A Concise Synthesis of 6*H*-Indolo[2,3-*b*]quinolines: Formal Synthesis of Neocryptolepine

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Abstract: A new two-step approach for the synthesis of 6*H*-indolo[2,3-*b*]quinolines is described using indole C3 alkylation and a one-pot reduction–cyclization–aromatization sequence. The synthesis of the parent 6*H*-indolo[2,3-*b*]quinoline system constitutes a formal synthesis of the alkaloid neocryptolepine (cryptotackieine).

Key words: alkaloid, alkylation, indoloquinoline, reduction–cyclization, domino reaction

In the past decade, indoloquinoline alkaloids have received attention owing to their striking biological properties[1,2] and novel structural features. A series of tetracyclic heteroaromatic compounds based on the indoloquinoline framework have been isolated from the roots of the West African plant *Cryptolepis sanguinolenta*, which were traditionally used by Ghanaian healers to treat a variety of disorders including malaria. Since 1974, a decoction of this plant has been used in the clinical therapy of rheumatism, urinary tract infections, malaria, and other diseases.[3–6] Cryptolepine (**1**), neocryptolepine (cryptotackieine) (**2**), and isocryptolepine (cryptosanguinolentine) (**3**) (Figure 1) are three major metabolites[7] out of a total of thirteen alkaloids isolated from *C. sanguinolenta*.

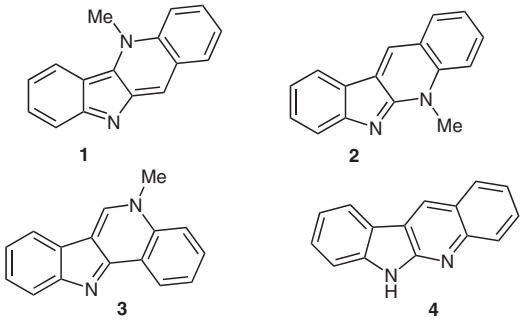

Figure 1 Cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**), and norcryptotackiene (**4a**)

Cryptolepine (**1**) and neocryptolepine (**2**) are linearly fused alkaloids with an indolo[3,2-*b*]quinoline and an indolo[2,3-*b*]quinoline ring system, respectively, while isocryptolepine (**3**) is an angularly fused alkaloid with an indolo[3,2-*c*]quinoline ring system. Chemically these are isomeric indoloquinolines, but more importantly they inhibit DNA replication and transcription[1] and exhibit promising antiplasmodial activity.[8] It has also been reported that, these compounds and some of their methyl derivatives displays promising antimuscarinic, antibacterial, antiviral, antimicotic, antihyperglycemic, and cytotoxic properties in vitro and antitumor activity in vivo.[9]

6*H*-Indolo[2,3-*b*]quinoline (**4a**), the immediate precursor to neocryptolepine (**2**), shares many biological properties with neocryptolepine (**2**) including the ability to interact with DNA as an intercalator and to inhibit topoisomerase II activity; it also has antimicrobial and cytotoxic activity.[9c,10] 6*H*-Indolo[2,3-*b*]quinoline (**4a**) itself is a natural product isolated from the leaves of *Justicia betonica*[10b] and is named norcryptotackeine.[11,12] Due to their significant biological activity and challenging structures, the indoloquinolines have been the target of synthetic and medicinal chemists. Their first synthesis was reported by Peczynska-Czoch and co-workers[9c] in 1994, before their isolation from natural sources. Thereafter, several syntheses of neocryptolepine were accomplished.[11–19] Recent synthetic studies include a photocyclization approach by Mohan and co-workers,[14] via C–N bond formation using tin(II) chloride dihydrate by Sharma and Kundu,[15] using the Pummerer reaction by Procter and co-workers,[16] using an intramolecular Wittig reaction by Kraus and Guo,[17] using the Friedlander quinoline synthesis followed by reduction, diazotization, and cyclization by Haddadin et al.,[12] and a palladium-catalyzed intramolecular direct arylation approach by Hostyn et al.[18] We reported the synthesis of 6*H*-indolo[2,3-*b*]quinolines by a double reduction–double cyclization approach in 2007[19a] and a one-pot, iodine-catalyzed[19b] protocol in 2009. More recently, we have also reported[19c] an efficient synthesis of neocryptolepine (**2**) using the Wittig reaction and a one-pot reduction–cyclization–dehydration sequence.

Continuing our interest[19a–d] in indoloquinoline alkaloids, herein we report a simple and concise method for the synthesis of 6*H*-indolo[2,3-*b*]quinolines. Our strategy is depicted in Scheme 1; alkylation of 1*H*-indole (**5a**) at its more reactive 3-position followed by reductive cyclization to provide tetracyclic compound **8a** that could be oxidized to 6*H*-indolo[2,3-*b*]quinoline (**4a**).

