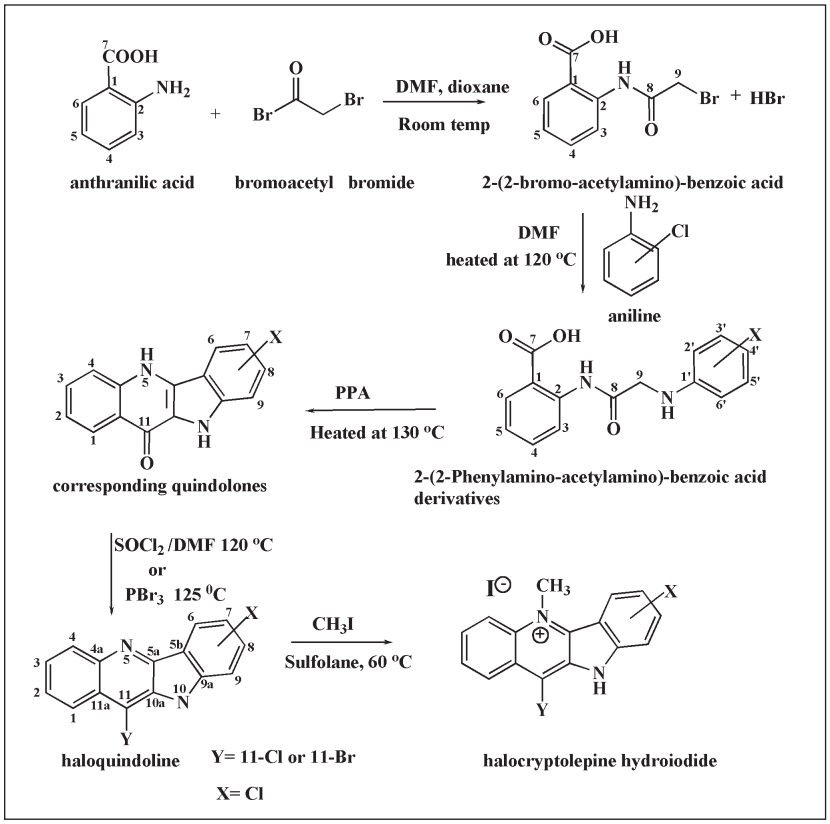
Srinivas Reddy Gouni, S. Carrington, and C. W. Wright

School of Pharmacy, University of Bradford, Bradford, BD7 1DP, UK

Received February 22, 2005



Cryptolepine (5-*N*-methyl-10-*H*-indolo[3,2-*b*]quinoline) is an indoloquinoline alkaloid present in the roots of *Cryptolepis Sanguinolenta*. In its hydrochloride form the alkaloid presents a number of bioactivities. The alkaloid also has cytotoxic properties that are likely to be due to its abilities to intercalate into DNA and inhibit the enzyme topoisomerase II, as well as the synthesis of DNA. In this research project five novel analogues of cryptolepine were chosen for synthesis.

J. Heterocyclic Chem., **43**, 171 (2006).

Introduction.

Cryptolepine is (5-*N*-methyl-10*H*-indolo[3,2-*b*]quinoline) (Figure 1), is an indoloquinoline alkaloid obtained from *Cryptolepis Sanguinolenta*, a member of the Asclepiadaceae family and the Periplocaceae subfamily, is a shrub indigenous to tropical West Africa. Cryptolepine and its derivatives present a large spectrum of biological activities which include antimicrobial, antibacterial, anti-inflammatory, antihypertensive, antipyretic, antimuscarinic, antithrombotic, noradrenergic receptor antagonistic and vasodilative properties [1]. Cryptolepine also possesses significant antiplasmodial activity [2] and as the major alkaloid of the plant, is a cytotoxic DNA intercalator that has promise as an anticancer agent [3]. Cryptolepine is a rare example of a natural product where synthesis was reported prior to its isolation from nature. It was first synthesized in 1906 by Fichter and co-

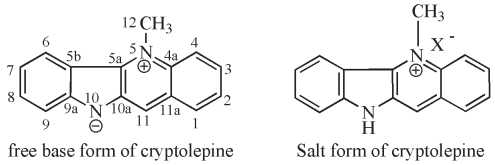


Figure 1. Various forms of Cryptolepine.

workers and its isolation was first reported by Clinquart in 1929 from *Cryptolepis Triangularis* [1,4,5]. As cryptolepine possesses a number of biological activities many analogues have been synthesized to identify its pharmacophoric groups. The structure of cryptolepine was also modified in order to enhance its potency [6]. Results of various experiments reveal that the alkaloid tightly binds to DNA and behaves as a typical intercalating agent. It stabilizes topoisomerase

