Isolation and Unambiguous Synthesis of Cryptolepinone: An Oxidation Artifact of Cryptolepine

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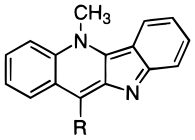
Cryptolepinone (**3**) was isolated as an artifact of extraction from *Cryptolepis sanguinolenta*. Previously, this compound had been identified as the natural products hydroxycryptolepine (**2**) and **3**. Synthesis via an unambiguous pathway has confirmed the structure of cryptolepinone. Spectroscopic studies in various solvents have shown that the natural product artifact or its synthetic equivalent can exist in the keto (cryptolepinone) or enol (hydroxycryptolepine) form.

The roots of the West African plant *Cryptolepis sanguinolenta* (Lindl.) Schlechter have been used by indigenous cultures as a dye[1,2] and to treat a variety of health disorders.[3] Root and stem decoctions have been used clinically to treat rheumatism, urinary and upper respiratory tract infections, and malaria,[4−7] and recently, a root decoction of *C. sanguinolenta* has been used to treat patients with diabetes.[8] Isolation efforts in recent years have shown that *C. sanguinolenta* contains a rich source of indoloquinoline alkaloids.[9] Among these alkaloids, ambiguity remains between hydroxycryptolepine (**2**) and cryptolepinone (**3**).

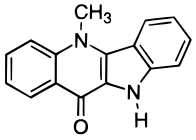
Hydroxycryptolepine was first isolated by Paulo et al. in 1995, as a natural product from *C. sanguinolenta*.[10] The subsequent isolation of quindolinone[11] and homocryptolepinone[12] from *C. sanguinolenta* cast doubt, however, on this structure. Joule et al. recently synthesized cryptolepinone (**3**),[13] and, based on a comparison of NMR and IR data, they concluded that the correct structure of the "natural product hydroxycryptolepine" was **3** instead of **2**. Their synthetic approach to **3**, however, contained regioisomeric ambiguity — introduction of the methyl group — that did not definitively establish the structure. Simultaneously, cryptolepinone was isolated by Sharaf et al.[14] Although they described the isolation procedure, no structure or structural elucidation details were described at that time.

In the course of studies on blood glucose-lowering properties of *C. sanguinolenta*, we isolated cryptolepine (**1**), together with other related alkaloids. We were intrigued by the presence of one alkaloid that was detectable in varying amounts depending on the isolation conditions, and we decided to investigate and determine its structure.[15] At the conclusion of our study we noted the recent report by Martin et al.[16]

We wish to report a synthetic approach to cryptolepinone (**3**), which unambiguously establishes its structure. We have carried out spectroscopic studies that indicate that the keto form **3** and enol form **2** both exist. Finally, we have determined that **3** is actually an oxidation artifact and not a naturally occurring plant metabolite from *C. sanguinolenta*.



1 R = H Cryptolepine
2 R = OH Hydroxycryptolepine



3 Cryptolepinone

Results and Discussion

Two alkaloids were isolated after liquid−liquid partition and chromatotron separation of a 1% acetic acid extract of the roots of *C. sanguinolenta*. The first alkaloid was identified as cryptolepine (**1**).[3] The second alkaloid was identified as cryptolepinone (**3**) on the basis of 1D and 2D NMR experiments acquired in a nanoprobe and HRMS. Our results are consistent with the data recently published by Martin et al. wherein the structure of **3** was elucidated as an 8% impurity in a sample of **1**.[16]

When the roots of *C. sanguinolenta* were extracted in neutral organic solvents, **3** was not detected in the extract. This observation indicates that **3** is not a natural product but an artifact of the extraction process under acidic conditions. A series of experiments was performed to determine whether the formation of **3** was catalyzed by the presence of acid, solvent, light and/or air. Compound **1** (>99% pure by HPLC analysis) was dissolved in organic solvents (MeOH or CH_3CN at 1 mg/mL) in the absence or presence of acid (HCl, 0.1 M), light, and/or air. Aliquots were taken periodically from the solutions over a span of 19 days and analyzed by HPLC. Over time, increasing amounts of cryptolepinone were detected. The highest concentration of **3** (2.5%) was detected in solutions that contained acid and were exposed to air. This experiment indicates that **3** is an oxidation product of **1**, and that its formation is catalyzed by the presence of acid and air during the alkaloid extraction (see Supporting Information). Further evidence to confirm that **3** is an oxidation product of **1** is provided by an independent chemical experiment. Treatment of **1** with *m*-chloroperbenzoic acid gave a 16.5% yield of a compound that was identical based on NMR spectral data to **3** obtained through isolation from *C. sanguinolenta*.