Thus, 1*H*-indole (**5a**) was treated with 2-nitrobenzyl alcohol (**6a**) under Mitsunobu reaction condition, however, no product formation was observed. Hence alkylation[20] was performed using 2-nitrobenzyl bromide (**6b**) in acetone–water (4:1) at 80 °C for 40 hours. Product **7a** was obtained

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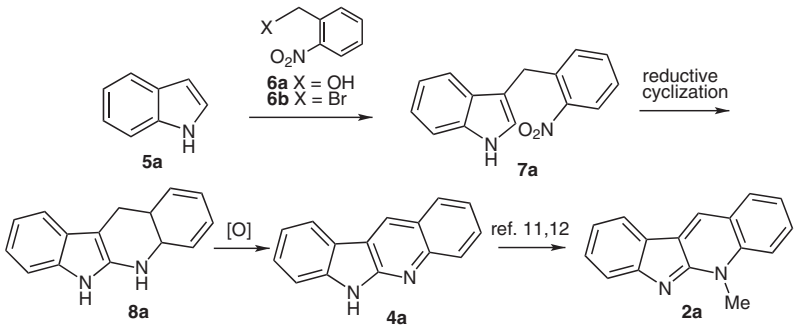


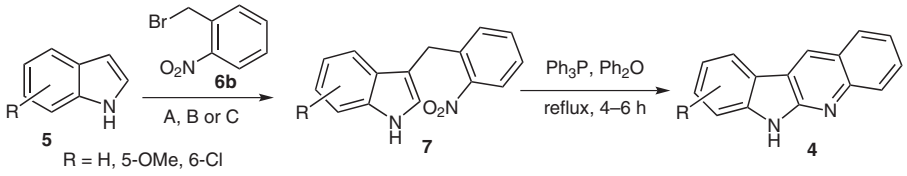
Scheme 1 Synthetic strategy

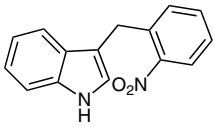
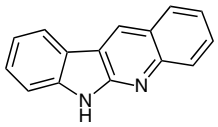
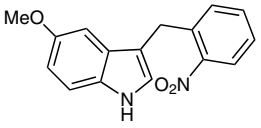
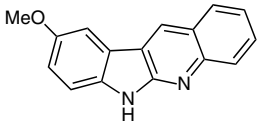
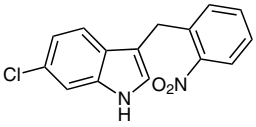
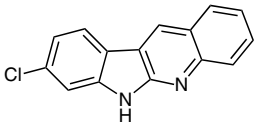
in 65% yield along with minor amounts of 2-nitrobenzyl alcohol, a hydrolyzed product. Recently, the alkylation of indole by microwave irradiation[21] using water as a solvent has been reported. When the reaction was attempted under these conditions, **7a** was obtained in 68% yield after 10 minutes. To achieve a further improvement in the yield, the alkylation was performed using methylmagnesium bromide as the base, wherein **7a** was obtained in 72% yield. The next step in the projected synthesis was reductive cyclization. This was first attempted using a molybdenum catalyst[22] without success. Later it was tried using Cadogan's protocol[23] using triethyl phosphite. This gave a complex mixture of products. Hence, triphenylphosphine in refluxing diphenyl ether[24] was used. After usual workup, the indoloquinoline **4a** was obtained directly in 63% yield. In this step, reductive cyclization yielded **8a** which under the reaction condition underwent aromatization to lead to **4a**. A plausible mechanism for the formation **4a** is depicted in Scheme 2.

The synthesis of 6*H*-indolo[2,3-*b*]quinoline (**4a**) constitutes the formal synthesis of naturally occurring indoloquinoline alkaloid neocryptolepine (**2**).

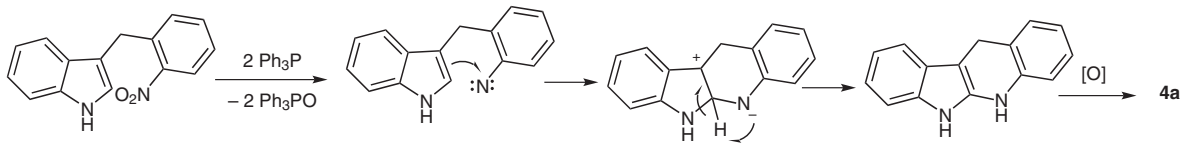
After successfully demonstrating the efficacy of our strategy with the parent indole **5a**, the methodology was extended to the synthesis of analogues of 6*H*-indolo[2,3-*b*]quinoline, i.e. 9-methoxy- (**4b**) and 8-chloro-6*H*-indolo[2,3-*b*]quinoline (**4c**) from the corresponding 5-methoxy- and 6-chloroindoles **5b**,**c** (Table 1).