II- DNA covalent complexes and stimulates the cutting of DNA at pre-existing topoisomerase II-DNA cleavage sites hence acts as a topoisomerase II poison. The drug blocks the cell cycle in the G2 or M phases. The alkaloid is more potent at inhibiting DNA synthesis rather than RNA and protein synthesis [7]. Wright *et al*. [2], synthesized various mono- and di-halogenated cryptolepine analogues and tested these for antiplasmodial and cytotoxic activities. Among these compounds, 2,7-dibromocryptolepine, 6,7- difluoro-cryptolepines showed promising *in vivo* antimalarial activity. The analogue 8,11-dichlorocryptolepine was 5 fold more active than cryptolepine as a cytotoxic agent and these dihalogenated cryptolepine analogues are important leads in the search for novel potent antitumor compounds [2].

Based on the cytotoxicity activity results of 11-halocryptolepine analogues synthesized by Wright *et al*. [2], various 11-substituted mono and dihalogenated analogues of cryptolepine were chosen for synthesis in an attempt to produce these previously untested compounds. These lead structures will be of great interest in the development of synthetic anti-cancer drugs.

Results and Discussion.

A series of 11-substituted quindoline and cryptolepine analogues were prepared by [2,8,9] using similar reaction schemes but with slight modifications, according to the intermediates required. The general reaction scheme involves the following five steps (Figure 2).

Setback of *N-5* Alkylation with Methyl Iodide.

These halogenated cryptolepines were identified by the presence of a single *N*-CH_3 peak between 5.01-5.05 ppm in the ^{1}H-NMR spectrum. This confirms that the methylation of the mono or disubstituted quindolines worked to yield the corresponding bromoderivatives. This led to the conclusion that despite the literature evidence, methyl iodide was not good for *N*-5 alkylation of 11-bromoquindolines. The possible reason for this setback is the activation of an aromatic nucleophilic substitution (SNAr). A bromoquindoline should quaternize easily with methyl iodide; this quaternization increases considerably the leaving ability of the 11-bromine toward nucleophiles [10]. One more reason is that the effect of aprotic solvent like sulfolane, which strongly interacts with cations and do not solvate or stabilize the anions well. Hence the cation-anion association in these solvents is little and this further increases the reactivity of iodide anions [11]. The best way to solve this setback would be to use methylating agents with poor nucleophile-character leaving groups such as methyltriflate, methyl methanesulfonate or dimethylsulfate [9] in a polar solvent like methanol or the Eschweiler-Clarke procedure for alkylation of amines with formaldehyde-formic acid [12].

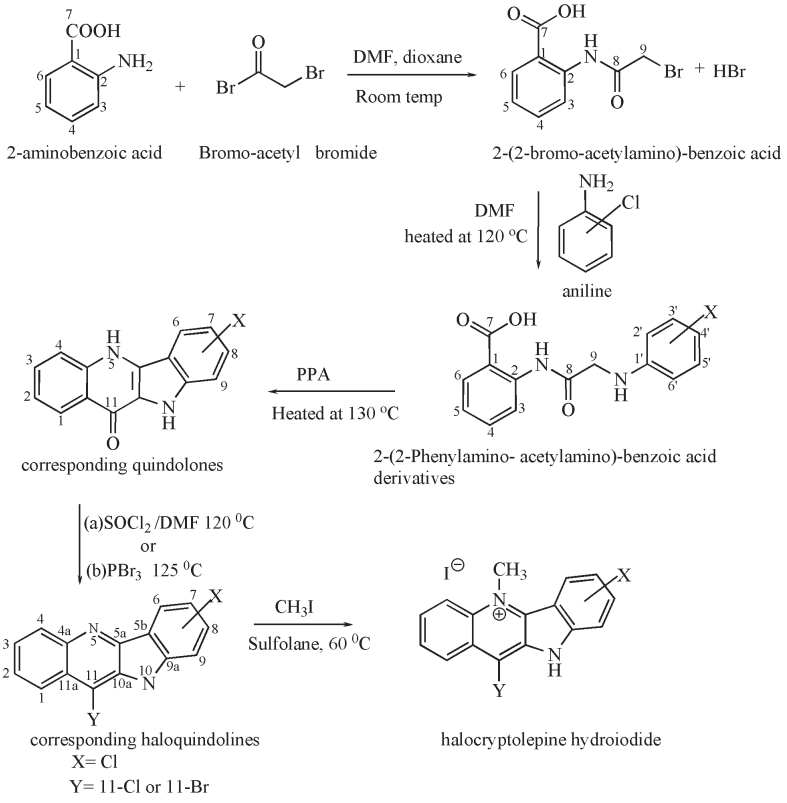


Figure 2. The General Reaction Scheme.