The synthesis of cryptolepinone (**3**) began with 11-chloroquindolinium hydrotriflate (**4**), which was prepared by literature methods (Scheme 1).[17] Hydrotriflate salt **4** could be converted to hydrochloride salt **5** using procedures

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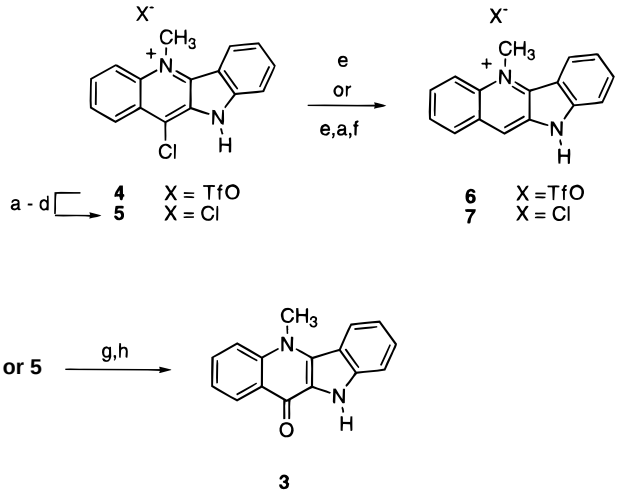
Scheme 1



[a] (a) Na_2CO_3; (b) basic alumina, $CHCl_3$; (c) MeOH−$CHCl_3$; (d) HCl−Et_2O; (e) H_2, Pd/C; (f) HCl−Et_2O; (g) NaOH or KOH; (h) HOAc.

described earlier.[3,17] Hydrogenation of either **4** or **5** afforded cryptolepine hydrotriflate (**6**) or cryptolepine hydrochloride (**7**), which were previously synthesized in an unambiguous manner.[3] With the structural integrity of the quindolinium salts **4**/**5** established, treatment of either compound with a concentrated solution of sodium or potassium hydroxide afforded the intermediate sodium or potassium salts of **3**. Subsequent reaction of both cryptolepinone salts with acetic acid afforded **3** in an unambiguous manner. Spectroscopic studies revealed that **3** can exist in two tautomeric forms. In MeCN-d_3, the keto and enol forms of **3** were present in a 4:1 ratio, respectively. In MeOH-d_4, the ratio was 9:1, with the keto form predominating. In all other solvents investigated, only the keto form was observed. The spectral data for synthetic **3** match in all respects with the natural product artifact **3** described above.

Experimental Section

General Experimental Methods. All NMR spectra were recorded at 400 MHz for ^{1}H and at 100 MHz for ^{13}C on a Varian Unity 400 using a nanoprobe (37 μL) manufactured by Varian and using TMS as an internal reference. Mass spectra were obtained on a Kratos MS-50 mass spectrometer; UV spectra, on a Perkin−Elmer UV−vis spectrometer; and IR spectra, on a Perkin−Elmer model 1600 FTIR. All solvents were HPLC grade from Fisher Scientific. A YMC-Pack Polymer C18 (6 μm) column (4.6 × 250 mm) was used for HPLC on a Hitachi model D-6500 equipped with an L-4500A diode array detector and a Sedex 55 light-scattering detector. The following solvents and HPLC conditions were used: A (0.1% TFAA in H_2O), B (0.1% TFAA in CH_3CN), and C (2-propanol); flow 1 mL/min; solvent gradient A/B (80:20) to B (100%) in 13 min, B (100%) for 2 min, B (100%) to B/C (30:70) for 10 min; diode array and light-scattering detection; sample concentration, 1 mg/mL; injection volume, 15 μL. Cryptolepine (**1**), 11-chlorocryptolepine hydrotriflate (**4**), and 11-chlorocryptolepine hydrochloride (**5**) were synthesized according to previously published methods.[3,17] TLC for synthetic intermediates was performed on E. Merck 230−400 mesh, 200 μ, Si gel plates, and visualized by UV detection. Elemental analyses were performed at the University of California, Berkeley. Melting points are uncorrected.

Plant Material. Roots of *Cryptolepis sanguinolenta* (Lindl.) Schlechter (Asclepiadaceae) were collected on June 9, 1994, in the village of Abetfi, Ghana, and identified by Roy Gereau of the Missouri Botanical Garden. Voucher specimens (#BKN106) are deposited in the reference collection, Department of Ethnobotany and Conservation, Shaman Pharmaceuticals, Inc.