Table 1 Synthesis of 6*H*-Indolo[2,3-*b*]quinoline and Derivatives



Entry	Compound **7**	Yield[a,b] (%) of method			Compound **4**	Yield[a] (%)
		A	B	C		
1	 **7a**	65	68	72	 **4a**	63
2	 **7b**	60	61	68	 **4b**	60
3	 **7c**	58	56	65	 **4c**	55

[a] Isolated yield.
[b] Reaction conditions: Method A: Na_2CO_3, acetone–H_2O (4:1), 80 °C, 40 h; Method B: H_2O, MW, 200 W, 150 °C, 10 min; Method C: MeMgBr, toluene, stir, r.t., 12 h.



Scheme 2 Proposed mechanism

The overall yield of 6*H*-indolo[2,3-*b*]quinolines **4** in this two-step sequence was found to be in the range 33–45%, which is comparable with most of the reported methods.

In conclusion, we have developed a new and a concise two-step method for the synthesis of 6*H*-indolo[2,3-*b*]quinolines using an alkylation and domino reduction–cyclization–aromatization approach. The usefulness of the method was demonstrated by synthesizing the analogues, 9-methoxy-6*H*-indolo[2,3-*b*]quinoline and 8-chloro-6*H*-indolo[2,3-*b*]quinoline.

Commercial reagents were purchased from Sigma-Aldrich and used without further purification. Solvents were distilled prior to use. Reactions were monitored by TLC (Kieselgel Merck 60) purchased from Merck. Column chromatography was performed on silica gel (60–120 mesh). Flash chromatography was performed on a Combiflash Companion with silica gel (230–400 mesh). Infrared spectra were recorded on Shimadzu FT-IR spectrophotometer. Microwave reactions were carried out using a Milestone Startsynth microwave instrument. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) were recorded on a Bruker 300 and Bruker 400 instrument using DMSO-d_6 and $CDCl_3$ as the solvent and TMS as an internal standard. LCMS were recorded on a Agilent Technologies instrument and GCMS on a Varian GC/MS instrument. HRMS were recorded on a MicroMass ES-QTOF. Melting points were recorded using a Thiele apparatus and are uncorrected.

3-(2-Nitrobenzyl)-1*H*-indoles 7a–c; General Procedure

Method A: A mixture of 2-nitrobenzyl bromide (**6b**, 432 mg, 2 mmol), indole **5a–c** (8 mmol), and Na_2CO_3 (424 mg, 4 mmol) in acetone–H_2O (4:1, 10 mL) were stirred at 80 °C for 40 h. On completion of the reaction (TLC monitoring), H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (anhyd Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (20% EtOAc–hexanes).

Method B: A mixture of 2-nitrobenzyl bromide (**6b**, 432 mg, 2 mmol) and indole **5a–c** (2.4 mmol) in H_2O (10 mL) were reacted in MW reactor at 150 °C (200 W) for 10 min. On completion of the reaction (TLC monitoring), H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. K_2CO_3, dried (anhyd Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography.

Method C: Indole **5a–c** (2 mmol) was dissolved in dry toluene (10 mL) and cooled to –5 °C. To this was added MeMgBr in Et_2O (2.1 mmol) and the mixture was stirred at –5 °C to r.t. for 1 h. The soln was again cooled to –5 °C and 2-nitrobenzyl bromide (**6b**, 432 mg, 2 mmol) in dry toluene (2 mL) was added and mixture was stirred at r.t. for 24 h. On completion of the reaction (TLC monitoring), H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. NH_4Cl, dried (anhyd Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography.

3-(2-Nitrobenzyl)-1*H*-indole (7a)[15,20]

Oily liquid; yield (Method C): 363 mg (72%).

IR (neat): 3417, 2924, 1606, 1519, 1456, 1348 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.47 (s, 2 H), 7.02–7.24 (m, 3 H), 7.33–7.48 (m, 5 H), 7.92 (d, *J* = 7.5 Hz, 1 H), 8.05 (br s, 1 H).

5-Methoxy-3-(2-nitrobenzyl)-1*H*-indole (7b)

Oily liquid; yield (Method C): 384 mg (68%).