EXPERIMENTAL

Chemicals and Reagents.

The chemicals and reagents were purchased from either Sigma-Aldrich (UK), Lancaster (UK) or BDH (UK) unless otherwise stated. All solvents were of either HPLC or laboratory grade, double distilled water was used to prepare aqueous solutions.

Thin Layer Chromatography (TLC).

Thin layer chromatography (TLC) was performed on F_{254}, 0.2 mm, 20 x 20 cm, silica gel sheets (Merck). Plates were spotted with substrate and were eluted with appropriate solvent systems, then stained with either $KMnO_4$ (1.5 g $KMnO_4$, 10 g K_2CO_3, 2.5 ml 5 % NaOH, 10 ml H_2O) solutions prepared in the laboratory. The developed plates were first analysed under UV 254 nm then stained with appropriate reagent.

Column Chromatography.

Column chromatography was performed using silica gel with a particle size of 50-70 µm, (BDH) or alumina STD grade CA 150 mesh (Aldrich) by preparing a slurry with the eluent mixture and packing it into the chromatography column. The collected sample fractions were analysed by TLC.

Nuclear Magnetic Resonance Spectroscopy (NMR).

^1H and ^{13}C spectra were acquired on a JEOL GX270 FT NMR spectrometer at 270.05 MHz for ^1H and 67.80 MHz for ^{13}C. The samples were prepared in $CDCl_3$ (deuterated chloroform), CD_3OD (deuterated methanol), or DMSO (deuterated dimethylsulfoxide) using TMS (tetramethylsilane) as the internal standard. Chemical shifts are expressed in δ ppm (parts per million). Coupling constants were measured in hertzs (Hz).

Mass Spectroscopy (MS).

Mass spectra were acquired on an AEI (Associated Electrical Industries Ltd.,) mass spectrometer type- MS 902 which was operated by Mr. Andrew Healy. For accurate mass measurements the samples were sent to university of Newcastle.

Melting Point Determination,

Melting points of different intermediate compounds were determined by using digital melting point apparatus (Electro Thermal IA 9200 series) and are uncorrected.

General Method for the Synthesis of Various Novel Haloginated Cryptolepine Analogues.

The procedure described by [2,8,9] involves five steps (Figure 2). The same procedure was followed for the synthesis of various novel haloginated cryptolepine analogues.

Synthesis of 11-iodocryptolepine (**1e**).

Step I. Synthesis of 2-(2-Bromo-acetylamino)-benzoic acid (**1a**)**.**

This compound was prepared according to the general procedure and obtained in 91 % yield; mp 162.8-163.4 °C. This was the common intermediate in step I for all the synthesised novel cryptolepine analogues; ^1H NMR (DMSO-d_6, δ ppm): 4.24 (2H, s, 9-H), 7.18 (1H, t, *J* = 7.9, 5-H), 7.60 (1H, t, *J* = 8.1, 4-H), 8.00 (1H, d, *J* = 7.9, 3-H), 8.45 (1H, d, *J* = 8.3, 6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 39.7 (C-9), 117.6 (C-3), 120.5 (C-1), 123.9 (C-5), 131.6 (C-4), 134.5 (C-6), 140.5 (C-2), 165.5 (C-8), 169.7 (C-7); MS. M/z (relative intensity, %): 257.6 (100) M^+, 241.6 (12), 213.7 (5), 193.0 (95), 142.8 (8).

Step II. Synthesis of 2-(2-Phenylamino-acetylamino)-benzoic acid (**1b**).

This compound was prepared according to the general procedure for **1c** and obtained in 93 % yield; mp 196.7-198.7 °C; ^1H NMR (DMSO-d_6, δ ppm): 3.85 (2H, s, 9-H), 6.62 (1H, t, *J* = 8.1, 4′-H), 7.10 (1H, d, *J* = 5.9, 2′-H/6′-H), 7.15 (1H, d, *J* = 7.1, 3′-H/5′-H), 7.59 (1H, t, *J* = 8.3, 4-H), 7.96 (1H, d, *J* = 7.9, 3-H), 8.76 (1H, d, *J* = 6.9, 6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 40.9 (C-9), 113.0 (C-2′/C-6′), 117.6 (C-3), 116.6 (C-4′), 120.0 (C-1), 123.2 (C-5), 129.5 (C-3′/C-5′), 131.6 (C-4), 134.6 (C-6), 141.1 (C-2), 148.7 (C-10), 169.6 (C-8), 171.4 (C-7); MS M/z (relative intensity, %): 270.8 (100) M^+, 268.9 (4), 142 (1) 106 (1).

