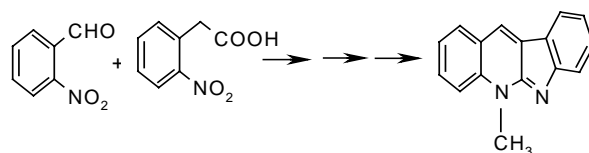


Graphical Abstract

Double reductive cyclization: A facile synthesis of the indoloquinoline alkaloid cryptotackieine

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and S. G. Tilve^{b, *}



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DOUBLE REDUCTIVE CYCLIZATION: A FACILE SYNTHESIS OF THE INDOLOQUINOLINE ALKALOID CRYPTOTACKIEINE

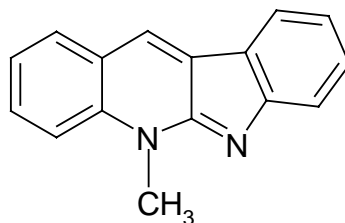
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Abstract— A new synthesis of the indoloquinoline alkaloid cryptotackieine, isolated from *Cryptolepis sanguinolenta*, is described via a Perkin reaction, a tandem double reduction-double cyclization reaction followed by regioselective methylation at the quinoline nitrogen.

Two independent groups reported the isolation of a new indoloquinoline alkaloid in 1996 from the ethanolic extracts of *Cryptolepis sanguinolenta*, a shrub indigenous to tropical West Africa, which was named as cryptotackieine **1** by one group¹, and neocryptolepine by the other group.² Cryptotackieine (neocryptolepine) which displays strong antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* strains³ was found to be the *N*-methyl derivative of the linear indolo[2,3-*b*]quinoline ring system. It has been reported that cryptotackieine (neocryptolepine) and various methyl derivatives of such systems display biological properties such as antimuscarinic, antibacterial, antiviral, antimicrobial, antihyperglycemic and cytotoxic activities in vivo, and significant antitumor properties in vitro.⁴



1

The interesting biological activity of **1** has generated an interest in developing a new synthetic pathway to polyheteroatomic ring systems such as 6*H*-indolo[2,3-*b*]quinoline, the precursor to cryptotackieine (neocryptolepine).⁵ In 1997, Alajarin et al.⁶ reported the synthesis of cryptotackieine **1** in three steps using an aza-Wittig reaction with an overall yield of 15%.

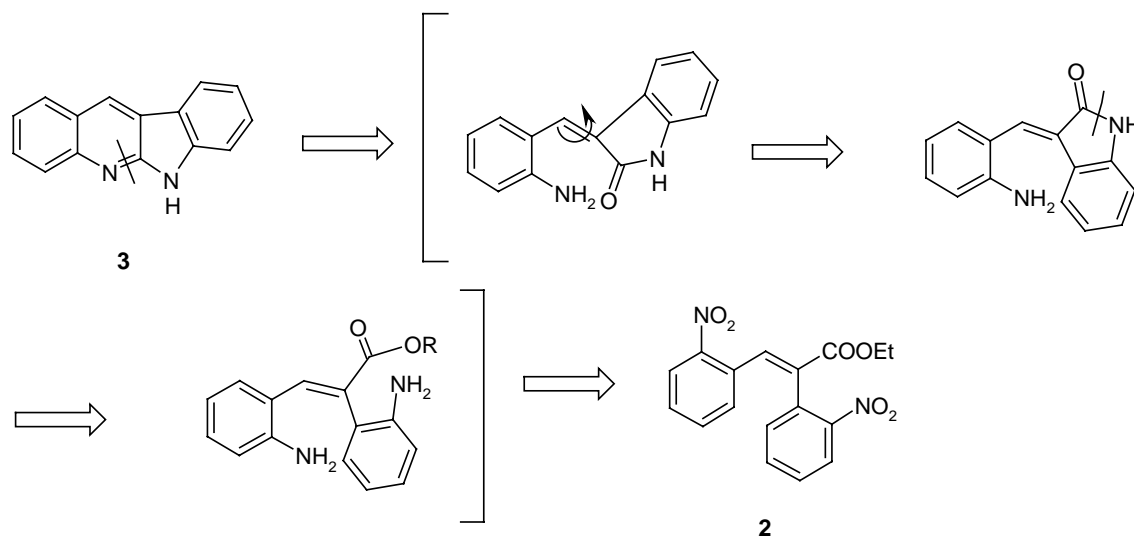
Keywords: Indoloquinoline alkaloid, Perkin reaction, Cryptotackieine, Neocryptolepine, tandem, reductive cyclization.

