Formal Total Synthesis of the Alkaloid Cryptotackieine (Neocryptolepine)

Mateo Alajarín,* Pedro Molina, and Angel Vidal

Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, E-30071 Murcia, Spain

Received March 17, 1997[⊗]

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

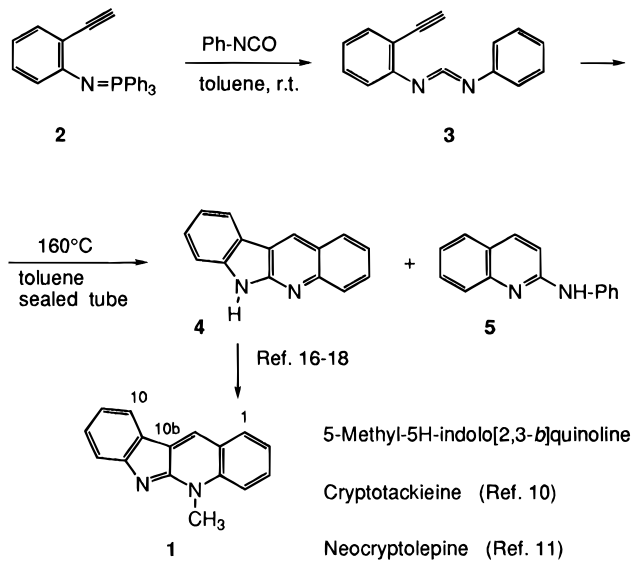
The roots of the West African plant *Cryptolepis sanguinolenta* have been traditionally used by the Ghanaian healers to treat a variety of health disorders including malaria,[1] and since 1974 a decoction of this plant has been used in the clinical therapy of rheumatism, urinary tract infections, malaria, 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 group[10] 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** (CH_3I, 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 (Me_2SO_4, 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 ^{13}C NMR spectrum. We observed some discrepancies between the ^{13}C 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 cryptotackieine[10] and $CDCl_3$ for neocryptolepine[11]). When our ^{13}C 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 $CDCl_3$, 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 ^{13}C NMR chemical shifts of cryptotackieine may be due to the low concentration in natural sample used in that ^{13}C NMR experiment.[10]

Scheme 1



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

* To whom correspondence should be addressed. Tel.: (+ 34 68) 30 71 00, ext 2253. Fax: (+ 34 68) 36 41 49. E-mail: alajarin@fcu.um.es.
⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

S0163-3864(97)00177-8 CCC: $14.00

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-anilinoquinoline[14] (**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**: ^{13}C NMR ($CDCl_3$, 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 (NCH_3); ^{13}C 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 (NCH_3).

Acknowledgment. We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (Project No. PB95-1019). Many thanks are also given to Francisco Baño Piñero for his help in the preparation of 2-ethynylaniline.

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NP970177F