Step III. Synthesis of 5,5a,10,10a-Tetrahydro-indolo[3,2-*b*]-quinolin-11-one (**1c**).

This compound was prepared according to the general procedure for **1d** and obtained in 9 % yield; mp > 300 °C; ^1H NMR (DMSO-d_6, δ ppm): 7.20 (1H, d, *J* = 6.6, 4-H), 7.26 (1H, d, *J* = 7.9, 2-H), 7.32 (^1H, d, *J* = 7.9, 7-H), 7.42-7.54 (1H, m, 8-H), 7.68 (1H, t, *J* = 8.3, 3-H), 7.76 (1H, d, *J* = 8.3, 9-H), 8.22 (1H, d, *J* = 7.9, 6-H/1-H), 8.37 (1H, d, *J* = 8.1, 1-H/6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 113.0 (C-9), 116.0 (C-4), 118.5 (C-2), 119.5 (C-11a), 121.0 (C-5b), 121.5 (C-8), 122.5 (C-6), 125.0 (C-7), 127.0 (C-1), 129.0 (C-5a), 131.0 (C-7), 139.0 (C-10a), 140.0 (C-9a), 168.0 (C-4a), 174.0 (C-11); MS M/z (relative intensity, %): 234.1 (100) M^+, 205 (11), 119 (7), 105.1 (68), 28 (12).

Step IV (b). Synthesis of 11-Bromo-10*H*-indolo[3,2-*b*]quinoline (**1d**).

This compound was prepared according to the general procedure for **1e** and obtained in 60 % yield; mp 118.4-199.6 °C; ^1H NMR (DMSO-d_6, δ ppm): 7.38 (1H, t, *J* = 8.1, 7-H), 7.69 (1H, t, *J* = 8.1, 8-H), 7.77 (1H, t, *J* = 8.1, 2-H), 7.87 (1H, t, *J* = 8.1, 3-H), 8.01 (1H, d, *J* = 8.1, 9-H), 8.37 (1H, d, *J* = 8.1, 6-H), 8.43 (1H, d, *J* = 8.1, 4-H), 8.58 (1H, d, *J* = 8.1, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 111.5 (C-5b), 118 (C-4), 121 (C-7), 122.5 (C-9), 123.8 (C-2), 124.1 (C-6), 126.5 (C-11a), 127.8 (C-11), 128.8 (C-3), 129.5 (C-1), 130.5 (C-8), 130.8 (C-4a), 131.9 (C-5a), 143.5 (C-10a), 157 (C-9a); MS M/z (relative intensity, %): 296 (100) M^+, 235 (7), 202 (8), 94 (5).

Step V. Synthesis of (**1e**).

This compound was prepared according to the general procedure and obtained in 69 % yield; mp 122.6 °C; ^1H NMR (CD_3OD-d_4, δ ppm): 5.00(3H, S, N-5-CH_3), 7.56 (1H, t, *J* = 8.1, 7-H), 7.89 (1H, t, *J* = 8.1, 8-H), 7.99 (1H, t, *J* = 8.1, 2-H), 8.20 (1H, t, *J* = 8.1, 3-H), 8.52 (1H, d, *J* = 8.1, 9-H), 8.62 (1H, d, *J* = 8.1, 6-H), 8.65 (1H, d, *J* = 8.1, 4-H), 8.71 (1H, d, *J* = 8.1, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 44.9 (C-12), 105.8 (C-11), 111.0 (C-9), 119.6 (C-8), 120.5 (C-6), 121.7 (C-7), 126.5 (C-4), 127.6 (C-5b), 128.3 (C-2), 129.1 (C-11a), 130.3 (C-3), 132.3 (C-1), 133.7 (C-10a), 135.5 (C-9a), 148.3 (C-4a), 152.2 (C-5a); HRMS Found: m/z 357.9967 Calcd for $C_{16}H_{15}N_2I$: M 358.

Anal. Calcd. for $C_{16}H_{15}N_2I$: C, 53.68; H, 4.24; N, 7.82. Found: C, 53.76; H, 4.27; N, 7.93.

Synthesis of 9,11-Dichlorocryptolepine (**2d**).

Step II. Synthesis of 2-[2-(2-Chloro-phenylamino)-acetylamino]-benzoic acid (**2a**).

