Synthesis of isocryptolepine, an alkaloid from *Cryptolepis sanguinolenta*

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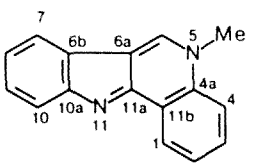
Isocryptolepine, an alkaloid recently isolated from the roots of *Cryptolepis sanguinolenta*, was synthesized by selective methylation at the N(5) atom of 11*H*-indolo[3,2-*c*]quinoline with excess MeI in toluene.

Key words: alkaloids, indolo[3,2-*c*]quinolines, isocryptolepine; methylation.

Isocryptolepine (**1**) is a tetracyclic alkaloid, which has been isolated recently from the roots of *Cryptolepis sanguinolenta* (Lindl) Schlechter (Asclepiadiaceae) sprouting in Eastern Africa.[1] Nothing has been reported on the biological activity of isocryptolepine; however, it is known that extracts from the roots of its producer are used in nontraditional medicine as vasodilatory, antimicrobial, and antimalarial remedies.[2,3]



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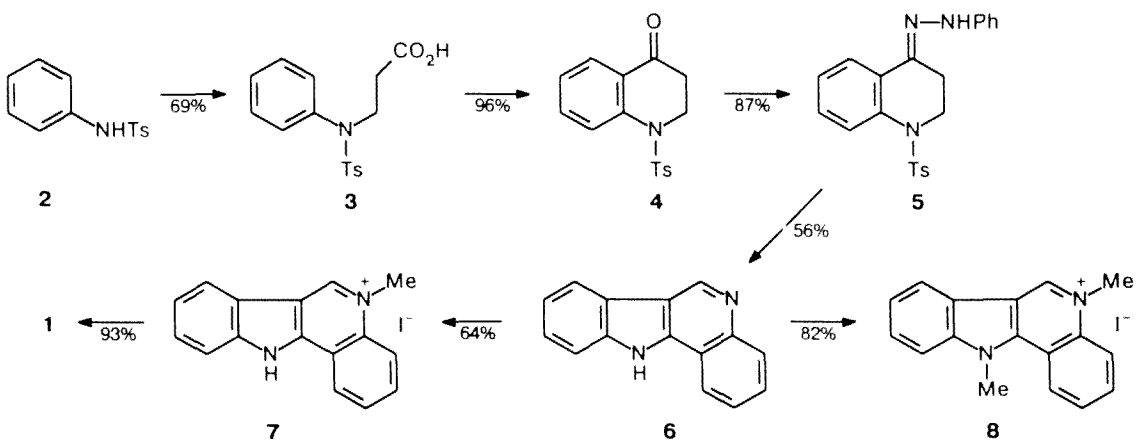
In the present work we report on the first synthesis of alkaloid **1** from 11*H*-indolo[3,2-*c*]quinoline (**6**)[4] (see Scheme 1). Unlike the procedure reported previously,[4] in our procedure, intermediate **4** was obtained from *N*-tosylaniline (**2**) in two steps. Indoloquinoline **6** was used further without purification. Its interaction with excess MeI in a toluene solution at ~20 °C afforded quaternary salt **7**, whereas the reaction carried out in boiling acetone in the presence of K_2CO_3 led to dimethyl derivative **8**. Treatment of an aqueous solution of salt **7** with potassium carbonate gave the target compound **1**, which was identical to natural isocryptolepine, according to its spectral characteristics (data of IR, UV, ^{13}C NMR, and mass spectra). However, the chemical shifts of the protons in the ^1H NMR spectrum of compound **1** differed from those in the spectrum of isocryptolepine[1] (on the average, by 0.3 ppm). This significant difference in the chemical shifts could have indicated that the methylation involved the indole rather than the quinoline nitrogen atom; however, the clear-cut nuclear Overhauser effect between the Me group and the proton at C-6 manifested in the ^1H NMR spectrum of **1** precludes this possibility. The above-mentioned distinction between the proton chemical shifts in the ^1H NMR spectra of the natural and synthetic products is apparently due to the concentration and solvation effects during the recording of the spectra.

Scheme 1



2 **3** **4** **5** **6** **7** **8** **1**

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Thus, isocryptolepine was obtained from *N*-tosylaniline **2** by a six-step synthesis in an overall yield of 19.2%.

