Studies Directed toward the Synthesis of Cryptoheptine

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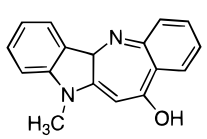
Synthesis of 5,10-dihydro-10-methylindolo[3,2-*b*][1]benzazepin-12(*11H*)-one (**2**), an isomer of the reported structure for cryptoheptine (**1**), is presented. Attempts to convert **2** to **1** led to 10-methylindolo[3,2-*b*][1]-benzazepin-12-one (**10**), an oxidation product of **2** and presumably **1**. These results highlight the potential instability of cryptoheptine and cast doubt on its proposed structure.

Cryptolepis sanguinolenta (Lindl.) Schlechter, a member of the Asclepiadaceae family and Periplocoideae subfamily, is a shrub indigenous to tropical West Africa with a long history of ethnomedical use.[1] In several West African nations, root decoctions have been used to treat a variety of illnesses, including hepatitis,[2] malaria,[3] and diabetes.[1,4] These indigenous uses have led to an extensive investigation of this plant, resulting in the isolation of a variety of indole-containing alkaloids.[5] Most of these alkaloids feature the indoloquinoline ring system. One exception to this commonality is cryptoheptine (**1**), which presents an interesting indolobenzazepine structure.[6] Our interest in searching for antidiabetic compounds from ethnobotanical plant sources, and the fascinating structure proposed for cryptoheptine, led us to pursue a total synthesis of this compound. This report describes the results of our study.



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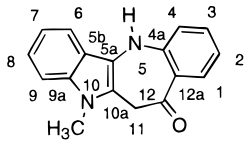

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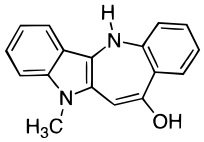

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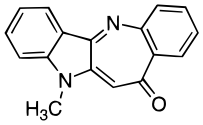

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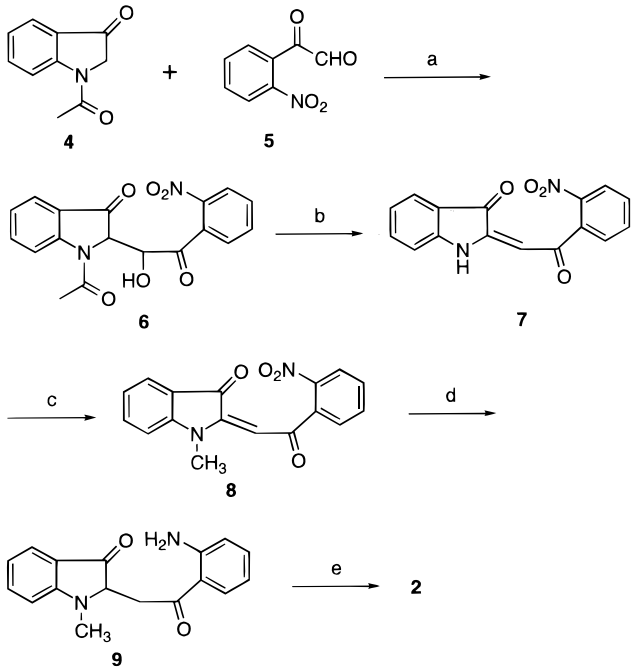
Results and Discussion

The proposed structure of cryptoheptine (**1**) contains a triply unsaturated azepine ring and an acidic benzylic proton at the 5a position.[6] This structure can exist in a number of different tautomeric forms, with indolobenzazepinones **2** and **3** being two reasonable (apparent) tautomers of **1**. Recognizing that a direct synthesis of **1** might prove difficult, we chose ketone **2** as our initial synthetic target.

Our synthesis began with known 1-acetyl-3-oxoindole (**4**).[1] Condensation of **4** with glyoxal **5**, which was prepared by selenium dioxide oxidation of 2-nitroacetophenone, gave hydroxyketone **6** in 78% yield (Scheme 1). Dehydration of **6** with concomitant removal of the acetyl protecting group in a refluxing solution of 10% HCl provided **7** in an 84% yield. Next, regiospecific introduction of the indole methyl group was accomplished using a NaH/MeI protocol. Hydrogenation of **8** (10% Pd/C, toluene) gave intermediate **9**, which was quickly treated with *para*-toluenesulfonic acid under Dean−Stark conditions to give the target keto isomer of cryptoheptine, **2**, in a 44% two-step yield.

Scheme 1[a]



[a] Reagents: (a) cat. piperidine, toluene, rt, 78%; (b) 10% HCl, THF, reflux, 84%; (c) (i) NaH, DMF, −10 °C, (ii) CH_3I, 83%; (d) H_2, 10% Pd/C, toluene; (e) *p*-TsOH, toluene, Dean-Stark, 44% over two steps.