This compound was prepared according to the general procedure for **2b** and obtained in 92 % yield. This was also the common intermediate for **3b** in Step II; mp 206.7-208.4 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 4.01 (2H, s, 9-H), 6.30 (1H, t, *J* = 5.6, 3′-H), 6.57 (1H, d, *J* = 8.1, 2′-H), 6.66 (1H, t, *J* = 7.5, 4′-H), 7.13 (1H, m, 5′-H), 7.30 (1H, d, *J* = 7.9, 5-H), 7.59 (1H, t, *J* = 8.3, 4-H), 7.96 (1H, d, *J* = 7.9, 3-H), 8.75 (1H, d, *J* = 8.3, 6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 49.1 (C-9), 111.7 (C-2′), 116.5 (C-6′), 118.2 (C-4′), 119.0 (C-3), 120.0 (C-1), 123.3 (C-5), 128.6 (C-3′), 129.6 (C-5′), 131.7 (C-4), 134.7 (C-6), 141.1 (C-2), 144.2 (C-1′), 169.7 (C-8), 170.6 (C-7); MS M/z (relative intensity, %): 304.8 (100) M$^+$, 226.8 (12), 213.7 (7), 142.7 (8), 139.8 (11), 87.8 (11).

Step III. Synthesis of 9-Chloro-5,5a,10,10a-tetrahydro-indolo[3,2-b]quinolin-11-one (**2b**).

This compound was prepared according to the general procedure for **2c** and obtained in 13 % yield. This was also the common intermediate for **3b** in Step III; mp > 300 °C; MS M/z (relative intensity, %): 268.7 (100) M$^+$, 199 (1), 139.8 (5), 121 (1), 100 (1).

Step IV (a). Synthesis of 9,11-Dichloro-10*H*-indolo[3,2-*b*]-quinoline (**2c**).

This compound was prepared according to the general procedure for **2d** and obtained in 31 % yield; mp 106.8- 107.3 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 7.28 (1H, t, *J* = 7.8, 7-H), 7.57 (1H, d, *J* = 7.62, 8-H), 7.65 (1H, t, *J* = 6.8, 2-H), 7.71 (1H, t, *J* = 8.3, 3-H), 8.26 (1H, d, *J* = 8.4, 6-H), 8.31 (1H, d, *J* = 8.3, 4-H), 8.37 (1H, d, *J* = 7.8, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 116.8 (C-5b), 120.4 (C-4), 120.8 (C-7), 121.7 (C-9), 122.7 (C-2), 124.1 (C-6), 124.5 (C-11a), 126.7 (C-11), 127.6 (C-3), 129.4 (C-1), 129.6 (C-8), 129.9 (C-4a), 140.1 (C-5a), 145.2 (C-10a), 145.9 (C-9a). MS M/z (relative intensity, %): 286 (100) M$^+$, 253 (12), 215 (25), 188 (6), 142 (12), 125 (12), 64 (5), 28 (4).

Step V. Synthesis of (**2d**).

This compound was prepared according to the general procedure and obtained in 34 % yield; mp 118.4 °C; ^{1}H NMR (CD_3OD-d_4, δ ppm): 5.09 (3H, S, N-5-CH_3), 7.57 (1H, t, *J* = 8.1, 7-H), 7.97 (1H, d, *J* = 8.1, 8-H), 8.03 (1H, t, *J* = 8.1, 2-H), 8.08 (1H, t, *J* = 8.1, 3-H), 8.21 (1H, d, *J* = 8.1, 6-H), 8.75 (1H, d, *J* = 8.1, 4-H), 8.80 (1H, d, *J* = 8.1, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 44.9 (C-12), 116.3 (C-9), 118.6 (C-6), 120.0 (C-8), 121.6 (C-10a), 123.1 (C-7), 124.3 (C-1), 125.0 (C-11a), 125.3 (C-4), 126.3 (C-2), 129.0 (C-5b), 131.8 (C-3), 135.9 (C-9a), 137.8 (C-11), 148.0 (C-4a), 150.3 (C-5a); HRMS Found: m/z 302.0431 Calcd for $C_{16}H_{14}N_2Cl_2$: M 302.

Anal. Calcd. for $C_{16}H_{14}N_2Cl_2$: C, 53.68; H, 4.67; N, 7.82. Found: C, 53.73; H, 4.59; N, 7.88.

Synthesis of 9-Chloro-11-iodocryptolepine (**3b**).

Step IV (b). Synthesis of 11-Bromo-9-chloro-10*H*-indolo[3,2-*b*]-Quinoline (**3a**).