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In the same year, Timari et al. reported a synthesis in five steps with an improved overall yield of 24%. The key reaction of this method was the Suzuki coupling reaction between 3-bromoquinoline and *N*-pivaloylaminophenylboronic acid.⁷ In 1999, Molina et al. described an iminophosphorane mediated approach to obtain **1** in 26% overall yield which involved eight steps.⁸ Molina has also prepared **1** in nine steps in 9% overall yield using an intramolecular aza-Wittig reaction⁹ as the key step. Wang and co-workers reported the synthesis of **1** in four steps via a biradical pathway¹⁰ with an overall yield of 5%. In 2004, Ila and co-workers reported a five-step synthesis of **1** with an overall yield of 27%, which involved heterocyclization as the key step.¹¹ More recently, Mohan and co-workers reported the synthesis of **1** via three steps using a photocyclization reaction as the key step with an overall yield of 40%.¹²

In continuation of our interest¹³ in domino reactions, we report herein a facile synthesis of 6*H*-indolo[2,3-*b*]quinoline **3**, the immediate chemical precursor of the alkaloid cryptotackieine (neocryptolepine). Our retrosynthetic analysis of **3** indicated that it should be possible to prepare **3** via a one-pot double reduction, isomerization and double cyclization (Scheme 1). The required unsaturated ester **2** could be easily assembled from

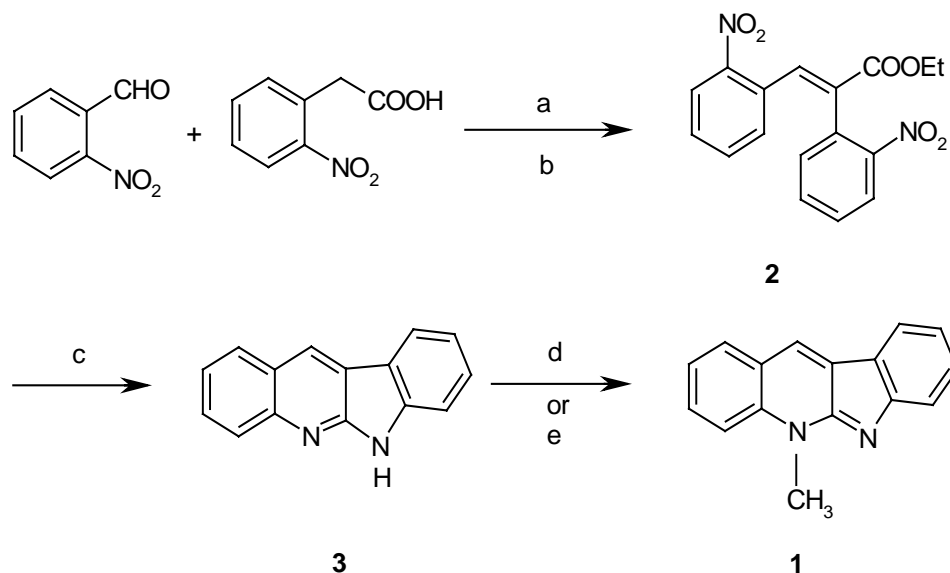


Scheme 1

commercially available *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid using the Perkin reaction.

Thus, condensation of *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid in the presence of Ac_2O and Et_3N yielded the corresponding α,β -unsaturated acid which on esterification afforded the required ester **2** in 71% yield.¹⁴ Reduction of **2** with Fe/AcOH in presence of HCl provided 6*H*-indolo[2,3-*b*]quinoline **3** in 74% in a single step.¹⁵ In this step, four reactions took place in a tandem manner, i.e. reduction of both the nitro groups, cycliz-

ation, isomerization at the intermediate *E*-amide to the *Z*-amide followed by a second cyclization. In the final step, compound **3** was subjected to regioselective methylation on the quinoline nitrogen as reported^{8, 12} to give cryptotackieine (neocryptolepine) **1** in 80% yield. The overall yield of **1** was found to be 42% over the three steps and is comparable with those reported (scheme 2). The spectral data for the compound **1** were identical with those reported¹ for the natural product.