Cryptoheptine isomer **2** was prepared as a yellow solid melting at 260 °C and having a molecular ion peak at *m*/*z* 262.1109. Elemental analysis confirmed the molecular formula of **2** as $C_{17}H_{14}N_2O$. An absorbance at 1628 cm^{-1} in the infrared spectrum and a downfield peak at δ 184.5 in the ^{13}C NMR spectrum indicated the presence of a carbonyl functionality. Three singlets were observed in the ^1H NMR spectrum. An exchangeable proton was observed at δ 6.86, corresponding to the NH proton of the azepine ring. A two-proton singlet was observed at δ 3.88, and a three-proton singlet was observed at δ 3.74, corresponding to the methylene protons of the azepine ring and the indole methyl group, respectively. As expected, the 2D COSY spectrum revealed two aromatic four-spin systems, each of which were correlated to their adjacent rings using HMQC and HMBC data. Comparisons of the NMR assign-

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Table 1. NMR Spectral Data (δ) of **2**[a] and Comparison to Cryptoheptine (**1**)[b,c]

	isomer **2**		cryptoheptine (**1**)	
atom no.	^{1}H	^{13}C	^{1}H	^{13}C
1	7.94, dd (8.0, 0.8)	131.6	7.96, d (8.1)	118.8
2	6.86, dd (7.6, 7.6)	117.5	7.24, dd (8.1, 6.6)	120.6
3	7.38, dd (7.6, 7.6)	132.6	7.45, dd (7.7, 6.6)	126.5
4	7.10, d (8.0)	118.2	7.92, d (7.7)	117.9
4a		144.6		125.5
5-NH	6.82, s, 1H			
5a		118.0	3.81, s, 1H	65.5
5b		119.6[d]		120.5
6	7.53, d (8.0)	116.1	8.95, d (8.0)	125.2
7	7.13, dd (7.6, 7.6)	119.3	7.65, dd (8.0, 6.7)	125.5
8	7.29, dd (8.0, 7.6)	122.1	7.75, dd (8.5, 6.7)	129.4
9	7.32, d (8.4)	109.8	7.72. d (8.5)	115.9
9a		136.4		135.5
10-CH_3	3.74, s, 3H	29.6	4.27, s, 3H	43.4
10a		119.5[d]		136.9
11	3.88, s, 2H	40.4	8.75, s, 1H	135.5
12		184.5	9.87, s, 1H	152.1
12a		123.1		124.4

[a] Recorded in $CDCl_3$ at 400 MHz for ^{1}H and at 100 MHz for ^{13}C. [b] Literature data from ref 6 recorded in $CDCl_3$ at 600 MHz. ^{13}C values are rounded for comparison purposes. [c] The numbering system used in ref 6 for cryptoheptine is used here. [d] Assignments may be reversed.

Table 2. ^{1}H COSY and HMBC Correlations for Isomer **2**[a]

proton	COSY	HMBC
1	H-2	C-3, C-4a, C-12
2	H-1, H-3	C-4, C-12a
3	H-2, H-4	C-1, C-4a
4	H-3	C-2, C-12a
5-NH		C-4
6	H-7	C-8, C-9a
7	H-6, H-8	C-5b, C-9
8	H-7, H-9	C-6, C-9a
9	H-8	C-5b, C-7
10-NCH_3		C-9a, C-10a
11		C-5a, C-10a, C-12, C-12a

[a] Recorded in $CDCl_3$ at 400 MHz for ^{1}H and at 100 MHz for ^{13}C.

ments for **2** with those described for cryptoheptine (**1**) are made in Table 1.

We then attempted to convert **2** to **1** under a variety of basic and acidic conditions. Treatment of **2** with NaH, potassium ethoxide in EtOH, or potassium *tert*-butoxide in *tert*-butanol gave a product having a molecular ion peak at *m/z* 260.0956. NMR analysis and elemental analysis confirmed that the product upon treatment of **2** with base was oxidation product **10**. The reaction of **2** with potassium *tert*-butoxide was a very fast reaction, with the complete conversion of **2** to **10** occurring within a matter of minutes. Treatment of **2** with a solution of HCl in THF also gave **10**. Interested in how labile tautomer **2** was to oxidation, we then treated **2** with a solution of $CHCl_3$−MeOH−35% NH_3 (90:10:1), which was the chromatography eluant used in the isolation of cryptoheptine.[6] As the reaction was monitored by TLC, a new spot began to form after a few minutes, and the reaction went to completion after stirring overnight at room temperature. As anticipated, the product from this experiment was again oxidation product **10**.

