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Fischer indole synthesis of the indoloquinoline alkaloid: cryptosanguinolentine

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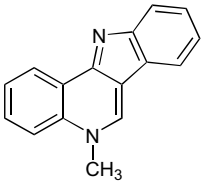
Abstract—A new synthesis of an indoloquinoline alkaloid, isolated from *Cryptolepis sanguinolenta*, is described using a Fischer indole cyclization. 4-Hydroxy-1-methyl-1*H*-quinolin-2-one reacted directly with phenylhydrazine hydrochloride to give the indoloquinoline, which was reacted with $POCl_3$ and then the resultant halide hydrogenolysed to give cryptosanguinolentine.

Cryptosanguinolentine **1** (also named isocryptolepine), one of the most important indoloquinoline alkaloids, was isolated a decade ago, from the roots of the West African plant *Cryptolepis sanguinolenta*.[1] In traditional folk medicine, a concoction of the root of this plant was used to treat fevers (including fever caused by malaria). In the recent years, much interest have been seen in the total synthesis of various types of hetero-aromatic alkaloids, mainly due to their potential applications in the medicinal field.[2,3] Many such alkaloids are known to intercalate in the DNA double helix resulting in dramatic changes in DNA conformation and, furthermore, they can also inhibit DNA replication and transcription.[4] The strength and mode of binding of these alkaloids to DNA have been investigated by spectroscopy and X-ray analysis.[5] It has been reported[6] that some *N*-methyl derivatives of these ring systems display important antimicrobial and cytotoxic activity.



1

In continuation of our work[7] with indoloquinoline alkaloids, we hereby report the total synthesis of cryptosanguinolentine **1** using a convenient route in comparison with the earlier reported procedures.[8–12]

Compounds with an angularly fused annelation pattern, such as cryptosanguinolentine **1**, have previously been prepared by intramolecular reactions of an iminophosphorane with an isocyanate,[8,9] by the regioselective thermocyclisation of the corresponding azide[10] and by an *ortho*-metalation-cross coupling strategy.[11]

Using a mixture of glacial acetic acid and concentrated hydrochloric acid, in the ratio of 4:1 (as described by Kent[13]), 4-hydroxy-1-methyl-1*H*-quinolin-2-one **2** reacted with phenylhydrazine hydrochloride to give the indoloquinoline moiety **4** in a single step (Scheme 1). With regard to this conversion[14–16] there are several relevant reports. Bucherer[17] first introduced this transformation in the synthesis of 11*H*-benzo[*a*]carbazole from 1-naphthol and phenylhydrazine using basic and acidic conditions. Recently, Mulwad et al.[18] described the conversion of 4-hydroxyquinolin-2-one into 4-hydrazinoquinolin-2-one derivatives. The resulting product existed predominantly in the hydroxy form **5** (5-methyl-5*H*-indolo[3,2-*c*]quinolin-6-ol),[19] as confirmed by its IR spectrum with an intense band at 3448–3550 cm^{-1}, and it is more stable when all the double bonds are present as a part of the aromatic system. The enol was easily converted into chloride **6**[20] by treatment with phosphorus oxychloride.[20] Finally, compound **6** underwent dehalogenation by the action of hydrogen with a palladium on carbon catalyst (10%) to afford cryptosanguinolentine **1**.[19] After purification,

Keywords: Fischer indole synthesis; Indoloquinoline alkaloid; Cryptosanguinolentine.
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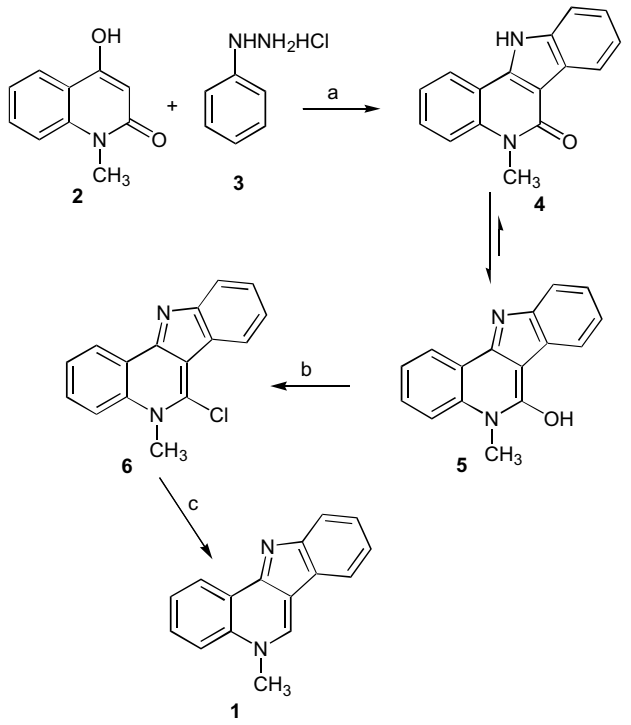

Scheme 1. Reagents and conditions: (a) Glacial acetic acid/concd HCl (4:1), reflux, 135 °C, 5 h, 65%. (b) $POCl_3$, reflux, 100 °C, 8 h, 62%. (c) H_2, Pd/C (10%), 70%.

the final product **1** was spectroscopically identical (^{1}H NMR, ^{13}C NMR) with the natural product.[1]

In conclusion, we have developed a convenient three-step synthesis of cryptosanguinolentine, using a modified Fischer indole cyclization, in excellent yields.

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19. To an equimolar mixture of compounds **2** and **3**, glacial acetic acid and concd HCl (4:1) were added and the mixture refluxed in an oil bath, the temperature being maintained at 135 °C for about 5 h. Then, the mixture was poured into crushed ice (300 g) and purified by silica gel column chromatography. In this conversion, the formation of the hydrazone was regiospecific for the quinoline C4-position as confirmed by the IR spectrum of the product **5**, which showed the disappearance of the C4–OH band (3000–3300 cm^{-1}) of compound **2**. Compared to the C4-carbon, the C2-carbon is less susceptible to nucleophilic attack[18] since the electronegative nitrogen attached to the C2-carbon shortens the N–C═O bond length and increases the electron density on the C2-carbon.
Data for **5**: (5-methyl-5*H*-indolo[3,2-*c*]quinolin-6-ol): mp 217 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) [δ/ppm] δ 3.79 (s, 3H, N-Me), 8.35 (d, 1H, C4-H, J = 7.9 Hz), 7.22–8.03 (m, 7H, Ar-H), 13.13 (s, 1H, –NH/OH); ^{13}C NMR ($CDCl_3$, 400 MHz) [δ/ppm] δ 36.72, 105.64, 110.33, 120.41, 120.93, 121.45, 122.79, 123.63, 126.54, 127.93, 128.23, 128.71, 136.12, 148.41, 151.65, 154.37; IR(KBr, ν_{max}) = 1605, 3448–3550 cm^{-1}; EI-MS (70 eV, *m/e*, M^+): 248; Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.53; H, 4.88; N, 11.04.
Data for **6**: mp 113 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) [δ/ppm] δ 3.76 (s, 3H, N-Me), 7.20–8.06 (m, 7H, Ar-H), 8.34 (d, 1H, C4-H, J = 8.0 Hz); IR(KBr, ν_{max}) = 1034, 1596 cm^{-1}; EI-MS (70 eV, *m/e*, M^+): 266, 268; Anal. Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 71.87; H, 4.30; N, 10.31.
Data for **1**: mp 132–133 °C, IR(KBr, ν_{max}) = 1610, 1585, 710 cm^{-1}. The ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 400 MHz) [δ/ppm] were identical with those published in Ref. 1.
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