Extraction and Isolation of Cryptolepinone (3) and Cryptolepine (1). Dry, powdered roots (1.12 kg) of *C. sanguinolenta* were percolated in 1% HOAc (10 L) at room temperature for 48 h. The filtered aqueous extract was extracted with $CHCl_3$ (3 × 5 L), and the $CHCl_3$ layer was separated and then discarded. The remaining aqueous extract was basified to pH 9 and extracted with $CHCl_3$ (3 × 5 L). The $CHCl_3$ layer was separated and concentrated under reduced pressure to dryness to yield 2.24 g (0.20%) of a crude alkaloid extract. The crude alkaloid extract was purified by chromatotron (3 × 560 mg sample, 2-mm Si gel plates, solvent system: toluene−EtOAc−diethylamine−MeOH, 60/25/10/15) to yield 1.5 g (0.13%) of **1** as dark purple needles, mp 178−179 °C (lit.[18] 175−178 °C) and 3.4 mg (0.0003%) of **3**, mp > 300 °C.

Cryptolepine (1): t_R (HPLC) = 11.2 min; HREIMS *m*/*z* 232.0994 (calcd for $C_{16}H_{12}N_2$, 232.1000); NMR spectral data agrees with reported values.[3]

Cryptolepinone (3): t_R (HPLC) = 13.9 min; HREIMS *m*/*z* 248.0946 (calcd for $C_{16}H_{12}N_2O$, 248.0950); NMR spectral data agrees with reported values.[13]

Cryptolepine Hydrotrifluoromethanesulfonate (6). A suspension of **4** (200 mg, 0.48 mmol) and 5% of Pd/C in EtOH (15 mL) was hydrogenated at atmospheric pressure at room temperature for 20 h. The reaction mixture was filtered through a short plug of Celite to remove the catalyst. The filtrate was concentrated under reduced pressure to give a yellow solid, which was recrystallized from $CHCl_3$ to give 150 mg (81%) of **6** as a yellow solid: mp 241−243 °C (lit.[3] mp 241−243 °C); IR (KBr) ν_{max} 3188, 1617, 1215, 1157, 1034, 746 cm^{-1}; NMR data were identical with that of **6** previously synthesized;[3] FABMS *m*/*z* 233 [M + H]$^+$; FABMS *m*/*z* [M$^-$] 148.9 (TfO$^-$); *anal.* C 53.1%, H 3.4%, N 7.2%, calcd for $C_{17}H_{13}N_2F_3O_3S$, C 53.3%, H 3.4%, N 7.3%.

Cryptolepine Hydrochloride (7). Method A. A suspension of **5** (18 mg, 0.060 mmol) and 10% Pd/C (7 mg) in EtOH (20 mL) was hydrogenated in a Parr shaker at 55 psi at room temperature for 2 h. The reaction mixture was filtered through a short plug of Celite to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2. The organic layer was washed with saturated K_2CO_3 and brine, dried, and then concentrated to give **1** as a purple solid. The product was dissolved in $CHCl_3$ and treated with 1N HCl to give a yellow precipitate. Filtration and drying gave 10 mg (63%) of **7**. The spectral data for the product were identical with those of **7** previously synthesized.[3]

Method B. Compound **6** was converted to **7** as previously described.[3]

5-Methylquindolin-11-one Sodium Salt. A suspension of **4** (2.0 g, 4.8 mmol) in dioxane (200 mL) was treated with a solution of NaOH (68 g, 1.7 mol) in H_2O (150 mL), and the two-phase mixture was refluxed for 8 h. After cooling, the precipitate that formed was filtered, washed sequentially with H_2O and Et_2O, and then dried to give 1.23 g (95.0%) of the title sodium salt: mp >250 °C (slowly sinters above 250 °C); UV (CH_3CN) λ_{max} (log ϵ) 234 (4.72), 2.72 (4.61), 309 (4.41), 363 (sh) (3.62), 379 (3.74), 400 (3.99) nm; IR (KBr) ν_{max} 3300, 1626, 1597, 1574, 1522, 1501, 1464, 1449, 1391, 1335, 1274, 1154, 1132, 1026, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.46 (1H, dd, J = 8.0, 1.6), 8.35 (1H, d, J = 8.4), 7.94 (1H, d, J = 8.8), 7.75 (1H, ddd, J = 8.8, 7.2, 1.6), 7.56 (1H, d, J = 8.4), 7.41 (1H, t, J = 7.2), 7.33 (1H, t, J = 7.2), 7.12 (1H, t, J = 7.6), 4.37 (3H, s); ^{13}C NMR δ (DMSO-d_6) 167.7, 140.9, 140.0, 130.8, 130.4, 126.2, 125.6, 123.1, 122.8, 120.1, 118.1, 116.3, 115.4, 114.1, 35.9; EIMS *m*/*z* 248 [M]$^+$; *anal.* C 64.1%, H 4.8%, N 9.3%, calcd for $C_{16}H_{11}N_2ONa\cdot1.65\ H_2O$, C 64.1%, H 4.9%, N 9.1%.