We have synthesized ketone **2**, an apparent tautomeric form of the proposed structure of cryptoheptine (**1**), in 18% overall yield and six steps from 2′-nitroacetophenone and 1-acetyl-3-oxoindole.[1] Ketone **2** is readily oxidized under acidic and basic conditions to ketone **10**. Enol **3** or cryptoheptine (**1**) were not observed under the experimental conditions studied. The relative ease with which a presumably stable isomer (apparent tautomer) of **1** is oxidized, and the fact that the chromatography solvent used to isolate cryptoheptine degrades **2** to **10**, highlights the potential instability of cryptoheptine and casts doubt on its proposed structure.

Experimental Section

General Experimental Procedures. Anhydrous DMF and toluene were obtained from Aldrich. Moisture- and air-sensitive reactions were performed under a nitrogen atmosphere. Analytical TLC was performed on E. Merck silica gel 60 F254 precoated plates (250 μm thickness) and analyzed using UV light. Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh) using nitrogen pressure. ^{1}H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, with NMR shifts being expressed in ppm (δ) downfield from TMS. NMR coupling constants (*J*) are reported in hertz. Mass spectrometry was performed on a Kratos MS 50 spectrometer. Combustion microanalysis was performed at the University of California, Berkeley. Melting points are uncorrected.

2′-Nitrophenylglyoxal (5). A mixture of selenium dioxide (16.1 g, 145.0 mmol), dioxane (75 mL), and water (5 mL) was stirred at 60 °C until dissolution occurred. 2′-Nitroacetophenone (20 g, 120.8 mmol) was then added in one portion. The mixture was refluxed for 4 h and stirred at room temperature overnight. The solid was filtered and washed with CH_2Cl_2. The filtrate was diluted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The crude product was purified by flash chromatography, eluting with ethyl acetate−hexane (1:2 to 1:1), affording 4.5 g (22.5%) of unreacted 2′-nitroacetophenone and a yellowish oil. The oil was distilled under vacuum to give 12.4 g (74%) of **5** as a thick oil: bp 145 °C/10 Torr (lit.[7] 124−125.5 °C/3.5 Torr); ^{1}H NMR ($CDCl_3$) δ 9.52 (1H, s), 8.23 (1H, dd, *J* = 8.4, 1.2), 7.86 (1H, ddd, *J* = 8.4, 7.2, 1.2), 7.78 (1H, ddd, *J* = 8.4, 8.4, 1.2), 7.60 (1H, dd, *J* = 7.6, 0.8); ^{13}C NMR ($CDCl_3$) δ 189.1, 186.5, 135.1, 132.8, 130.8, 130.1, 124.1.

1-Acetyl-2-[2-(2-nitrophenyl)-2-oxo-1-hydroxyethyl]-1,2-dihydroindole-3-one (6). Piperidine (20 drops) was added to a solution of 1-acetyl-3-oxoindole[8] (**4**) (6.5 g, 37.1 mmol) and **5** (6.5 g, 36.3 mmol) in 20 mL of toluene. The mixture was stirred overnight, with a precipitate being formed as the reaction proceeded. The solid was filtered, washed with toluene and diethyl ether, and then dried under vacuum to give 10.1 g (78%) of **6**: mp 206 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.10 (1H, d, *J* = 8.4), 7.95 (1H, ddd, *J* = 7.6, 7.6, 1.2), 7.77−7.68 (3H, m), 7.58 (1H, d, *J* = 7.6), 7.20 (1H, dd, *J* = 7.6, 7.6), 6.55 (1H, very broad), 5.17 (3H, s, br), 2.42 (3H, s, br); ^{13}C NMR (DMSO-d_6) δ 204.2, 196.4, 168.7, 146.9, 136.9, 135.0, 134.7, 131.1, 129.5, 124.8, 123.5, 123.2, 122.9, 75.3, 69.4, 24.6; FABMS *m/z* 355 $[M+1]^+$; *anal.* C 60.85%, H 3.85%, N 7.72%, calcd for $C_{18}H_{14}N_2O_6$, C 61.01%, H 3.98%, N 7.91%.

2-[2-(2-Nitrophenyl)-2-oxoethylidiene]-1,2-dihydroindole-3-one (7). A 10% solution of HCl (50 mL) was added at room temperature to a solution of oxoindole **6** (5.0 g, 14.2 mmol) in 500 mL of THF, and the mixture was refluxed for 4 h. The deep red solution was concentrated, and the residue was treated with saturated $NaHCO_3$ solution and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried over $MgSO_4$, filtered, and then concentrated to give the crude product. Purification of the crude product by flash chromatography, eluting with CH_2Cl_2, afforded 3.5 g (84%) of **7** as a deep red solid: mp 187−188 °C (lit.[9] 194 °C); ^{1}H NMR (DMSO-d_6) δ 11.26 (1H, s), 8.03 (1H, dd, *J* = 7.6, 1.6), 7.92 (1H, dd, *J* = 7.6, 1.6), 7.84 (1H, ddd, *J* = 7.6, 7.6, 1.2), 7.78 (1H, ddd, *J* = 7.6, 7.6, 1.6), 7.65−7.56 (2H, m), 7.30 (1H, d, *J* = 8.0), 7.05 (1H, ddd, *J* = 7.6, 7.6, 0.8), 6.40 (1H, s); ^{13}C NMR (DMSO-d_6) δ 190.1, 188.2, 154.0, 147.5, 143.3, 137.7, 134.9, 133.4, 132.0, 128.8, 124.8, 124.2, 122.2, 118.8, 113.5, 95.4; EIMS *m/z* 294 $[M]^+$, 160 (100).