This compound was prepared according to the general procedure for **3b** and obtained in 41 % yield; mp 106.2-107.4 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 7.31(1H, t, *J* = 7.9, 7-H), 7.58 (1H, d, *J* = 7.9, 8-H), 7.65 (^{1}H, t, *J* = 8.1, 2-H), 7.69 (1H, t, *J* = 8.1, 3-H), 8.22 (1H, d, *J* = 8.3, 6-H), 8.28 (1H, d, *J* = 8.1, 4-H), 8.35 (1H, d, *J* = 7.6, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 111.5 (C-5b), 116.8 (C-4), 121 (C-7), 121.7 (C-9), 124.2 (C-2), 125.1 (C-6), 125.7 (C-11a), 126.9 (C-11), 127.6 (C-3), 129.4 (C-1), 129.7 (C-8), 132 (C-4a), 140 (C-5a), 145.1 (C-10a), 145.4 (C-9a) MS M/z (relative intensity, %): 332.1 (100) M$^+$, 251 (10), 215 (22), 166 (13), 107.5 (12), 28 (21).

Step V. Synthesis of (**3b**).

This compound was prepared according to the general procedure and obtained in 90 % yield; mp 113.8 °C; ^{1}H NMR (CD_3OD-d_4, δ ppm): 5.05(3H, S, N-5-CH_3), 7.55(1H, t, *J* = 8.2, 7-H), 8.00 (1H, d, *J* = 7.9, 8-H), 8.02 (1H, t, *J* = 7.8, 2-H), 8.23 (1H, t, *J* = 7.1, 3-H), 8.59 (1H, d, *J* = 8.8, 6-H), 8.66 (1H, d, *J* = 8.8, 4-H), 8.72 (1H, d, *J* = 8.2, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 44.9 (C-12), 105.8 (C-11), 116.3 (C-9), 118.6 (C-6), 120.0 (C-8), 123.1 (C-7), 126.5 (C-4), 128.3 (C-2), 129.0 (C-5b), 129.1 (C11a), 130.6 (C-3), 132.3 (C-1), 133.7 (C-10a), 135.9 (C-9a), 148.3 (C-4a), 152.2 (C-5a); HRMS Found: m/z 391.9577 Calcd for $C_{16}H_{14}N_2ClI$: M 392.

Anal. Calcd. for $C_{16}H_{14}N_2ClI$: C, 53.68; H, 4.67; N, 7.82. Found: C, 53.57; H, 4.72; N, 7.95.

Synthesis of 8-Chloro-11-iodocryptolepine (**4d**).

Step II. Synthesis of 2-[2-(3-Chloro-phenylamino)-acetylamino]-benzoic acid (**4a**).

This compound was prepared according to the general procedure for **4b** and obtained in 80 % yield; mp 201.3-202.6 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 3.94 (2H, s, 9-H), 6.59- 6.60 (1H, m, 2′-H/6′-H), 6.63 (1H, t, *J* = 7.9, 4′-H), 6.70 (1H, d, *J* = 4.1, 3′-H), 7.10 (1H, t, *J* = 8.1, 5-H), 7.57 (1H, t, *J* = 8.1, 4-H), 7.98 (1H, d, *J* = 7.9, 3-H), 8.78 (1H, d, *J* = 8.3, 6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 49.0 (C-9), 111.3 (C-2′), 112.6 (C-6′), 116.5 (C-4′), 117.1 (C-3), 120.0 (C-1), 123.2 (C-5), 131 (C-3′), 131.7 (C-5′), 134.2 (C-4), 134.6 (C-6), 141.1 (C-2), 150.1 (C-1′), 169.8 (C-8), 170.7 (C-7); MS M/z (relative intensity, %): 304.7 (100) M$^+$, 226.8 (2), 213.9 (3), 142.8 (4), 117.8 (2), 87.9 (5).

Step III. Synthesis of 8-Chloro-5,5a,10,10a-tetrahydro-indolo-[3,2-*b*]quinolin-11-one (**4b**).

This compound was prepared according to the general procedure for **4c** and obtained in 13.2 % yield; mp > 300 °C; MS M/z (relative intensity, %): 268.7 (100) M$^+$, 197.8 (2), 139.8 (5), 117.8 (4), 99.9 (5).

Step IV (b). Synthesis of 11-Bromo-8-chloro-10*H*-indolo[3,2-*b*]quinoline (**4c**).

