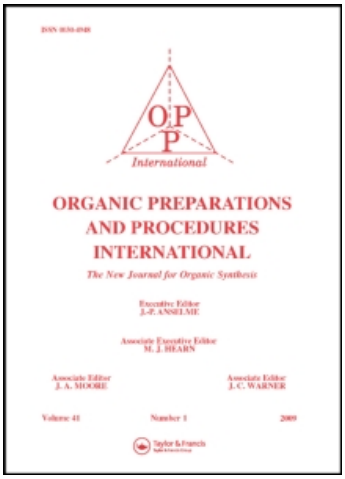


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF NEOCRYPTOLEPINE

Robert Engqvist[a]; Jan Bergman[a]
[a] Unit for Organic Chemistry, CNT, Department of Biosciences at Novum Karolinska Institute, Novum Research Park and Södertörn University College, Huddinge, SWEDEN

To cite this Article Engqvist, Robert and Bergman, Jan(2004) 'AN IMPROVED SYNTHESIS OF NEOCRYPTOLEPINE', Organic Preparations and Procedures International, 36: 4, 386 — 390
To link to this Article: DOI: 10.1080/00304940409458686
URL: http://dx.doi.org/10.1080/00304940409458686

3. (a) M. E. Jung, and L. M. Zeng, *Tetrahedron Lett.*, **24**, 4533 (1983). (b) T. Imamato, H. Yokoyama, and M. Yokoyama, *Tetrahedron Lett.*, **22**, 1803 (1981). (c) T. Kamijo, H. Harada, and K. Lizuka, *Chem. Pharm. Bull*, **32**, 2560 (1984).

4. (a) S. G. Pai, A. R. Bajpai, A. B. Desphande, and S. D. Samant, *Synth. Commun.*, **27**, 379 (1997). (b) H. M. Meshram, *Synth. Commun.*, **27**, 379 (1997).

5. (a) H. Kath, R. Glaser, and J. Wietkam, *J. Chem. Eng. Technol.*, **24**, 2 (2001). (b) M. A. Cambor, A. Corma, and U. P. Garquimica, *J.Catal.*, **177**, 267 (1988).

6. S. Chandrasekhar, and K. Gopalaiah, *Tetrahedron Lett.*, **44**, 756 (2003).

7. S. Chandrasekhar, and K. Gopalaiah, *Tetrahedron Lett.*, **43**, 2455 (2002).

8. S. Kobayashi, *Eur. J. Org. Chem.*, 15 (**1999**). (b) S. Kobayashi, *Synlett*, 689 (**1994**).

9. J. K. Chakraborti, and T. M. Hotten, *J. Chem. Soc., Chem. Commun.*, 1226 (**1972**).

10. (a) *Dictonary of Organic Compounds*, 6 th Ed. Chapman & Hall, New York (b) D. R. Lide, and G. W. A. Milne, *Handbook of Data on Common Organic Compounds*, CRC Press, London.

****

AN IMPROVED SYNTHESIS OF NEOCRYPTOLEPINE

Submitted by (06/08/04) Robert Engqvist and Jan Bergman*

Unit for Organic Chemistry, CNT, Department of Biosciences at Novum
Karolinska Institute, Novum Research Park
and
Södertörn University College, SE-141 57 Huddinge, SWEDEN
**e-mail: jabe@cnt.ki.se*

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 ellip-

ticine (**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**).

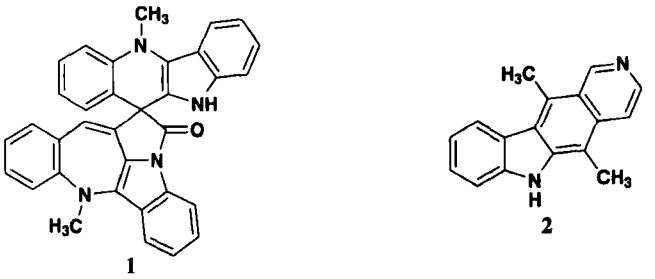
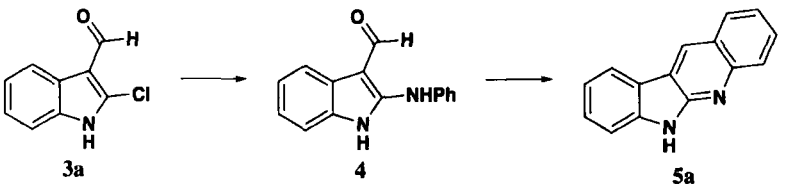


