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A photochemical route to synthesize cryptosanguinolentine

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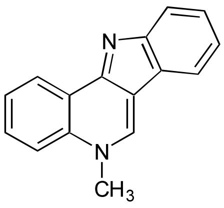
Abstract—A synthesis of an indoloquinoline based alkaloid, isolated from *Cryptolepis sanguinolenta* is reported. The formation of a Schiff base between aniline and indole-3-carbaldehyde and subsequent photochemical transformation afforded the desired alkaloid. © 2002 Elsevier Science Ltd. All rights reserved.

Cryptosanguinolentine **1**, an indoloquinoline alkaloid, was isolated from a West African plant *Cryptolepis sanguinolenta*.[1] Recent years have witnessed increased interest in the total synthesis of various types of heteroaromatic alkaloids, mainly due to their potential in medical treatment.[2,3] These alkaloids may intercalate in the DNA double helix resulting in dramatic changes in DNA conformation and furthermore, can also inhibit DNA replication and transcription.[4]



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Our program of synthesis of heteroannelated acridines, in particular the indoloacridines[5] by photochemical routes[6,7] prompted us to develop a total synthesis of the indoloquinoline alkaloid **1** using the same technique. With an angularly fused annelation pattern, cryptosanguinolentine **1** is an indolo[3,2-*c*]quinoline derivative. Compounds of these types have been prepared by intramolecular reaction of iminophosphorane with isocyanate,[8,9] by the regioselective thermocyclization of the corresponding azide[10] or by an *ortho*-metalation-cross coupling strategy.[11]

Herein we report our investigations which have resulted in a three-step, convenient total synthesis of cryptosanguinolentine via a photo-induced cyclization (Scheme 1).[12] The reaction of indole-3-carbaldehyde **2** with aniline **3** in glacial acetic acid for 3 h afforded the Schiff base **4**. Compound **4** having a 1,3,5-hexatriene system would be expected to undergo a photo-induced cyclization, to give a cyclohexadiene system,[13,14] via initial photo-isomerization of the *E*- to the *Z*-isomer, in which the S_1 state undergoes orbital symmetry controlled conrotatory ring closure to give the cyclohexadiene system. Dihydro intermediates of this type are known[15,16] to be sensitive to traces of oxygen. Hence, in the presence of oxidizing agents like iodine, they readily undergo loss of the allylic hydrogens to give the corresponding aromatized dehydro product **6**. Reaction of **6** with dimethyl sulfate in acetonitrile was found to be regioselective for the quinoline nitrogen.[17] After purification, the methylated product **1** proved to be spectroscopically identical (^{1}H NMR, ^{13}C NMR) with that isolated from *C. sanguinolenta*.[1]

In conclusion, we have developed an easy three-step synthesis of cryptosanguinolentine, using a photo-induced cyclization in excellent yields, which will enable a biological evaluation.

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Keywords: aniline; indole-3-carbaldehyde; photo-induced cyclization; cryptosanguinolentine.

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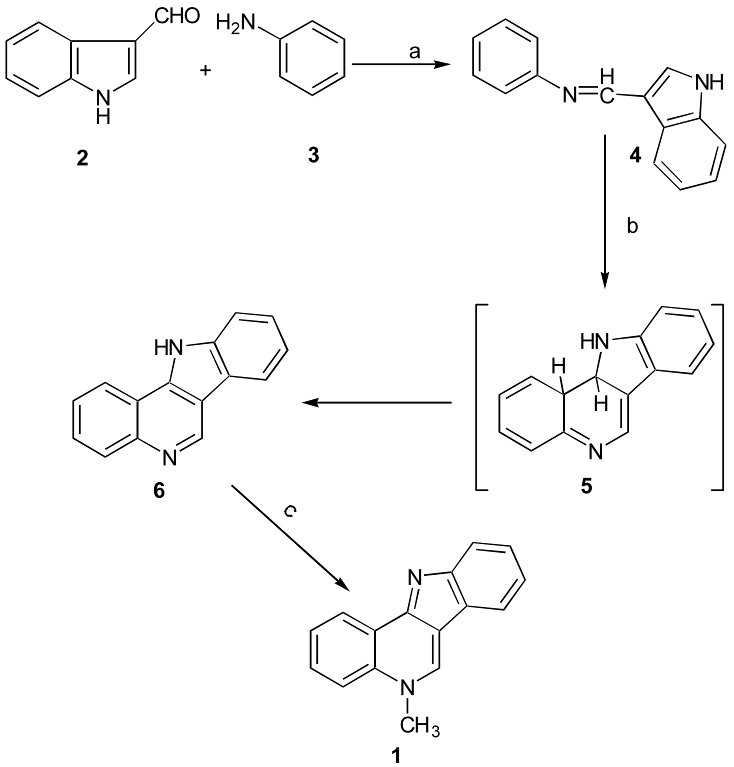

Scheme 1. (a) Glacial acetic acid, reflux, 117°C, 3 h, 85%, (b) *hν*, 253.7 nm, rt, 2:1 (C_6H_6/MeOH), I_2, 48 h, 67%, (c) Me_2SO_4, CH_3CN, reflux, 6 h, K_2CO_3, 83%.

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12. Data for **4**: mp 165°C, ^{1}H NMR ($CDCl_3$, 400 MHz) [δ/ppm] δ 8.9 (1H, indole-NH, bs), 8.3 (1H, C$\underline{H}$–NH, s), 7.2–7.7 (10H, Ar-H and N=C$\underline{H}$, m); IR (KBr, ν_{max}) = 1590, 3300 cm^{-1}; MS (70 eV, *m*/*e*, *M*$^+$): 220; Anal. Found: C, 81.67; H, 5.41; N, 12.74. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.89.

    Data for **6**: decomp. >220°C, ^{1}H NMR ($CDCl_3$, 400 MHz) [δ/ppm] δ 12.80 (1H, –NH, s), 7.3–8.5 (9H, Ar-H, m); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) [δ/ppm] δ 143.6, 138.8, 137.5, 128.6, 128.1, 125.3, 124.9, 122.3, 121.7, 119.8, 119.3, 111.8; IR(KBr, ν_{max}) = 3330, 1570, 1605; MS (70 eV, *m*/*e*, *M*$^+$): 218; Anal. Found: C, 82.41; H, 4.51; N, 12.79. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84.

    Data for **1**: mp 131–133°C, IR(KBr, ν_{max}) = 1610, 1585, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) [δ/ppm] were identical with those published in Ref. 1.
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