Scheme 2 : Reagents and Conditions : a) Ac_2O , Et_3N , reflux, 5h
 b) EtOH , H_2SO_4 , reflux, 24h, 71%
 c) $\text{Fe}/\text{AcOH}:\text{EtOH}:\text{H}_2\text{O}/\text{HCl}$, 120 °C, 24h, 74%
 d) MW, $\text{Me}_2\text{SO}_4/\text{DMF}$, 140 °C, 5min., 75%
 e) Me_2SO_4 , CH_3CN , reflux, 6h, K_2CO_3 , 80%

In conclusion, we have developed a new and efficient three step synthesis of the alkaloid cryptotackieine (neocryptolepine) using a Perkin reaction followed by a ‘one-pot’ double reduction, double cyclization, isomerization in excellent yield. Due to the easy availability of the starting materials and high yields realized in the different steps, this approach represents an efficient synthesis of the title compound.

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14. Experimental procedure for the preparation of α,β -unsaturated ester derivative **2**: A mixture of *o*-nitrobenzaldehyde (1.06g, 7.01mmol), *o*-nitrophenylacetic acid (1.27g, 7.01mmol), Et₃N (1.1mL), and Ac₂O (15mL) were heated at reflux for 5h. The mixture was allowed to cool and poured into water (50mL). This was then extracted with CHCl₃ (3 x 15mL) and the combined organic extracts were washed with aqueous sat. Na₂CO₃ solution (3x15mL). The combined Na₂CO₃ washings were acidified with 6N HCl. The resulting solid was filtered, dried, redissolved in EtOH (15mL), H₂SO₄ (5 drops) were added and refluxed for 24h. The reaction

- mixture was cooled to room temp. and after 6h, the α,β -unsaturated ester **2** (1.71g, 71%) precipitated as a crystalline white solid and was isolated by filtration. IR (KBr, cm^{-1}): ν 1524, 1570, 1611, 1701; 1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.28 (t, 3H, $J = 7.2$ Hz, $-OCH_2CH_3$), 4.29 (q, 2H, $J = 7.2$ Hz, $-OCH_2CH_3$), 7.02-7.08 (m, 2H, Ar-H), 7.28-7.41 (m, 3H, Ar-H), 8.12- 8.16 (m, 3H, Ar-H), 8.22 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 13.99, 61.84, 76.60, 77.03, 77.45, 124.56, 124.66, 129.26, 129.37, 131.00, 131.58, 131.68, 133.01, 133.10, 133.55, 133.58, 137.25; HRMS m/z : $[M+Na]^+$ Calcd for $C_{17}H_{14}N_2O_6$, 365.0750; found, 365.0746.
15. Experimental procedure for the preparation of 6*H*-Indolo[2,3-*b*]quinoline **3**: Ester derivative **2** (0.55g, 1.61mmol) and Fe powder (3.6g) were added to a mixture of EtOH (10mL), acetic acid (10mL), and H₂O (5mL). To this mixture 5 drops of conc. HCl were added and the suspension was heated at 120 °C while stirring for 24h. The mixture was allowed to cool to room temp. and then filtered through celite. The filtrate was diluted with water (50mL) and then extracted with $CHCl_3$ (3 x 15mL). The combined organic extract was washed with 10% aqueous $NaHCO_3$ (25mL) and H₂O (3 x 15mL), dried over anhydrous Na_2SO_4 and concentrated to dryness to give a yellow solid. The solid was washed with Et_2O and air dried to give 6*H*-indolo[2,3-*b*]quinoline **3** (0.26g, 74%). mp > 300 °C (Lit.¹⁶ mp: 346 °C); IR (KBr, cm^{-1}): ν 1231, 1406, 1460, 1614, 3144; 1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 7.27 (tm, 1H, H-9), 7.46-7.57 (m, 3H, H-2, H-7, H-8), 7.72 (ddd, 1H, $J=8.1, 7.2, 0.9$ Hz, H-3), 7.98 (d, 1H, $J=8.4$ Hz, H-9), 8.11 (d, 1H, $J=8.1$ Hz, H-1), 8.27 (d, 1H, $J=7.8$ Hz, H-10), 9.05 (s, 1H, H-11), 11.70 (s, 1H, NH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 111.39 (C-7), 118.37 (C-10b), 120.14 (C-9), 120.76 (C-11a), 122.29 (C-10), 123.20 (C-2), 124.15 (C-10a), 127.45 (C-1), 128.01 (C-11), 128.67 (C-4), 129.13 (C-8 + C-3), 141.93 (C-6a), 146.79 (C-4a), 153.36 (C-5a).
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