Fig. 1

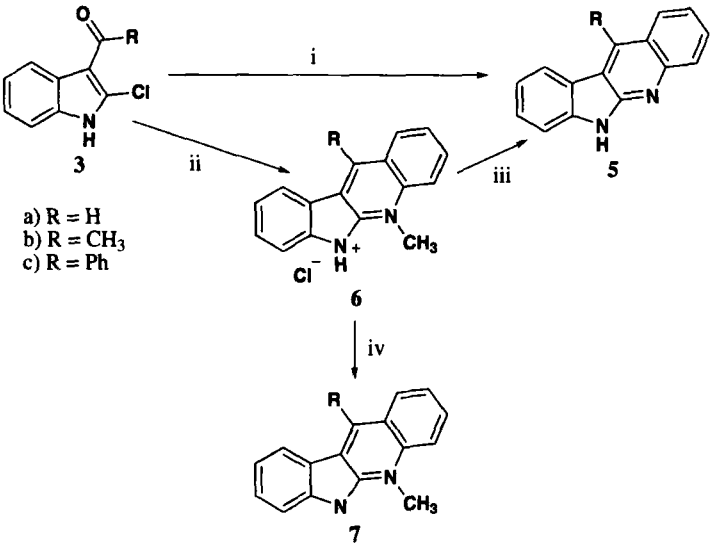
Stoess and collaborators have described a two-step synthesis of the basic structure indolo[2,3-*b*]quinoline (**5a**) starting from the easily available compound **3a** *via* the indole (**4a**) (by refluxing **3a** with aniline.) The anilinoaldehyde **4a** was subsequently heated at 255°C giving the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



Scheme 1

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. $NaHCO_3$ (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-d_6 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-chloroindole[15] and 3-benzoyl-2-chloroindole[15] 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.

^{1}H 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). ^{13}C 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 $NaHCO_3$ 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. ^{1}H 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. ^{1}H 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. ^{1}H 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]

REFERENCES

1. M. H. M. Sharaf, P. L. Schiff Jr., A. N. Tackie, C. H. Phoebe Jr., and G. E. Martin, *J. Heterocyclic Chem.*, **33**, 239 (1996).

2. M. H. M. Sharaf, P. L. Schiff Jr., A. N. Tackie, C. H. Phoebe Jr., R. L. Johnson, D. Minick, C. W. Andrews, R. C. Crouch, and G. E. Martin, *J. Heterocyclic Chem.*, **33**, 789 (1996).

3. K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys, and A. Vlietnick, *Tetrahedron Lett.*, **37**, 1703 (1996).

4. W. Peczynska-Czoch, F. Pognan, L. Kaczmarek, and J. Boratynski, *J. Med. Chem.*, **37**, 3503 (1994).

5. K. Cimanga, T. De Bruyne, L. Pieters, and A. Vlietnick, *J. Nat. Prod.*, **60**, 688 (1997).

6. T. H. M. Jonckers, S. Van Miert, K. Cimanga, C. Bailly, P. Colson, M-C. De Pauw-Gillet, H. van den Heuvel, M. Claeys, F. Lemiere, E. L. Esmans, J. Rozenski, L. Quirijnen, L. Maes, R. Dommisse, G. L. Lemiere, A. Vlietinck, and L. Pieters, *J. Med. Chem.*, **45**, 3497 (2002).

7. S. J. Holt, and V. Petrow, *J. Chem. Soc.*, 922 (1948).

8. M. Alajarn, P. Molina, and A. Vidal, *J. Nat. Prod.*, **60**, 747 (1997).

9. G. Timari, T. Soos, and G. Hajos, *Synlett*, 1067 (1997).

10. C. Shi, Q. Zhang, and K. K. Wang, *J. Org. Chem.*, **64**, 925 (1999).

11. P. M. Fresneda, P. Molina, and S. Delgado, *Tetrahedron,* **57**, 6197 (2001).

12. T-L. Ho, and D-G. Jou, *Helv. Chim. Acta,* **85**, 3823 (2002).

13. K. E. Schulte, J. Reisch, and U. Stoess, *Arch. Pharm.,* **305**, 523 (1972).

14. H. Showalter, A. Sercel, B. Leja, C. Wolfangel, L. Ambroso, W. Elliott, D. Fry, A. Kraker, C. Howard, G. Lu, C. Moore, J. Nelson, B. Roberts, P. Vincent, W. Denny, and A. Thompson, *J. Med. Chem.,* **40**, 413 (1993).

15. A. Monge, J. Palop, C. Ramirez, M. Font, and E. Fernandez-Alvarez, *Eur. J. Med. Chem.,* **26**, 179 (1991).

16. L. Kaczmarek, R. Balicki, P. Nantka-Namirski, W. Peczy´nska-Czoch, and M. Mordarski, *Arch. Pharm. (Weinheim),* **321**, 463 (1988).

17. J. Bergman, R. Engqvist, C. Stålhandske, and H. Wallberg, *Tetrahedron,* **57**, 1033 (2003).