **4c**	A / 23% B / 58%	 **2c**
4	 **4d**	A / 16% B / 26%	 **2d**

a. *Conditions*: A. Keto-acid, xylene, reflux, 12 h; B. Keto-acid, DCC (1.2 equiv.), DMAP (cat.), THF, rt., 12 h;
b. Yields refer to isolated yields for two steps.

In conclusion, a simple and convenient synthesis of tetracyclic azepino-indole derivatives bearing a substituent at the angular position has been accomplished through *N*-acyliminium ion cyclization. In view of the ready availability of 4- or 5-keto-acids, this approach seems very useful to provide a wide variety of pyrrolidino- or piperidino-azepino-indole derivatives.

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Varian Gemini-300 (75 MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16F-PC FT-IR and MIDAC 101025 using a potassium bromide pellet. Low (EI) resolution mass spectra were determined on HP GC 5972 and HP MS 5988A system at 70eV and high (EI) resolution mass spectra were determined on VG70-VSEQ (VG ANALITICAL, UK) at 70eV. Flash column chromatographies were performed with Merck Kiesegel 60 Art 9385 (230 - 400mesh).

General Procedure for the Preparation of Angular-substituted Pyrrolo- or Pyrido-azepino-indole Derivatives (2a~2d). Method A: A solution of 2-(2-phenylindol-3-yl)ethylamine (**3**, 1.0 mmol) and keto-acid (**4**, 1.05 mmol) in toluene (15 ml) was heated at reflux for 12 h. After evaporation of solvent, the crude mixture was dissolved in formic acid (10 ml) and heated at reflux for 6 h. The mixture was concentrated and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/*n*-hexane = 1:1) to afford **2**.

Method B: To a solution of keto-acid (**4**, 1.05 mmol) in THF (10 ml) were added DCC (105 mg, 1.2 mmol), 2-(2-phenylindol-3-yl)ethylamine (**3**, 1.0 mmol), and a catalytic amount of DMAP and the reaction mixture was stirred at room temperature for 12h. After evaporation of solvent, the residue was diluted with EtOAc (10 ml). The resulting precipitate was removed by filtration and the filtrate was concentrated, dissolved in formic acid (10 ml) and heated at reflux for 6 h. The reaction mixture was concentrated and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/*n*-hexane = 1:1) to afford **2**.

(±)-1,3,6,7,8,8a-Hexahydro-8a-methyl-2-phenyl-4*H*-pyrrolo[1',2';1,2]azepino[5,4,3-*cd*]indol-6(8a*H*)-one (2a): mp 226~227 °C; IR (KBr) 3236, 2936, 1682, 1412 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, s, NH), 7.53 (2H, d, *J*=7.2 Hz, , H-2' & H-6' of phenyl), 7.41–7.46 (2H, m, H-3' & H-5' of phenyl), 7.26-7.36 (2H, m, H-11 & H-4' of phenyl), 7.19 (1H, t, *J*=7.7 Hz, H-10), 6.96 (1H, d, *J*=7.0 Hz, H-9), 4.24 (1H, m, H-4), 3.45 (1H, m, H-4), 3.29 (1H, m, H-3), 3.01 (1H, m, H-3), 2.46 (4H, br s, 2 x H-7, 2 x H-8), 1.68 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.47, 141.10, 136.93, 134.08, 132.91, 128.75, 127.97, 127.64, 122.15, 117.41, 111.34, 109.50, 68.31, 39.78, 36.69, 29.77, 29.20, 28.08; MS (*m/z*; rel. intensity, %) 316 (M^+, 16), 301 (100), 258 (4), 243 (4), 230 (5), 217 (4), 204 (2), 158 (4), 150

(6), 127 (3), 115 (4); HRMS (EI) Calcd for $C_{21}H_{20}N_2O$: (M^+) *m/z* 316.1576. Found: 316.1577.

(±)-8,8a,-Dimethyl-1,3,6,7,8,8a-hexahydro-2-phenyl-4*H*-pyrrolo[1',2';1,2]azepino[5,4,3-*cd*]indol-6(8a*H*)-one (2b): mp 235~236 °C; IR (KBr) 3314, 2972, 1664, 1418 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.73 (1H, s, NH), 7.54 (2H, d, *J*=7.3 Hz, H-2' & H-6' of phenyl), 7.44 (2H, m, H-3' & H-5' of phenyl), 7.27-7.36 (2H, m, H-11 & H-4' of phenyl), 7.18 (1H, t, *J*= 7.7 Hz, H-10), 7.03 (1H, d, *J*=7.4 Hz, H-9), 4.24 (1H, m, H-4), 3.48 (1H, m, H-4), 3.26 (1H, m, H-3), 2.96 (1H, m, H-3), 2.50-2.60 (2H, m, 2 x H-7), 2.16 (1H, m, H-8), 1.39 (3H, s, CH_3), 1.23 (3H, d, *J*=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.57, 140.87, 137.17, 134.11, 132.86, 131.46, 128.76, 127.91, 127.70, 121.88, 116.85, 111.60, 109.90, 70.58, 40.32, 40.12, 38.48, 38.40, 28.40, 22.70; MS (*m/z*; rel. intensity, %) 330 (M^+, 23), 315 (100), 300 (11), 259 (4), 245 (7), 230 (5), 217 (5), 165 (4), 115 (3); HRMS (EI) Calcd for $C_{22}H_{22}N_2O$: (M^+) *m/z* 330.1732. Found: 330.1731.