This compound was prepared according to the general procedure for **4d** and obtained in 42 % yield; mp 108.7-109.2 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 6.76 (1H, d, *J* = 9.1, 7-H), 7.38 (1H, d, *J* = 9.1, 9-H/6-H), 7.65 (1H, t, *J* = 7.5, 2-H), 7.79 (1H, t, *J* = 8.9, 3-H), 7.8-7.9 (1H, m, 6-H/9-H), 8.28 (1H, m, *J* = 7.0, 4-H), 8.37 (1H, d, *J* = 8, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 109.6 (C-5b), 111.6 (C-4), 121.7 (C-7), 122.2 (C-9), 123.5 (C-2), 124.7 (C-6), 125.1 (C-11a), 126.8 (C-11), 127 (C-3), 127.1 (C-1), 130.3 (C-4a), 130.5 (C-5a), 144 (C-10a), 145.2 (C-9a); MS M/z (relative intensity, %): 331.9 (100) M$^+$, 251 (11), 215 (22), 165.9 (10), 94.5 (6), 39 (3).

Step V. Synthesis of (**4d**).

This compound was prepared according to the general procedure and obtained in 25% yield; mp 121.7 °C; ^{1}H NMR (CD_3OD-d_4, δ ppm): 5.01(3H, S, N-5-CH_3), 7.53 (1H, dd, *J* = 9,

8.9, 7-H), 7.90 (1H, d, *J* = 8.6, 9-H/6-H), 8.00 (1H, t, *J* = 8.6, 2-H), 8.22 (1H, t, *J* = 7.4, 3-H), 8.60 (1H, d, *J* = 4.6, 6-H/9-H), 8.64 (1H, d, *J* = 4.8, 4-H), 8.70 (1H, d, *J* = 8.8, 1-H); ^{13}C NMR ($CDCl_3$, δ ppm): 44.9 (C-12), 105.8 (C-11), 111.4 (C-9), 121.9 (C-6), 122.1 (C-7), 124.9 (C-8), 125.7 (C-5b), 126.5 (C-4), 128.6 (C-2), 129.1 (C-11a), 130.3 (C-3), 132.3 (C-1), 133.7 (C-10a), 136.9 (C-9a), 148.3 (C-4a), 152.2 (C-5a); HRMS Found: m/z 391.9577 Calcd. for $C_{16}H_{14}N_2ClI$: M 392.

Anal. Calcd. for $C_{16}H_{14}N_2ClI$: C, 53.68; H, 4.67; N, 7.82. Found: C, 53.68; H, 4.77; N, 7.84.

Synthesis of 7-Chloro-11-iodocryptolepine (**5d**).

Step II. Synthesis of 2-[2-(4-Chloro-phenylamino)-acetylamino]-benzoic acid (**5a**).

This compound was prepared according to the general procedure for **5b** and obtained in 88 % yield; mp 215.5-217.8 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 3.89 (2H, s, 9-H), 6.65 (1H, d, *J* = 8.8, 2′-H/6′-H), 7.14 (1H, t, *J* = 8.3, 5-H), 7.47 (1H, s, 3′-H/5′-H), 7.57 (1H, t, *J* = 8.1, 4-H), 7.97 (1H, d, *J* = 7.9, 3-H), 8.77 (1H, d, *J* = 8.3, 6-H); ^{13}C NMR ($CDCl_3$, δ ppm): 114.4 (C-2′/C-6′), 116.5 (C-4′), 120.0 (C-3), 121.0 (C-1), 123.2 (C-5), 129.2 (C-3′/C-5′), 131.7 (C-4), 134.6 (C-6), 141.1 (C-2), 147.6 (C-1′), 169.7 (C-8), 170.9 (C-7); MS M/z (relative intensity, %): 304.8 (100) M$^+$, 226.8 (18), 213.7 (11), 150.7 (3), 142.8 (5), 117.8 (4), 87.8 (25).

Step III. Synthesis of 7-Chloro-5,5a,10,10a-tetrahydro-indolo-[3,2-*b*]quinolin-11-one (**5b**).

This compound was prepared according to the general procedure for **5c** and obtained in 6 % yield; mp > 300 °C; MS M/z (relative intensity, %): 268.7 (100) M$^+$, 139.7 (5), 121 (3), 100 (2), 88 (2).

Step IV (b). Synthesis of 11-Bromo-7-chloro-10*H*-indolo[3,2-*b*]-quinoline (**5c**).

