A Short Synthesis of the Hexahydropyrido[4,3-*b*]carbazole Core Structure For the Synthesis of Aspidosperma Alkaloids

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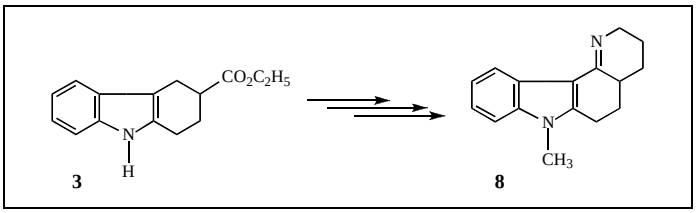

A short synthesis of the hexahydropyrido[4,3-*b*]carbazole derivative **8** which is important for the preparation of aspidosperma alkaloids was described. Construction of the tetracyclic structure was achieved *via* a short synthetic route and some new carbazolone derivatives (**4**, **5**, **6** and **7**) were synthesized.

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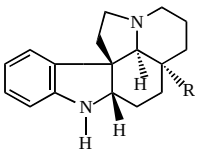
The Aspidosperma alkaloids constitute a large family of natural products. Over the last three decades, aspidosperma alkaloids have caught the attention of synthetic chemists due to the unique structural features of many of their members and because of their important biological properties [1]. Aspidospermidine and deethylaspidospermidine (**1a**, **1b**), which are parent structures have been the primary target molecules toward aspidosperma alkaloids and many creative and useful synthetic strategies have been developed [2-12]. Among these strategies, Stork's Fischer indol approach, Harley-Mason's indoloquinolizidine rearrangement approach, Overman's aza-Cope rearrangement, Buchi, Kuehne, Magnus and Wenkert's Diels-Alder approach and Urritia, d'Angelo and Gramain's carbazolone-cyclization approach have considerably enriched the chemistry of aspidosperma alkaloids.

In the synthetic approaches, the [*ABCD*] type tetracycles (**2**), so-called hexahydropyrido[4,3-*b*]carbazoles, have been elaborated in the penultimate stage for the synthesis of aspidosperma alkaloids. Especially in the Urritia and d'Angelo's studies, the [*ABCD*] type tetracycles have been stereo selectively synthesized in many steps and elaborated. These [*ABCD*] type tetracycles are not only subunits of pentacyclic aspidosperma alkaloids but also hexacyclic indole alkaloid kopsijasmine and the heptacyclic indole alkaloid kopsine [13,14].



1a R = C_2H_5
1b R = H

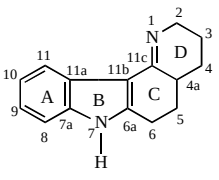


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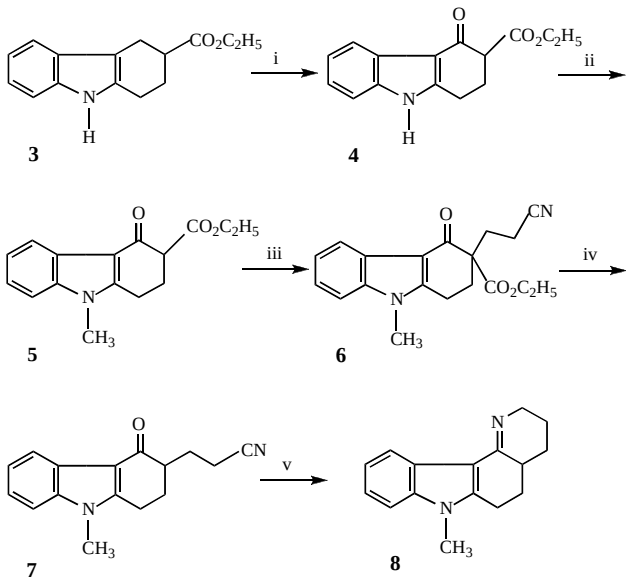
Figure 1

Herein, we have synthesized hexahydropyrido[4,3-*b*]-carbazole core structure in five steps with 15 % overall yield (Scheme 1). For this purpose we selected a tetrahydrocarbazole ester derivative **3** as the starting material, which was synthesized from ethyl 4-oxocyclohexanecarboxylate and phenylhydrazine in one step *via* the Fischer-indol method previously described [15]. Compound **3** was selectively oxidized at position 4 with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in tetrahydrofuran (90%) at -5 ºC to yield the carbazolone ester **4** [16]. Later we protected the indole nitrogen atom of **4** using tetrabutylammonium hydrogen sulfate and methyl iodide