Experimental

UV spectra were obtained on a Specord M-40 instrument; IR spectra were recorded on a Specord M-82 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker WM-250 spectrometer. Mass spectra (EI, 70 eV) were obtained on an LKB-9000 instrument with direct injection.

The transformation of compound **2** into **3** was carried out by a known procedure,[5] and **3** was converted into **4** according to a procedure similar to that described previously.[6] Compound **5** was synthesized with a twofold volume of the solvent with respect to that used in the original procedure.

11*H*-Indolo[3,2-*c*]quinoline (6). This compound was prepared from **4** by a known procedure,[4] m.p. 329—331 °C (from MeOH) (*cf.* Ref. 4: 333 °C). ^{1}H NMR (CD_3OD), δ: 7.35 (ddd, 1 H, H-8, *J* = 8 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.50 (ddd, 1 H, H-9, *J* = 8 Hz, *J* = 8 Hz, *J* =1.5 Hz); 7.63—7.70 (m, 2 H, H-2 and H-10); 7.75 (ddd, 1 H, H-3, *J* = 8.5 Hz, *J* = 8 Hz, *J* = 2 Hz); 8.12 (dd, 1 H, H-4, *J* = 8.5 Hz, *J* = 1.5 Hz); 8.22 (dd, 1 H, H-7, *J* = 8 Hz, *J* = 1.5 Hz); 8.40 (dd, 1 H, H-1, *J* = 8.5 Hz, *J* = 2 Hz); 9.43 (s, 1 H, H-6). ^{1}H NMR (DMSO-d_6), δ: 12.78 (br.s, 1 H, NH).

5-Methyl-5*H*-indolo[3,2-*c*]quinoline (isocryptolepine) (1). A solution of compound **6** (218 mg, 1 mmol) and MeI (355 mg, 2.5 mmol) in 15 mL of anhydrous toluene was kept for 48 h at ~20 °C. The precipitate was filtered off, washed with toluene, and dried to give 230 mg (64%) of 5-methyl-11*H*-indolo[3,2-*c*]quinolinium iodide (**7**) as a greenish powder, m.p. >300 °C (dec.). Found (%): C, 53.21; H, 3.77; I, 35.41; N, 8.06. $C_{16}H_{13}IN_2$. Calculated (%): C, 53.35; H, 3.64; I, 35.23; N, 7.78. ^{1}H NMR (CD_3OD), δ: 4.62 (s, 3 H, NMe); 7.55 (ddd, 1 H, H-8, *J* = 8.5 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.70 (ddd, 1 H, H-9, *J* = 9 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.82 (dd, 1 H, H-10, *J* = 9 Hz, *J* = 1 Hz); 8.03 (ddd, 1 H, H-2, *J* = 8.5 Hz, *J* = 8.5 Hz, *J* = 1 Hz); 8.17 (ddd, 1 H, H-3, *J* = 8.5 Hz, *J* = 8.5 Hz, *J* = 1.8 Hz); 8.39 (dd, 1 H, H-4, *J* = 8.5 Hz, *J* = 1 Hz); 8.44 (dd, 1 H, H-7, *J* = 8.5 Hz, *J* = 1 Hz); 8.71 (dd, 1 H, H-1, *J* = 8.5 Hz, *J* = 1.8 Hz); 9.96 (s, 1 H, H-6). MS, *m/z* (I_{rel} (%)): 233 $[M-I]^+$ (100); 218 $[M-I-Me]^+$ (26).