This compound was prepared according to the general procedure for **5d** and obtained in 48 % yield; mp 111.6-113.2 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 7.39 (1H, d, *J* = 8.6, 8-H), 7.49 (1H, t, *J* = 9.1, 2-H), 7.65 (1H, d, *J* = 8.3, 9-H), 7.71 (1H, d, *J* = 8.1, 6-H/1-H), 7.81 (1H, t, *J* =8.1 3-H), 8.19 (1H, d, *J* = 8.1, 6-H/1-H), 8.27 (1H, d, *J* =8, 4-H); ^{13}C NMR ($CDCl_3$, δ ppm): 111.5 (C-5b), 112.4 (C-4), 122.2 (C-7), 123.7 (C-9), 125 (C-2), 125.7 (C-6), 126.5 (C-11a), 126.9 (C-11), 127.4 (C-3), 129.6 (C-1), 130.2 (C-8) 132.7 (C-4a), 134.8 (C-5a), 141.3 (C-10a), 145 (C-9a); MS M/z (relative intensity, %): 332 (100) M$^+$, 251 (12), 215 (28), 166 (9), 94.5 (6), 28 (8).

Step V. Synthesis of (**5d**).

This compound was prepared according to the general procedure and obtained in 33 % yield; mp 124.2 °C; ^{1}H NMR (CD_3OD-d_4, δ ppm): 5.02 (3H, S, N-5-CH_3), 7.87 (1H, d, *J* = 8.3, 8-H), 7.93 (1H, d, *J* = 8.9, 9-H/6-H), 8.02 (1H, t, *J* = 8.3, 2-H), 8.24 (1H, t, *J* = 6.8, 3-H), 8.62 (1H, d, *J* = 8.5 6-H/9-H), 8.64 (1H, d, *J* = 9.1, 4-H/1-H), 8.77 (1H, d, *J* = 8, 1-H/ 4-H); ^{13}C NMR ($CDCl_3$, δ ppm): 44.9 (C-12), 105.8 (C-11), 112.4 (C-9), 120.9 (C-6), 127.0 (C-7), 120.0 (C-8), 129 (C-5b), 126.5 (C-4), 128.6 (C-2), 129.1 (C-11a), 130.3 (C-3), 132.3 (C-1), 133.7 (C-10a), 136.9 (C-9a), 148.3 (C-4a), 152.2 (C-5a); HRMS Found: m/z 391.9577 Calcd for $C_{16}H_{14}N_2ClI$: M 392.

Anal. Calcd. for $C_{16}H_{14}N_2ClI$: C, 53.68; H, 4.67; N, 7.82. Found: C, 53.76; H, 4.71; N, 7.82.

Acknowledgements.

I gratefully acknowledge my supervisors S. Carrington and C. W. Wright.

REFERENCES AND NOTES

[1] D. E. Bierer, D. M. Fort, C. D. Mendez, J. Luo, P. A. Imbach, L. G. Dubenko, S. D. Jolad, R. E. Gerber, J. Litvak, Q. Lu, P. S. Zhang, M. J. Reed, N. Waldeck, R. C. Bruening, B. K. Noamesi, R. F. Hector, T. J. Carlson, S. R. King, *J. Med. Chem.,* **41**, 894 (1998).

[2] C. W. Wright, J. Addae-Kyereme, A. G. Breen, J. E. Brown, M. F. Cox, S. L. Croft, Y. Gokcek, H. Kendrick, R. M. Phillips, P. L. Pollet, *J. Med. Chem.*, **44**, 3187 (2001).

[3] C. Ansah, N. J. Gooderham, *Toxico. Sci.*, **70**, 245 (2002).

[4] Fichter, Boehringer, *Chem. Ber.,* **39**, 3932 (1906).

[5] Clinquart, *Bull. Acad. Rev. Med., Belgium*., **12**, 627 (1929).

[6] G. M. Leroy, P. C. Fan, S. Y. Ablordeppy, *Med. Chem. Res.*, **9**, 118 (1999).

[7] J. N. Lisgarten, M. Coll, J. Portugal, C. W. Wright, J. Aymami, *Nat. Struct. Biol*., **9**, 57 (2002).

[8] M. Yamato, Y. Takeuchi, M. Chang, K. Hashigaki, T. Tsuruo, T. Tashiro, S. Tsukagoshi, *Chem. Pharm. Bull.*, **38**, 3048 (1990).

[9] D. E. Bierer, L. G. Dubenko, P. S. Zhang, Q. Lu, P. A. Imbach, A. W. Garofalo, P. W. Phuan, D. M. Fort, J. Litvak, R. E. Gerber, B. Sloan, J. Luo, R. Cooper, G. M. Reaven, *J. Med. Chem.*, **41**, 2754 (1998).

[10] J. March, Advanced organic chemistry reactions, mechanisms, and structure, John Wiley & Sons, New York, NY, 1992**,** pp 649-650.

[11] J. Miller, Aromatic nucleophilic substitution, Elsevier, New York, NY, 1968, pp 61-136.

[12] M. L. Moore, *Org. Reactions*, **5**, 309 (1949).