Scheme 1



Reagents and conditions: i) DDQ, THF (90%), -5 ºC, 10 min., 33%; ii) TBAHS, NaOH (50%), CH_2Cl_2, CH_3I, 0 ºC, 1h, 91%; iii) Cs_2CO_3, *tert*-ButOH, acrylonitrile, reflux, 5h, 94%; iv) KOH, H_2O-$(CH_3)_2CHOH$, rt, 4h, 72%; v) $NiCl_2.6H_2O$, $NaBH_4$, $NH_2NH_2.H_2O$, N_2, stirred, 80 ºC, 5h, 76%.

which resulted in compound **5** [17]. Cyanoethylation of compound **5** utilizing cesium carbonate in *tert*-butyl alcohol gave the Michael adduct compound **6** [18]. Compound **7** was obtained by hydrolysis and following decarboxylation of **6** with potassium hydroxide [19]. Finally, the reduction of the nitrile to amino group in compound **7** was carried out with nickel boride as catalyst, which was prepared *in situ* by reduction of nickel(II) chloride hexahydrate with sodium borohydride in ethanol, using hydrazine hydrate as the hydrogen generator [20,21]. During the reduction of the nitrile group, an intramolecular condensation occurred and gave hexahydropyrido[4,3-*b*]carbazole **8**. From **8**, octahydropyrido[3,2-*c*]carbazole and pentacyclic aspidosperma alkaloids can be easily synthesized in a queue.

EXPERIMENTAL

All melting points were measured in sealed tubes using an electro thermal digital melting point apparatus (Gallenkamp) and uncorrected. Infrared spectra were recorded on a Hitachi 270-30 infrared spectrometer. ^{1}H nmr and ^{13}C nmr spectra were obtained on a Bruker WH-400 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were determined with a Micromass UK Platform II LC-MS spectrometer and a combined 5980 gas chromatography-HP 5971 mass system. Combustion analysis of compounds was performed on a CHNS-932-LECO. Analytical and preparative thin layer chromatographies were carried out using silica gel 60 HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 mm, Merck) and neutral aluminum oxide (Merck).

Ethyl-4-oxo-1,2,3,4-tetrahydro-9*H*-carbazole-3-carboxylate (4). To a solution of 5 g (20.60 mmoles) of **3** in 50 mL of tetrahydrofuran (90%), a solution of 9.36 g (41.20 mmoles) of 2,3-dichloro-5,6-dicyano-p-benzoquinone in 20 mL of tetrahydrofuran was added dropwise at -5 ºC. The reaction mixture was stirred for 10 minutes at -5 ºC then the solution was pored into 500 mL of 10% sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was removed. The residue was purified by chromatography using silica gel and ethyl acetate. After the solvent was evaporated, the product was recrystallized from ether to afford 1.75 g (33%) of **4**, mp 123-124 ºC; rf: 0.39 (ethyl acetate); ir (potassium bromide): ν 3284 (NH), 2980 (CH), 1703 (C=O, ester), 1633 (C=O, ketone) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.27 (t, 3H, J= 7.14 Hz, CH_2CH_3), 2.37-2.49 (m, 1H, CH), 2.55-2.66 (m, 1H, CH), 2.93-3.06 (m, 1H, CH), 3.20 (dt, 1H, J= 17.57 and 5.52 Hz, C_1H), 3.63 (dd, 1H, J= 8.95 and 4.7, C_3H), 4.23 (q, 2H, J=7.12 Hz, CH_2CH_3), 7.19-7.33 (m, 2H, aromatic protons), 7.40 (m, 1H, aromatic proton), 8.20 (m, 1H, aromatic proton), 9.43 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.21, 30.14, 32.21, 62.15, 70.43, 110.04, 112.41, 120.36, 124.28, 124.82, 125.72, 144.36, 150.27, 172.63, 187.58; ms: m/z 257(7.3) $[M]^+$, 256(100) $[M-H]^+$, 229(17.4) $[M-C_2H_4]^+$, 210(4.3) $[M-C_2H_7O]^+$. *Anal.* Calcd. for $C_{15}H_{15}NO_3$: C, 70.03; H, 5.84; N, 5.45. Found: C, 69.95; H, 5.87; N, 5.48.