5-Methylquindolin-11-one Potassium Salt. A suspension of **4** (4.0 g, 9.6 mmol) in dioxane (200 mL) was treated with a solution of KOH (112 g, 2.0 mol) in H_2O (150 mL), and the two-phase reaction mixture was refluxed for 4 h. After cooling, the yellow precipitate that formed was filtered, washed

sequentially with H_2O and Et_2O, and then dried to give 2.08 g (75.6%) of the title potassium salt: mp 280−281 °C; UV (CH_3-CN) λ_{max} (log ϵ) 209 (4.55), 234 (4.46), 271 (4.73), 308 (4.25), 363 (sh) (3.73), 381 (4.03), 400 (4.13) nm; IR (KBr) ν_{max} 3202, 1625, 1593, 1572, 1523, 1503, 1460, 1388, 1336, 1274, 1132, 1028, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.46 (1H, dd, J = 8, 1.2), 8.33 (1H, d, J = 8.4), 7.92 (1H, d, J = 8.8), 7.74 (1H, ddd, J = 8.8, 7.2, 2), 7.54 (1H, d, J = 8), 7.37 (1H, t, J = 6.8), 7.31 (1H, t, J = 7.2), 7.08 (1H, t, J = 7.2), 4.36 (3H, s); ^{13}C NMR (DMSO-d_6) δ 167.8, 141.0, 139.9, 130.6, 130.3, 125.8, 125.7, 123.2, 122.7, 119.8, 117.9, 116.2, 115.6, 114.2, 35.8; *anal.* C 62.8%, H 4.4%, N 9.2%, calcd for $C_{16}H_{11}N_2OK \cdot 1.1\ H_2O$, C 63.1%, H 4.8%, N 8.8%.

5-Methylquindolin-11-one (Cryptolepinone, 3). The intermediate sodium salt (1.23 g, 4.55 mmol) was dissolved in HOAc (200 mL), and the mixture was stirred for 24 h and then diluted with ice-water (500 mL). After stirring for 1 h, the precipitate that formed was filtered, washed with H_2O, and then washed successively with 5% $NaHCO_3$ solution, H_2O, and Et_2O. After drying, 1.0 g (84%) of **3** was obtained as a yellow solid: mp >300 °C.