(±)-1,3,6,7,8,9-Hexahydro-9a-methyl-2-phenyl-4*H*,9a*H*-pyrido[1',2';1,2]azepino[5,4,3-*cd*]indol-6-one (2c): mp 294~295 °C; IR(KBr) 3280, 1614, 1478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (1H, s, NH), 7.58 (2H, d, *J*=7.4 Hz, H-2' & H-6' of phenyl), 7.45 (2H m, H-3' & H-5' of phenyl), 7.29-7.36 (2H, m, H-12 & H-4' of phenyl), 7.18 (1H, t, *J*=7.7 Hz, H-11), 6.97 (1H, d, *J*=7.4 Hz, H-10), 4.49 (1H, m, H-4), 3.69 (1H, m, H-4), 3.48 (1H, m, H-3), 2.93 (1H, m, H-3), 2.40-2.57 (3H, m, H7, 2 x H-9), 2.18 (1H, m, H-7), 1.75 (3H, s, CH_3), 1.70-1.85 (2H, m, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.90, 140.43, 137.12, 133.70, 132.92, 132.05, 128.77, 127.76, 127.57, 121.98, 116.97, 112.40, 109.64, 65.60, 42.98, 39.94, 33.18, 30.93, 27.31, 17.57; MS (*m/z*; rel. intensity, %) 330 (M^+, 25), 316 (23), 315 (100), 245 (12), 244 (10), 230 (11), 206 (13), 165 (6), 114 (5), 54 (8); HRMS (EI) Calcd for $C_{22}H_{22}N_2O$: (M^+) *m/z* 330.1732. Found: 330.1735.

5-Oxo-*N*-[2-(2-phenylindol-3-yl)ethyl]hexanamide (5c). To a solution of 4-acetylbutyric acid (120 mg, 0.92 mmol) in THF (10 ml) were added DCC (229 mg, 1.11 mmol), 2-(2-phenylindol-3-yl)ethylamine (**3**, 207 mg, 0.88 mmol), and a catalytic amount of DMAP and the reaction mixture was stirred at room temperature for 12 h. After evaporation of solvent, the residue was diluted with EtOAc (10 ml). The resulting precipitate was removed by filtration and the filtrate was concentrated and purified by flash column chromatography (EtOAc/*n*-hexane = 2:1) to afford **5c** (258 mg, 80%) as an oil. This compound was further cyclized in refluxing formic acid to give **2c** in 72% yield. Data for **5c**: IR(KBr) 3294, 2932, 1708, 1642, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, s, NH), 7.26-7.61 (7H, m, aromatic), 7.18 (1H, t, *J*=7.8 Hz, H-6 of indole), 7.10 (1H, t, *J*=7.6 Hz, H-5 of indole), 5.84 (1H, br s, NHCO), 3.50 (2H, m, CH_2CH_2NH), 3.07 (2H, t, *J*=6.4 Hz, indole-CH_2CH_2), 2.29 (2H, t, *J*=7.2 Hz, $NHCOCH_2CH_2$), 2.00 (3H, s, CH_3CO), 1.90 (2H, t, *J*=7.1 Hz, $CH_3COCH_2CH_2$), 1.65-1.75 (2H, m, $COCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.84, 172.65, 136.20, 135.45, 133.10, 129.09, 128.93, 128.12, 127.73, 122.33, 119.66, 118.87, 111.28, 109.50, 42.52, 40.17, 35.22, 24.63, 19.55; HRMS (EI) Calcd for $C_{22}H_{24}N_2O_2$: (M^+) *m/z* 348.1838. Found: 348.1839.

(±)-2,8a-Diphenyl-1,3,6,7,8,8a-hexahydro-4*H*-pyrrolo[1',2';1,2]azepino[5,4,3-*cd*]indol-6(8a*H*)-one (2d): mp 246~247 °C; IR (KBr) 3348, 2936, 1666, 1444, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, s, NH), 7.05-7.54 (13H, m, aromatic), 4.02 (1H, dt, *J*=13.5 Hz, 3.9 Hz, H-4), 3.46 (1H, td, J=13.5 Hz, 4.1 Hz, H-4), 2.56-3.11 (6H, m, 2 x H-3, 2 x H-7, 2 x H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.87, 146.25, 137.03, 136.83, 134.12, 132.89, 128.79, 128.38, 128.05, 127.77, 127.47, 121.56, 120.05, 111.60, 110.13, 74.62, 41.18, 38.66, 30.68, 26.28; MS (*m/z*; rel. intensity, %) 378 (M^+, 17), 301 (100), 258 (4), 230 (3), 217 (4), 189 (4), 150 (6), 136 (5), 115 (3), 77 (4), 51 (2); HRMS (EI) Calcd for $C_{26}H_{22}N_2O$: (M^+) *m/z* 378.1732. Found: 378.1732.

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