Ethyl-4-oxo-1,2,3,4-tetrahydro-9-methyl-carbazole-3-carboxylate (5). A solution of 2.5 g (9.7 mmoles) of **4** in 25 mL of dichloromethane was cooled to 0ºC. After that, 5 mL of 50% sodium hydroxide, 100 mg of tetrabutylammonium hydrogen sulfate and 1.42 g (10 mmoles) of methyl iodide were added, and the mixture was stirred for 1 hour at 0 ºC, washed with 50 mL 10% hydrochloric acid, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was chromatographed using silica gel and ethyl acetate-hexane (1:1). The solvent was removed and then the product was recrystallized from ether to afford 2.4 g (91%) of **5**, mp 120-121 ºC; rf: 0.45 (ethyl acetate); ir (potassium bromide): ν 2957 (CH), 1727 (C=O, ester), 1635 (C=O, ketone) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.23 (t, 3H, J= 7.16 Hz, CH_2CH_3), 2.32-2.43 (m, 1H, CH), 2.56-2.62 (m, 1H, CH), 2.82-2.89 (m, 1H, CH), 3.12 (dt, 1H, J= 17.53 and 5.52 Hz, C_1H), 3.52 (dd, 1H, J= 8.90 and 4.6, C_3H), 3.64 (s, 3H, N-CH_3), 4.16 (q, 2H, J=7.13 Hz, CH_2CH_3), 7.12-7.28 (m, 3H, aromatic protons), 8.16 (m,1H, aromatic proton); ^{13}C nmr (deuteriochloroform): δ 14.62, 29.11, 30.25, 32.14, 60.41, 71.17, 109.12, 115.29, 120.86, 122.41, 124.70, 125.22, 137.43, 154.49, 170.41, 190.27; ms: m/z 272(2.3) $[M+1]^+$, 270(12.3) $[M-H]^+$, 255(6.2) $[M-CH_4]^+$, 228(3.3) $[M-C_3H_7]^+$, 127(100) $[M-C_7H_{12}O_3]^+$. *Anal.* Calcd. for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.83; H, 6.25; N, 5.23.

Ethyl-3-(cyanoethyl)-4-oxo-1,2,3,4-tetrahydro-9-methyl-carbazole-3-carboxylate (6). A mixture of 2 g (7.4 mmoles) of **5**, 2.5 g (7.7 mmoles) of cesium carbonate and 0.41 g (7.7 mmoles) of acrylonitrile in 50 ml of *tert*-butyl alcohol was refluxed for 5 hours under a nitrogen atmosphere. The reaction mixture was poured into 50 mL of 5% hydrochloric acid solution and extracted with ethyl acetate. The solvent was evaporated under reduced pressure and the resulting residue was chromatographed using silica gel and ethyl acetate-hexane (1:1). The solvent was removed and then the product was recrystallized from methanol to afford 2.25 g (94%) of **6**, mp 110-111 ºC; rf: 0.42 (ethyl acetate); ir (potassium bromide): ν 2970 (CH), 2245 (CN), 1717 (C=O, ester), 1648 (C=O, ketone) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.26 (t, 3H, J= 7.13 Hz, CH_2CH_3), 2.24-2.45 (m, 3H, CH and CH_2), 2.56-2.72 (m, 2H, CH_2), 2.78-2.81 (m, 1H, CH), 3.02 (dt, 1H, J= 17.54 and 5.50 Hz, C_1H), 3.14-3.22 (m, 1H, CH), 3.73 (s, 3H, CH_3), 4.22 (q, 2H, J=7.14 Hz, CH_2CH_3), 7.29-7.37 (m, 3H, aromatic protons), 8.23 (m, 1H, aromatic proton); ^{13}C nmr (deuteriochloroform): δ 13.46, 14.08, 19.07, 29.91, 29.98, 31.27, 56.15, 61.77, 109.32, 111.55, 119.80, 121.82, 123.11, 123.62, 124.26, 140.17, 151.81, 171.25, 188.58; ms: m/z 323(27.4) $[M-H]^+$, 309(14) $[M-CH_3]^+$, 249(46) $[M-C_3H_7O_2]^+$, 201(100) $[M-C_4H_{13}NO_3]^+$, 127(35.4) $[M-C_{10}H_{15}NO_3]^+$. *Anal.* Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.48; H, 6.15; N, 8.58