5-Methylquindolin-11-one (Cryptolepinone, 3). The intermediate potassium salt (1.8 g, 6.28 mmol) was dissolved in HOAc (250 mL), and the mixture was stirred 24 h and then diluted with ice-water (500 mL). After stirring for 1 h, the precipitate that formed was filtered, washed with H_2O, and then washed successively with 5% $NaHCO_3$ solution, H_2O, and Et_2O. After drying, 1.4 g (90%) of **3** was obtained as a bright yellow solid: mp > 300 °C; UV (CH_3OH) λ_{max} (log ϵ) 217 (4.02), 233 (4.18), 272 (4.55), 311 (4.13), 326 (4.08), 368 (sh) (3.66), 386 (3.92), 405 (4.02) nm; IR (KBr) ν_{max} 3070, 1623, 1589, 1525, 1459, 1383, 1335, 1290, 1129, 1050, 747 cm^{-1}; ^1H NMR (MeCN-d_3) two sets of signals were observed in MeCN-d_3, in a 4:1 ratio: keto form δ 9.93 (1H, br s), 8.53 (1H, dd, J = 7.6, 1.2), 8.38 (1H, dd, J = 8.4, 1.2), 7.91 (1H, dd, J = 8.8, 1.2), 7.81 (1H, td, J = 7.8, 1.6), 7.66 (1H, dd, J = 8.4, 1.2), 7.53 (1H, td, J = 7.6, 1.2), 7.38 (1H, td, J = 7.4, 1.2), 7.27 (1H, td, J = 7.8, 1.2), 4.38 (3H, s); enol form δ 8.69 (1H, td, J = 8.4, 1.2), 8.58 (1H, dd, J = 8.8, 1.2), 8.24 (1H, dd, J = 8.8, 1.2), 8.06 (1H, td, J = 6.8, 1.2), 7.98 (1H, td, J = 7.6, 0.8), 7.74 (1H, dd, J = 8.0, 1.2), 7.70 (1H, dd, J = 7.6, 1.2), 7.60 (1H, td, J = 7.6, 1.2), 4.47 (3H, s); ^1H NMR (CD_3OD) δ 8.57 (1H, dd, J = 8.4, 1.2), 8.41 (1H, d, J = 8.4), 7.99 (1H, d, J = 8.8), 7.84 (1H, td, J = 7.8, 1.2), 7.64 (1H, dd, J = 7.2, 1.2), 7.55 (1H, td, J = 7.6, 0.8), 7.44 (1H, td, J = 7.6, 0.8), 7.27 (1H, td, J = 7.6, 1.2), 4.50 (3H, s); ^1H NMR (CD_3COCD_3) δ 11.2 (1H, s), 8.57 (1H, d, J = 8.4), 8.45 (1H, d, J = 8.4), 7.98 (1H, d, J = 8.0), 7.82 (1H, t, J = 7.2), 7.72 (1H, d, J = 8.0), 7.54 (1H, t, J = 8.4), 7.39 (1H, t, J = 7.2), 7.26 (1H, t, J = 8.0), 4.51 (3H, s); ^1H NMR (DMSO-d_6) δ 11.95 (1H, s, N−H), 8.44 (1H, d, J = 7.6, H-1), 8.38 (1H, d, J = 8.0, H-6), 7.95 (1H, d, J = 8.4, H-4), 7.78 (1H, dd, J = 8.4, 6.8, H-3), 7.57 (1H, d, J = 8.0, H-9), 7.48 (1H, dd, J = 8.0, 7.2, H-8), 7.36 (1H, dd, J = 7.6, 6.8, H-2), 7.20 (1H, dd, J = 7.6, 7.2, H-7), 4.28 (3H, s, N−CH_3); ^{13}C NMR (DMSO-d_6) δ 167.1 (C-11), 140.3 (C-4a), 138.8 (C-9a), 131.4 (C-3), 130.6 (C-5a), 127.3 (C-8), 125.7 (C-1), 123.6 (C-11a), 123.4 (C-10a), 123.2 (C-6), 120.7 (C-2), 119.3 (C-7), 116.3 (C-5b), 115.8 (C-4), 113.0 (C-9), 36.0 (N−CH_3); ^1H NMR (pyridine-d_5) δ 13.6 (1H, s), 9.12 (1H, dd, J = 8.0, 1.2), 8.28 (1H, dd, J = 8.4, 1.2), 7.90 (1H, dd, J = 8.0, 0.8), 7.67−7.69 (2H, m), 7.57 (1H, td, J = 7.6, 1.2), 7.38 (1H, ddd, J = 8.0, 8.0, 1.6), 7.28 (1H, td, J = 7.8, 1.2), 4.15 (3H, s); ^{13}C NMR (pyridine-d_5) δ 168.7, 141.2, 139.8, 131.4, 127.4, 126.8, 125.3, 125.0, 123.9, 123.0, 120.9, 119.6, 117.5, 115.4, 113.5, 35.9; EIMS m/z 248 $[M]^+$; *anal.* C 73.6%, H 5.2%, N 10.8%, calcd for $C_{16}H_{12}N_2O \cdot 0.75\ H_2O$, C 73.4%, H 5.2%, N 10.7%.

Preparation of Cryptolepinone (3) by Chemical Oxidation of Cryptolepine (1). *m*-Chloroperbenzoic acid (175 mg, 1.01 mmol) was added to a solution of cryptolepine (200 mg, 0.86 mmol) in $CHCl_3$ (10 mL) at 0 °C and the reaction mixture was left in a freezer at 0 °C for 24 h with occasional shaking. The reaction mixture was washed with a 10% NaOH solution (30 mL), and the separated $CHCl_3$ layer was dried and then concentrated. The crude product was purified on a basic alumina column, eluting first with $CHCl_3$, and then with a gradient of 0.1−2% MeOH in $CHCl_3$, to give 35 mg (16.5%) of **2** along with 90 mg (45%) of unreacted **1**. Spectral data of **2** from this experiment were consistent with samples of cryptolepinone synthesized from **4** (Scheme 1) and isolated as an artifact from *C. sanguinolenta*.

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Supporting Information Available: A figure describing the percent conversion of **1** to **3** under various conditions (1 page). Ordering information is given on any current masthead page.

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