Salt **7** (170 mg, 0.472 mmol) was dissolved with heating in 15 mL of water, the solution was cooled to ~20 °C, and an excess of K_2CO_3 was added to it. The precipitate that formed was filtered off, washed with water, and dried to give 102 mg (93%) of isocryptolepine **1** as a bright yellow powder, m.p. 107—109 °C (from EtOH—H_2O, 3 : 1). Found (%): C, 82.62; H, 5.30; N, 12.26. $C_{16}H_{12}N_2$. Calculated (%): C, 82.73; H, 5.21; N, 12.06. IR (KBr), ν/cm^{-1}: 3047 (CH); 2940 (CH); 1636, 1616, 1596, 1558 (C=C, C=N); 1488, 1456, 1352, 1316, 1220, 1116, 1068, 752. UV (EtOH), λ_{max}/nm (log ε): 238 (4.19); 286 (4.28); 355 (3.61). ^{1}H NMR (CD_3OD), δ: 4.14 (s, 3 H, NMe); 7.26 (ddd, 1 H, H-8, *J* = 8 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.46 (ddd, 1 H, H-9, *J* = 8.5 Hz, *J* = 8 Hz, *J* = 1.1 Hz); 7.64 (ddd, 1 H, H-2, *J* = 8 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.73 (dd, 1 H, H-10, *J* = 8.5, *J* = 1 Hz); 7.77 (ddd, 1 H, H-3, *J* = 9 Hz, *J* = 8 Hz, *J* = 1.8 Hz); 7.89 (dd, 1 H, H-4, *J* = 9 Hz, *J* = 1 Hz); 7.98 (dd, 1 H, H-7, *J* = 8 Hz, *J* = 1.1 Hz); 8.62 (dd, 1 H, H-1, *J* = 8 Hz, *J* = 1.8 Hz); 8.90 (s, 1 H, H-6). ^{13}C NMR (CD_3OD), δ: 42.9 (Me); 117.0 (C-10); 117.8 (C-6a); 117.9 (C-4); 120.4 (C-7); 120.6 (C-11b); 121.8 (C-8); 124.9 (C-1); 125.6 (C-6b); 126.5 (C-2); 127.2 (C-9); 130.7 (C-3); 136.5 (C-4a); 138.6 (C-6); 152.1 (C-10a); 152.2 (C-11a). MS, *m/z* (I_{rel}(%)): 232$[M]^+$ (100); 217$[M-Me]^+$ (14); 204 (4); 190 (11); 116 (14); 102 (6); 89 (4).

5,11-Dimethyl-11*H*-indolo[3,2-*c*]quinolinium iodide (8). A mixture or indoloquinoline **6** (218 mg, 1 mmol), MeI (1.14 g, 8 mmol), freshly calcined K_2CO_3 (0.5 g), and 20 mL of dry acetone was boiled for 3 h, and then the solvent was removed under reduced pressure. EtOH (7 mL) was added to the residue, the mixture was heated to boiling and immediately filtered, and the filtrate was allowed to stand in a refrigerator for 12 h. The precipitate that formed was filtered off, washed with cold EtOH, and dried to give 306 mg (82%) of salt **8** as a cream-colored powder, m.p. 275—278 °C. Found (%): C, 54.38; H, 4.09; I, 34.12; N, 7.60. $C_{17}H_{15}IN_2$. Calculated (%): C, 54.54; H, 4.04; I, 33.93; N, 7.49. IR (KBr), ν/cm^{-1}: 3019, 2972, 2948 (CH); 1636, 1613, 1604, 1548 (C=C); 1504 (C=N$^+$); 1456, 1372, 1324, 1288, 1256, 1156, 1120, 1040, 836, 752. ^{1}H NMR (CD_3OD), δ: 4.58 (s, 3 H, N(11)-Me); 4.62 (br.s, 3 H, N(5)-Me); 7.61 (ddd, 1 H, H-8, *J* = 8.5 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.78 (ddd, 1 H, H-9, *J* = 9 Hz, *J* = 8 Hz, *J* = 1 Hz); 7.98 (dd, 1 H, H-10, *J* = 9 Hz, *J* = 1 Hz); 8.07 (ddd, 1 H, H-2, *J* = 9 Hz, *J* = 8.5 Hz, *J* = 1 Hz); 8.19 (ddd, 1 H, H-3, *J* = 8.5 Hz, *J* = 8.5 Hz, *J* = 1.8 Hz); 8.39 (dd, 1 H, H-4, *J* = 8.5 Hz, *J* = 1 Hz); 8.48 (dd, 1 H, H-7, *J* = 8.5 Hz, *J* = 1 Hz); 9.12 (dd, 1 H, H-1, *J* = 9 Hz, *J* = 1.8 Hz); 9.97 (br.s, 1 H, H-6). MS, *m/z* (I_{rel} (%)): 247 $[M-I]^+$ (100); 232 $[M-I-Me]^+$ (36); 217 $[M-I-2Me]^+$ (19).

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