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AN IMPROVED SYNTHESIS OF NEOCRYPTOLEPINE

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The plant *Cryptolepis sanguinolenta* has been used in traditional West African medicine (Ghana, Congo) for the treatment of various disorders such as malaria, infections of the respiratory, urogenital and urinary tracts, colic, and rheumatism. For this reason, many research workers have focused on the isolation and identification of the active compounds in this plant, which include complex molecules such as 1 and 7a.¹⁻³ One of these, neocryptolepine, also named cryptotackieine (7a), has considerable structural resemblance to the highly potent alkaloid ellipticine (2), and also shows significant antitumor activity. Interestingly, neocryptolepine displays a strong antiplasmodial activity against *Plasmodium falciparum* D-6 (chloroquine-sensitive strain), K-1, and W-2 (chloroquine-resistant strains).⁴⁻⁶

The first synthesis of **7a** was achieved 40 years before its identification as a natural product.⁷ Since then, several syntheses of the alkaloid have been described; however, they all suffer from either low overall yields or lengthy and complicated synthetic routes.^{6, 8-12} Herein, we present a short and highly efficient synthesis of **7a** from the readily available precursor 2-chloroindole-3-formylindole (**3a**).



Fig. 1

Stoess and collaborators have described a two-step synthesis of the basic structure indolo[2,3-b]quinoline (5a) starting from the easily available compound 3a via the indole (4a) (by refluxing 3a with aniline.) The anilinoaldehyde 4a was subsequently heated at 255°C giving the indolo[2,3-b]quinoline (5a) (Scheme 1).¹³



If **3a** and **3b** respectively were heated at reflux in neat *N*-methylaniline (5 equivalents) instead of aniline, for 15 minutes to 2 h depending on the substituent at the carbonyl group, a nucleophilic substitution and subsequent intramolecular cyclization led to the hydrochloride salts of **7a** and **7b** which were isolated; subsequent treatment with sodium bicarbonate released **7a** and **7b** in good yields (50-75%). However, this reaction could not be extended to the 3-benzoyl derivative (**3c**) as attempted cyclization of **3c** failed. Running the reaction of **3a** for 3 h with a larger excess of *N*-methylaniline (10 equivalents) to increase the solubility, gave the parent compound **5a** in 82% yield instead of **7a** (*i.e.* a demethylation had taken place) in 82% yield. Heating of isolated **6a** with *N*-methylaniline also resulted in demethylation to afford **5a**. (*Scheme 2*)

In summary, we have presented an improved synthesis of the alkaloid neocryptolepine (7a) with the yield of 75% from the easily available indole 3a. This is a considerably simpler and more efficient method than the syntheses previously described for 7a.



Reagents and conditions: i) N-methylaniline (10 eq.), rx, 4 h; ii) N-methylaniline (5 eq.), rx. 0.25 h (3a), or rx. 2 h (3b); iii) N-methylaniline, rx, 3 h; iv) aq. NaHCO₃ (sat.), 25°C, 1 h

Scheme 2

EXPERIMENTAL SECTION

Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. 1 H NMR spectra were recorded on a Brucker 300 MHz in DMSO-d₆ as solvent both and internal standard. The IR spectra were recorded on an Avantar 330 FT-IR ThermoNicolet. Solvents were of analytical grade and used as received. 2-Chloroindole-3-formylindole,¹⁴ 3-acetyl-2-chloroindole¹⁵ and 3-benzoyl-2-chloroindole¹⁵ were prepared as described in the literature.

General Procedure. Synthesis of 5-methylindolo[2,3-b]quinolines (7a and 7b).-

N-Methylaniline (10.71 g, 100 mmol) and 2-chloro-3-formylindole (**3a**) (3.59 g; 20 mmol) were heated at reflux for 15 min. Thereafter the reaction mixture was allowed to cool to room temperature. The yellow solid thus formed was collected, washed with 2-propanol and dried to afford 4.10 g (76%) of neocryptolepine•HCl (**6a**), mp 290-291°C.

¹H NMR: δ 14.39 (bs, 1H), 9.68 (s, 1H), 8.43-8.38 (m, 3H), 8.15 (t, 1H), 7.88-7.69 (m, 3H), 7.51 (t, 1H) and 4.56 (s, 3H). ¹³C NMR: δ 147.9, 140.6, 135.9, 135.5, 133.3, 130.8, 130.1, 125.8, 123.2, 122.9, 122.4, 122.1, 120.1, 116.8, 112.9 and 36.9. IR (neat): 3016, 2560, 1644, 1613, 1502, 767 and 744 cm⁻¹.

Stirring of **6a** (2.68g; 10mmol) with 25 mL of saturated aqueous NaHCO₃ for 1 h at room temperature gave a yellow solid which was collected, washed with water and dried to yield 2.29 g (99%) of neocryptolepine (**7a**), mp. 108-109°C, *lit.*⁷ mp. 108-110°C. ¹H NMR: δ 8.98 (s, 1H), 8.16 (m, 2H), 8.01 (d, 1H), 7.86 (t, 1H), 7.59 (d, 1H), 7.55-7.48 (m, 2H), 7.18 (t, 1H) and 4.33 (s, 1H). The spectral data were in agreement with those published.¹²

The related molecule, 5,11-dimethylindolo[2,3-*b*]quinoline (**7b**), was prepared similarly (reaction time 2 h) in 50% yield, mp 222-223°C, *lit.*⁴ mp 222-223°C. ¹H NMR: δ 8.34 (d, 1H), 8.22 (d, 1H), 8.98 (d, 1H), 7.87 (t, 1H), 7.60-7.45 (m, 3H), 7.20 (t, 1H), 4.28 (s, 3H) and 3.12 (s, 3H). The spectral data were in agreement with those published.¹⁶

Synthesis of Indolo[2,3-b]quinoline (5a). Method A.- A mixture of 3a (0.89 g; 5.0 mmol) and *N*-methylaniline (5.36 g; 50 mmol) was heated at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and the white solid thus formed was collected, washed with cold ethanol and dried to yield 0.89 g (82%) of 5a, mp. 346-347°C, *lit.*¹⁷ mp. 347-348°C.

Method B.- *N*-Methylaniline (2 mL) and **6a** (268 mg; 1.0 mmol) were heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and 5 mL of ethanol was added. The white solid which precipitated was collected, washed with ethanol and dried to yield 165 mg (76%) of **5a**, mp. 346-347°C, *lit.*¹⁷ mp. 347-348°C. ¹H NMR: δ 11.69 (s, 1H), 9.04 (s, 1H), 8.26 (d, 1H), 8.10 (d, 1H), 7.98 (d, 1H), 7.71 (t, 1H), 7.54-7.45 (m, 3H) and 7.26 (t, 1H). The spectral data were in agreement with those published.¹²

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