IR (neat): 3415, 2960, 1581, 1521, 1485, 1350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.43 (s, 2 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.90 (s, 1 H), 6.97 (s, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.34–7.39 (m, 2 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 8.03 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (CH_2), 56.0 (CH_3), 100.0 (CH), 112.0 (CH), 112.3 (CH), 112.6 (C_q), 123.9 (CH), 124.6 (CH), 127.0 (CH), 127.6 (C_q), 131.4 (C_q), 131.7 (CH), 132.8 (CH), 136.0 (C_q), 149.4 (C_q), 154.0 (C_q).

GC-MS: *m*/*z* = 282 [M$^+$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_3Na$: 305.0902; found: 305.0902.

6-Chloro-3-(2-nitrobenzyl)-1*H*-indole (7c)

Orange solid; yield (Method C): 373 mg (65%); mp 112–114 °C.

IR (KBr): 3355, 2980, 1562, 1511, 1465, 1346 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43 (s, 2 H), 6.99 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.35–7.39 (m, 4 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.11 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (CH_2), 111.2 (CH), 113.1 (C_q), 119.7 (CH), 120.3 (CH), 123.8 (CH), 124.7 (CH), 125.8 (C_q), 127.3 (CH), 128.1 (C_q), 131.7 (CH), 133.0 (CH), 135.7 (C_q), 136.6 (C_q), 149.3 (C_q).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{11}N_2O_2ClNa$: 309.0407; found: 309.0406.

Indoloquinolines 4a–c; General Procedure

A mixture of 3-substituted indole derivative **7a–c** (1 mmol) and Ph_3P (576 mg, 2.2 mmol) were refluxed in Ph_2O under a N_2 atmosphere for 4–6 h. After cooling, the mixture was chromatographed (silica gel), Ph_2O was removed eluting with hexanes, further elution with 20% EtOAc–hexanes afforded the indoloquinolines **4a–c**.

6*H*-Indolo[2,3-*b*]quinoline (4a)

Reaction time: 4 h; yellow solid; yield: 138 mg (63%); mp >300 °C (Lit.[13] 342–346 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.27 (t, *J* = 7.5 Hz, 1 H), 7.45–7.56 (m, 3 H), 7.72 (t, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 9.0 Hz, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 8.26 (d, *J* = 9.0 Hz, 1 H), 9.05 (s, 1 H), 11.69 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 111.4 (CH), 118.3 (C_q), 120.1 (CH), 120.7 (C_q), 122.3 (CH), 123.2 (CH), 124.1 (C_q), 127.4 (CH), 128.0 (CH), 128.6 (CH), 129.1 (2 CH), 141.9 (C_q), 146.8 (C_q), 153.3 (C_q).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}N_2$: 219.0922; found: 219.0926.

9-Methoxy-6*H*-indolo[2,3-*b*]quinoline (4b)

Reaction time: 6 h; light-green solid; yield: 149 mg (60%); mp 284–286 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s 3 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.46 (t, J = 8.4 Hz, 1 H), 7.71 (t, J = 8.0 Hz, 1 H), 7.88 (s 1 H), 7.96 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 9.04 (s, 1 H), 11.51 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1 (CH_3), 105.8 (CH), 112.1 (CH), 117.0 (CH), 118.6 (C_q), 121.0 (C_q), 123.0 (CH), 123.8 (C_q), 127.4 (CH), 128.1 (CH), 129.1 (2 CH), 136.3 (C_q), 146.8 (C_q), 153.7 (C_q), 154.0 (C_q).

LCMS: m/z = 249 $[M + H]^+$.

HRMS: m/z $[M + Na]^+$ calcd for $C_{16}H_{12}N_2ONa$: 271.0864; found: 271.0847.

8-Chloro-6*H*-indolo[2,3-*b*]quinoline (4c)
Reaction time: 5 h; colorless solid; yield: 139 mg (55%); mp 296–298 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29 (d, J = 8.4 Hz, 1 H), 7.50–7.52 (m, 2 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.4 Hz, 1 H), 8.11 (d, J = 8.4 Hz, 1 H), 8.27 (d, J = 8.4 Hz, 1 H), 9.07 (s, 1 H), 11.86 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 111.1 (CH), 117.6 (C_q), 119.7 (C_q), 120.3 (CH), 123.6 (CH), 123.7 (CH), 124.2 (C_q), 127.4 (CH), 128.6 (CH), 129.2 (CH), 129.5 (CH), 132.9 (C_q), 142.6 (C_q), 146.7 (C_q), 153.4 (C_q).

LCMS: m/z = 253 $[M + H]^+$, 251 $[M – H]^+$.

HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{10}N_2Cl$: 253.0533; found: 253.0531.

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