1-Methyl-2-[2-(2-nitrophenyl)-2-oxoethylidiene]-1,2-dihydro-indole-3-one (8). Sodium hydride (0.72 g, 60% in oil, 18.12 mmol) was added to a solution of oxoindole **7** (4.44 g,

15.1 mmol) in 80 mL of DMF at −10 °C. The mixture was stirred for 15 min, then CH_3I was added. After stirring the mixture at −10 °C for 2 h and then at room temperature for 2 h, the reaction mixture was quenched with water and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried over $MgSO_4$, filtered, and then concentrated. Purification of the crude product by column chromatography, eluting with ethyl acetate−hexane (1:2), afforded 3.85 g (83%) of **8** as a deep red solid: mp 160−161 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 8.0), 7.74 (1H, dd, J = 8.0, 8.0), 7.70−7.55 (4H, m), 7.10−7.00 (2H, m), 6.30 (1H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 190.1, 187.8, 155.5, 146.7, 143.0, 138.2, 137.4, 133.8, 130.6, 128.3, 125.2, 124.4, 122.3, 120.1, 110.1, 99.0, 33.7; *anal.* C 66.23%, H 4.04%, N 9.06%, calcd for $C_{17}H_{12}N_2O_4$, C 66.23%, H 3.92%, N 9.09%.

5,10-Dihydro-10-methylindolo[3,2-*b*][1]benzazepin-12(*11H*)-one (2). A mixture of oxoindole **8** (3.3 g, 10.71 mmol) and Pd/C (10%, 1.0 g) in 500 mL of toluene was stirred at room temperature under H_2 (balloon) for 4 h. The balloon was removed, and *p*-toluenesulfonic acid (300 mg, 1.75 mmol) was added. The mixture was refluxed for 30 min, using a Dean−Stark trap to remove the water formed during the reaction. The mixture was then cooled to room temperature, the catalyst was removed by filtration over Celite, and then the filtrate was concentrated. Purification of the crude product by column chromatography, eluting with CH_2Cl_2, afforded 1.25 g (44%) of **2** as a yellow solid: mp 260 °C (dec); see Table 1 for ^{1}H and ^{13}C NMR data; IR (film) cm^{-1} 3303, 1628, 1612, 1597, 1473, 1379, 1300, 1221, 742; HREIMS *m*/*z* 262.1109 [M]$^+$, calcd for $C_{17}H_{14}N_2O$ 262.1106; *anal.* C 77.88%, H 5.55%, N 10.72%, calcd for $C_{17}H_{14}N_2O$, C 77.84%, H 5.38%, N 10.68%.

10-Methylindolo[3,2-*b*][1]benzazepin-12-one (10). Sodium ethoxide (52 mg, 0.762 mmol) was added at room temperature to a solution of ketone **2** (100 mg, 0.381 mmol) in 10 mL of ethanol, and the mixture was stirred for 3 h. The solvent was removed by rotary evaporation, and the residue was quenched with aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried over $MgSO_4$, filtered, and then concentrated to give the crude product. The crude product was washed with ethyl ether to give 91 mg (92%) of ketone **10** as a orange solid: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (1H, dd, J = 8.0, 1.2), 8.28−8.20 (2H, m), 7.87 (1H, ddd, J = 8.4, 8.4, 1.6), 7.71 (1H, ddd, J = 8.0, 8.0, 1.2), 7.61 (1H, ddd, J = 8.0, 8.0, 0.8), 7.25 (1H, dd, J = 7.6, 7.6), 7.14 (1H, d, J = 8.4), 6.95 (1H, s), 3.57 (3H, s); ^{13}C NMR ($CDCl_3$) δ 182.4, 153.2, 147.9, 144.9, 142.6, 136.1, 133.6, 133.1, 132.7, 130.6, 130.1, 124.3, 123.4, 121.8, 113.9, 108.6, 29.1; HREIMS *m*/*z* 260.0957 [M]$^+$, calcd for $C_{17}H_{12}N_2O$ 260.0950; *anal.* C 77.30%, H 4.96%, N 10.46%, calcd for $C_{17}H_{12}N_2O\cdot0.25H_2O$, C 77.11%, H 4.76%, N 10.58%.

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