A Convenient Synthesis of Two New Indoloquinoline Alkaloids

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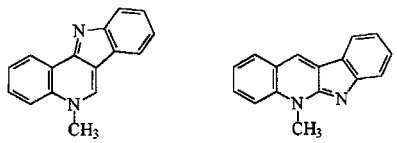
Abstract: A concise synthesis of two new indoloquinoline-based alkaloids (**1** and **2**), isolated from *Cryptolepis sanguinolenta*, is reported. The palladium-catalyzed cross-coupling reaction of 3-bromoquinoline derivatives with N-pivaloylamino phenylboronic acid gave the corresponding biaryls from which the indoloquinolines could be synthesized.

Cryptosanguinolentine (**1**) and cryptotackieine (or neocryptolepine) (**2**), members of a family of indoloquinoline alkaloids, have recently been isolated[1] from a West African plant *Cryptolepis sanguinolenta*. In recent years considerable interest arose for the total synthesis of polyheteroaromatic alkaloids[2], mostly due to their potential effectiveness in medical treatment. These compounds can intercalate in the DNA double helix to result in dramatic changes in DNA conformation and, furthermore, can also inhibit DNA replication and transcription[3].

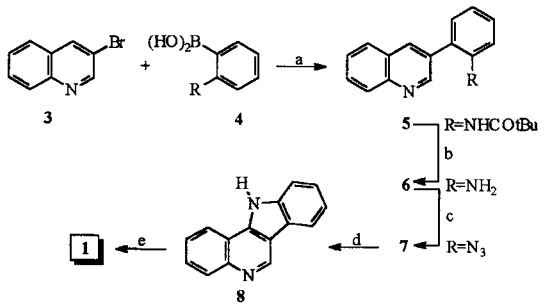


1 **2**

In our program concerning the synthesis and studies on biological activity of planar heteroaromatic molecules[4] showing very promising reverse transcriptase inhibitory effect[5], we decided to elaborate the total synthesis of **1** and **2**. The designed synthetic routes are outlined in Schemes 1 and 2.

Cryptosanguinolentine (**1**) can be classified as an indolo[3,2-c]quinoline derivative exhibiting an angularly fused annelation pattern. Compounds of this type have been prepared by intramolecular reaction of iminophosphorane with isocyanate[6] or by the regioselective thermocyclisation of the corresponding azide.[7]

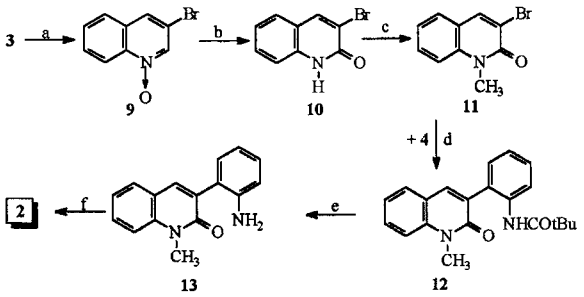
For the synthesis of **1** we applied the *ortho* metalation-cross coupling strategy (Scheme 1)[8], which was successfully used for the preparation of several marine alkaloids and other polyheteroaromatics.[9]



Scheme 1. (a) Pd(0), DME, H_2O, $NaHCO_3$, reflux, 4 h, 90%; (b) 20% H_2SO_4, reflux, 1 d, 93%; (c) cc.HCl, $NaNO_2$, 0°C, 1 h, then NaN_3, 0°C, 1 h, 80%; (d) *o*-dichlorobenzene, 180°C, 5 h, 75%; (e) Me_2SO_4, CH_3CN, reflux, 5 h, K_2CO_3, 93%.

Pd(0) catalyzed cross-coupling reaction of N-pivaloylamino phenylboronic acid[10] (**4**) with 3-bromoquinoline (**3**) under modified Suzuki conditions[11] afforded the desired biaryl compound **5** in 90% yield. After removing the protecting group, the free amine **6** was transferred to an azide derivative **7**[12] *via* diazotation followed by the reaction with sodium azide. Thermal cyclization of **7** was performed in boiling dichlorobenzene and resulted exclusively in the desired 4-substituted quinoline derivative **8**. Reaction of **8** with dimethyl sulfate in acetonitrile was found to be regioselective[13] since the "quinoline-methylated" compound **1** was isolated as the only product (i.e. no methylation at the "indole-nitrogen" was observed). After purification, the methylated product **1** proved to be entirely identical spectroscopically (^1H NMR, ^{13}C, NOE experiment) with that isolated from *Cryptolepis sanguinolenta*.[1]

In contrast to **1**, cryptotackieine (**2**) has a linear annellation pattern and, thus, a different procedure (**Scheme 2**)[14] had to be applied for its synthesis. Although several approaches for the synthesis of this type of ring system have been known from the literature[15], our strategy for the preparation of **2** seemed to be more simple and straightforward. 3-Bromo-1H-2-quinolone (**10**) was prepared from the commercially available 3-bromoquinoline (**3**) *via* its N-oxide derivative **9** according to literature procedure[16]. Compound **10** was reacted with methyl iodide in the presence of potassium carbonate to give the N-methyl compound **11**. Coupling reaction of this compound **11** with N-pivaloylamino phenylboronic acid (**4**) led to the formation of the biaryl compound **12** which was hydrolyzed to the amine **13** considered to be the key intermediate for the preparation of **2**. When **13** was exposed to the action of two equivalents of $POCl_3$ in refluxing benzene, a condensation reaction between the amine group and the amide moiety took place to give the ring-closed product **2**, whose spectral properties (^1H NMR, ^{13}C) were identical with the naturally occurring **2**.



