

Formal Total Synthesis of the Alkaloid Cryptotackieine (Neocryptolepine)

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A straightforward synthesis of quinindoline (**4**), the immediate chemical precursor of the alkaloid cryptotackieine (neocryptolepine) (**1**), is described.

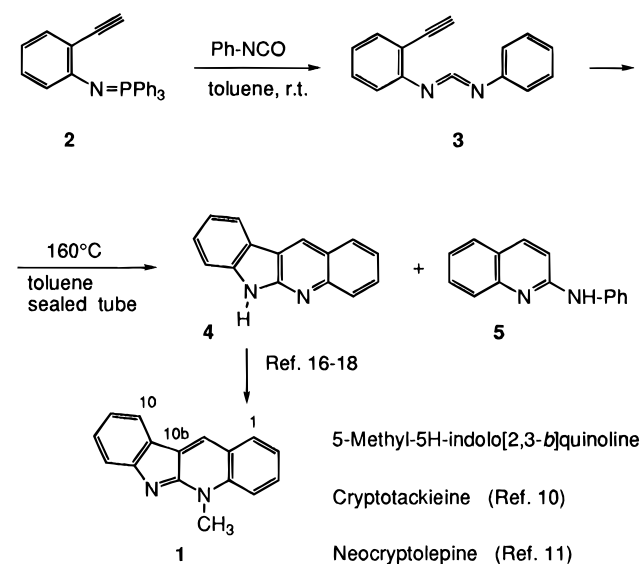
The roots of the West African plant *Cryptolepis sanguinolenta* have been traditionally used by the Ghanaian healers to treat a variety of health disorders including malaria,¹ and since 1974 a decoction of this plant has been used in the clinical therapy of rheumatism, urinary tract infections, malaria, and other diseases.^{1,2} This plant has proved to be a rich source of indoloquinoline alkaloids isolated through the efforts of several research groups.^{3–9} Quite recently, two of these teams described,^{10,11} independently, the isolation, from the extracts of *C. sanguinolenta*, of a new alkaloid 5-methyl-5H-indolo[2,3-*b*]quinoline (**1**), which was given the name of cryptotackieine by the Schiff group¹⁰ and neocryptolepine by the Pieters group;¹¹ this is not the only case of dual naming of an alkaloid isolated from this plant.¹² Both groups based the structural determination of **1** on spectroscopic methods, basically on two-dimensional NMR techniques.

In the course of a study on the pericyclic reactivity of C=C-conjugated carbodiimides, we gained experience in the preparation of derivatives of the indolo[2,3-*b*]quinoline ring system,^{13–15} and here we report the application of that methodology to the synthesis of the alkaloid **1**.

The aza-Wittig-type reaction of the iminophosphorane **2**¹⁴ with phenyl isocyanate in toluene led to triphenylphosphine oxide and the carbodiimide **3**. This was submitted without further purification to thermal treatment, giving rise to quinindoline **4** in 19% overall yield and 2-anilinoquinoline **5** (40%) (Scheme 1). After a first unsuccessful attempt to methylate the quinoline nitrogen of **4** (CH₃I, benzene, reflux), we performed a literature search for more specific conditions to achieve this transformation. To our surprise, we found that the methylation and subsequent deprotonation of quinindoline (Me₂SO₄, nitrobenzene, 160 °C, 1 h, then aqueous NaOH) was already described,^{16–19} and so the alkaloid **1** was in fact a known compound. Because of this, our preparation of quinindoline **4** is a straightforward formal total synthesis of cryptotackieine (neocryptolepine).

Nevertheless, we carried out the transformation **4** → **1** under the above-mentioned conditions, and with **1** in hand we recorded its ¹³C NMR spectrum. We observed some discrepancies between the ¹³C chemical shifts reported for the two alkaloids of assigned structure **1** that could hardly be attributed to the different deuterated solvents used in the respective NMR experiments (DMSO-*d*₆ for cryptotackieine¹⁰ and CDCl₃ for neocryp-

Scheme 1



tolepine¹¹). When our ¹³C NMR data for synthetic **1** in both solvents were compared with the reported ones, only minor deviations in relation to neocryptolepine were detected: $\Delta\delta \leq 0.4$ ppm for all carbon atoms in CDCl₃, with most signals being coincident. The differences with respect to cryptotackieine were more pronounced, $\Delta\delta \leq 1.5$ ppm in DMSO-*d*₆ with a mean deviation of 0.95 ppm. We obtained a value of 126.8 ppm for C-10b, which is notably different from the reported value of 119.7 ppm for cryptotackieine.¹⁰ High-resolution proton spectra of cryptotackieine, neocryptolepine, and synthetic **1** were basically identical. We conclude that these three compounds are the same, and the above-cited deviations from the reported ¹³C NMR chemical shifts of cryptotackieine may be due to the low concentration in natural sample used in that ¹³C NMR experiment.¹⁰

Experimental Section

Preparation of Quinindoline (4). To a solution of 2-ethynyl-1-[(triphenylphosphoranylidene)amino]benzene (**2**) (1.13 g, 3 mmol) in 10 mL of dry toluene was added phenyl isocyanate (0.36 g, 3 mmol). The reaction mixture was stirred at room temperature for 15 min and then heated in a sealed tube at 160 °C for 10 h. After the mixture was cooled to room temperature for 4 h quinindoline (**4**) (0.13 g, 19%) precipitated as a crystalline solid that was isolated by filtration and recrystallized from toluene as yellow prisms, mp 342–346 °C (lit.¹⁶ mp 346 °C). The toluene from the reaction mother

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liquors was removed under reduced pressure, and the residual material was chromatographed on a silica gel column using *n*-hexane/ethyl acetate (4:1, v/v) as eluent to yield 2-anilinoquinoline¹⁴ (**5**) (0.26 g, 40%).

Quinindoline (**4**) was transformed into 5-methyl-5*H*-indolo[2,3-*b*]quinoline (**1**) following the reported procedure.¹⁶

Selected spectral data of compound **1**: ¹³C NMR (CDCl₃, 75 MHz) δ 156.3 (C-5a), 155.6 (C-6a), 137.0 (C-4a), 130.4 (C-3), 129.9 (C-1), 129.3 (C-8), 128.2 (C-10b), 128.0 (C-11), 124.0 (C-10a), 121.9 (C-1), 121.0 (C-10), 120.8 (C-11a), 119.9 (C-9), 117.7 (C-7), 114.1 (C-4), 33.0 (NCH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 155.2 (C-5a), 155.1 (C-6a), 136.5 (C-4a), 130.5 (C-3), 129.8 (C-1), 128.8 (C-11), 128.6 (C-8), 126.8 (C-10b), 123.7 (C-10a), 121.7 (C-2), 121.3 (C-10), 120.1 (C-11a), 119.1 (C-9), 117.0 (C-7), 114.7 (C-4), 32.6 (NCH₃).

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