3-(Cyanoethyl)-4-oxo-1,2,3,4-tetrahydro-9-methyl-carbazole (7). A 100 mL solution of 0.5 *M* potassium hydroxide in water-isopropyl alcohol (1:5) was added to 2.5 g (7.7 mmoles) of **6** and the reaction mixture was stirred for 4 hours. Then the mixture was poured into 100 mL of cold water and extracted with ether. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate-hexane. After the solvent was evaporated, a yield of 1.40 g (72%) of **7,** mp 164-165 ºC, rf: 0.36 (ethyl acetate) was obtained; ir (potassium bromide): ν 2940 (CH), 2245 (CN), 1645 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.18-2.22 (m, 1H, CH), 2.24-2.34 (m, 2H, CH_2), 2.52-2.64 (m, 2H, CH_2), 2.70-2.76(m, 1H, CH), 2.92 (dt, 1H, J= 17.22 and 5.43 Hz, C_1H), 3.07-3.16 (m, 1H, CH), 3.30-3.42 (m, 1H, C_3H), 3.52 (s, 3H, CH_3), 7.14-7.25 (m, 2H, aromatic protons), 7.30 (d,

1H, J= 8.25 Hz, aromatic proton), 7.92 (d, 1H, J=8.17 Hz, aromatic proton); ^{13}C nmr (deuteriochloroform): δ 13.86, 19.27, 28.21, 29.83, 30.23, 49.90, 110.04, 111.38, 118.41, 120.62, 122.35, 122.88, 124.81, 141.67, 150.72, 190.02; ms: m/z 253(1.9) $[M+1]^+$, 252(7.2) $[M]^+$, 212(10.1) $[M-C_2H_2N]^+$, 184(61) $[M-C_4H_6N]^+$, 129(100) $[M-C_7H_9NO]^+$. *Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found; C, 76.25; H, 6.38; N, 11.06.

2,3,4,4a,5,6-hexahydro-7-methyl-pyrido[4,3-*b*]carbazole (8). To a solution of 2.73 g (11.5 mmoles) of nickel(II) chloride hexahydrate in 5 mL of ethanol, under nitrogen atmosphere at 0 ºC, were successively dropped a solution of 23 mL (1 *M*, 23 mmoles) of sodium borohydride in ethanol and a solution of 23 mL (0.1 *M*) of sodium hydroxide in ethanol and the mixture was stirred for 30 minutes at room temperature. Then, a solution of 1 g (3.97 mmoles) of **7** in ethanol was added, and the mixture was heated to 80 ºC and then 3.80 mL (79.2 mmoles) of hydrazine hydrate was added and stirred at 80 ºC for 5 hours. The residual catalyst was filtered, and the solvent was removed. The residue was hydrolyzed with 25 mL of 10% acetic acid and the mixture was neutralized with sodium carbonate and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. Then the residue was chromatographed with neutral aluminum oxide using ethyl acetate-hexane (2:1). The solvent was removed and then the product was recrystallized from ether to afford 720 mg (76%) of hexahydropyrido[4,3-*b*]carbazoles **8**, mp 116-117 ºC; ir (potassium bromide): ν 2953 (CH), 1605 (C=C) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.56-1.68 (m, 1H, CH), 1.75-1.80 (m, 2H, CH_2), 1.94-2.06 (m, 2H, CH_2), 2.66-2.74 (m, 2H, CH_2), 2.84-3.30 (m, 4H, 2xCH_2), 3.72 (s, 3H, CH_3), 7.15-7.38 (m, 2H, aromatic protons), 7.52 (d, 1H, J= 7.83 Hz, aromatic proton) 7.96 (d, 1H, J=7.39 Hz, aromatic proton); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 21.41, 22.63, 30.73, 32.61, 34.22, 35.03, 48.14, 109.83, 111.94, 119.35, 120.56, 121.27, 125.38, 137.02, 142.61, 169.62; ms: m/z 239(5.4) $[M+1]^+$, 238(27) $[M]^+$, 168(100) $[M-C_4H_8N]^+$, 143(100) $[M-C_6H_9N]^+$. *Anal.* Calcd. for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.76. Found; C, 80.61; H, 7.59; N, 11.72.

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