Scheme 2. (a) MCPBA, $CHCl_3$, r.t., 1 d, 98%; (b) TsCl, $CHCl_3/K_2CO_3$, r.t, 6 h, 55%; (c) MeI, DMF, 60°C, 3 h, 81%; (d) Pd(0), DME, H_2O, $NaHCO_3$, 3 h, 85%; (e) 20% H_2SO_4/ ethanol(1:1), reflux, 2 d, ~100%; (f) $POCl_3$, benzene, reflux, 3 h, 65%.

In conclusion, we have developed a convenient synthesis of two new minor indoloquinoline alkaloids (**1** and **2**) which affords these desired natural products in excellent yield and opens the way for their biological evaluation. This route seems to provide a general method for the preparation of various substituted derivatives using appropriately substituted bromoquinolines and substituted N-pivaloylamino arylboronic acids.

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(8) Selected data for compounds in **Scheme 1**:
Data for **5**: mp 150-152 °C, ^{1}H NMR ($CDCl_3$) δ 12.08(1H, s), 8.21(1H, dd, J = 8, 8Hz), 7.83(1H, dd, J = 8, 2Hz), 7.76(1H, ddd, J = 7, 8, 2Hz), 7.60(1H, ddd, J=7, 8, 2Hz), 7.43(1H, ddd, J = 7, 8, 2Hz), 7.34(1H, dd, J = 8, 2Hz), 7.25(1H, ddd, J = 7, 8, 2Hz), 1.10(9H, s); IR (KBr) ν= 3250, 1670, 1520 cm^{-1}.
Data for **6**: mp 115-117 °C, ^{1}H NMR ($CDCl_3$) δ 9.03(1H, d, J = 2Hz), 8.26(1H, d, J = 2Hz), 8.15(1H, d, J = 8Hz), 7.85(1H, dd, J = 8, 2Hz), 7.74(1H, ddd, J = 8, 7, 2Hz), 7.58(1H, ddd, J = 8, 7, 2Hz), 7.23-7.15(2H, m), 7.10(1H, ddd, J = 8, 7, 2Hz), 7.03(1H, dd, J = 8, 2Hz), 3.80(2H, s, br); IR (KBr) ν = 3420, 3320, 1640, 1490 cm^{-1}.
Data for **7**: mp 78 °C (decomp), ^{1}H NMR ($CDCl_3$) δ 9.03(1H, d, J = 2Hz), 8.23(1H, d, J = 2Hz), 8.15(1H, d, J = 9Hz), 7.89(1H, d, J = 8Hz), 7.72(1H, ddd, J = 8, 7, 2Hz), 7.60(1H, dd, J = 8, 2Hz), 7.55-7.45(2H, m), 7.30-7.20(2H, m); IR (KBr) ν = 2270, 1500, 1310 cm^{-1}.
Data for **8**: mp >250 °C, ^{1}H NMR (DMSO-d_6) δ 12.72(1H, s), 9.89(1H, s), 8.52(1H, dd, J = 8, 2Hz), 8.31(1H, dd, J = 8, 2Hz), 8.12(1H, dd, J = 8, 2Hz), 7.70-7.80(2H, m), 7.50(1H, t, J = 8Hz), 7.32(1H, t, J = 8Hz); ^{13}C (DMSO-d_6) δ 144.8, 139.7, 138.7, 129.5, 128.0, 125.7, 125.5, 122.1, 121.8, 120.6, 120.1, 111.8; IR (KBr) ν = 3300, 1610, 1560 cm^{-1}.
Data for **1**: mp 132-133 °C (CH_3CN), IR (KBr) ν = 1620, 1590, 1340, 1210, 720 cm^{-1}. ^{1}H NMR, ^{13}C and NOE experiment were identical with those published in ref 1.

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(14) Selected data for compounds in **Scheme 2:**
Data for **11**: ^{1}H NMR ($CDCl_3$) δ 8.13(1H, s), 7.61(1H, ddd, J = 8.5, 7, 1.5Hz), 7.53(1H, dd, 7.5, 1.5Hz), 7.37(1H, d, J = 8.5Hz), 7.26(1H, ddd, J = 7.5, 7, 1Hz), 3.81(3H, s).
Data for **12**: mp 179-80 °C, ^{1}H NMR ($CDCl_3$) δ 9.09(1H, s), 7.84(1H, s), 7.81(1H, dd, J = 8, 1Hz), 7.63-7.70(2H, m), 7.49(1H, d, J = 8Hz), 7.43(1H, ddd, J = 8, 8, 1.5Hz), 7.34(1H, dd, J = 7, 1Hz), 7.32(1H, dd, J = 8, 1.5Hz), 7.21(1H, ddd, J = 8, 8, 1Hz), 3.88(3H, s), 1.17(9H, s); IR (KBr) ν = 2965, 1684, 1625, 1580, 1529, 1440, 755 cm^{-1}.
Data for **13**: mp 172-174 °C, ^{1}H NMR ($CDCl_3$) δ 7.81(1H, s), 7.58-7.63(2H, m), 7.42(1H, d, J = 8Hz), 7.28(1H, ddd, J = 8, 7, 1Hz), 7.18-7.23(2H, m), 6.85(1H, ddd, J = 7.5, 7.5, 1Hz), 6.79(1H, dd, J = 7, 1Hz); IR (KBr) ν = 3423, 3333, 1642, 1643, 1581, 1493, 753 cm^{-1}.
Data for **2**: mp 104 °C ($CHCl_3$/hexane), IR (KBr) ν = 1647, 1610, 1496, 1200, 746, 743 cm^{-1}. ^{1}H NMR and ^{13}C experiment gave identical results with those published in ref 1.

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