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A Synthesis of the Tricyclic Pyrroloquinoline Core of Martinelline

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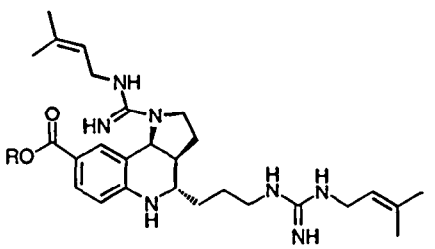
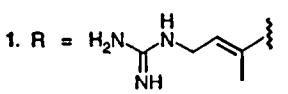
Abstract: Radical cyclisation of the *N*-(2'-iodophenyl)pyrrole-3-carboxamides **5** and **6** gave the tricyclic pyrrolo [3,2-*c*]quinolone ring system found in the recently isolated martinelline **1** and martinellic acid **2**.

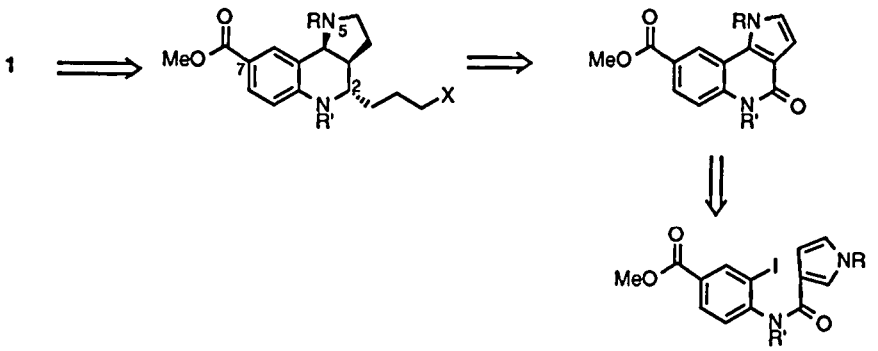
The South American plant *Martinella iquitosenis* has been used as an eye medication by many ethnic groups across the whole of South America. In 1995, a group at Merck reported the isolation of two novel alkaloids from the root of *M. iquitosensis* which they named martinelline **1** and martinellic acid **2**.[1] The Merck group further showed that both compounds but martinelline **1** in particular show bradykinin B_1 and B_2 receptor antagonist activity and martinelline has affinity for a range of other important receptors. Finally, martinelline **1** was demonstrated to possess modest antiobiotic activity against both Gram-positive and Gram-negative bacteria. The tricyclic core of these two new alkaloids, the pyrrolo[3,2-*c*]quinoline system, had not been reported previously in any natural product and coupled with their interesting biological activity, we were attracted to the possibility of total synthesis of these compounds by a flexible route which would allow other analogues to be prepared and tested. No synthetic studies on these alkaloids have been reported.



1. R = 

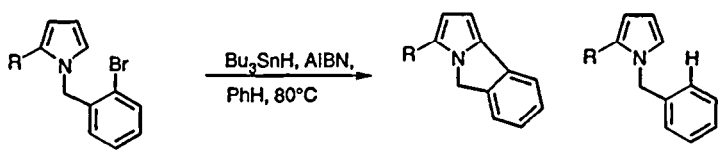
2. R = H

Our synthetic approach to martinelline system is outlined in Scheme 1. Elaboration of the guanidine-containing sidechains at C-2, N-5 and the C-7 carboxylate is envisaged as a late step in the synthesis. This requires the synthesis of the reduced pyrroloquinoline system containing a sidechain at C-2 suitable for conversion to the natural product. This may be achieved by addition of a suitable organolithium to the pyrroloquinolone carbonyl group using the chemistry first described by Fowler[2] and elaborated by ourselves.[3] Reduction of the pyrrole ring would also be required. Finally, the novel tricyclic core could be made by cyclisation of the aryl radical derived from an aryl iodide onto the pyrrole ring.



Scheme 1

The addition of aryl radicals to benzenoid aromatic rings in both an inter- and intra-molecular sense has been thoroughly explored by Hey and collaborators.[4] More recently, Toga has shown that such cyclisations in which the two benzene rings are linked by an amide can occur in high yield to give quinolones.[5] The mechanism of such reactions, particularly the mechanism of rearomatisation of the ring undergoing addition, has been the subject of much debate and the suggestion of Bowman[6] that an $S_{RN}1$ mechanism operates seems to be the currently favoured explanation. However, the addition of radicals to the pyrrole nucleus has received far less attention.[7] Muchowski[8] and Baciocchi[9] reported almost simultaneously the addition of electrophilic carbon radicals to the unsubstituted α-position of pyrroles under oxidative conditions [$Mn(OAc)_3$ and $Fe(II)/H_2O_2$ respectively]. Subsequently, Muchowski reported the oxidative cyclisation of ω-iodoalkylpyrroles as a key step in the synthesis of the pyrrolizidine alkaloid (-)-monomorine.[10] The only examples of addition of aryl radicals to pyrroles under reductive conditions is also due to Muchowski[11] and is summarised in Scheme 2. The requirement for an electron-withdrawing group at the C-2 position of the pyrrole in order to observe cyclisation is notable. In contrast, similar reactions involving indole have been shown to lead to dihydroindoles.[12]

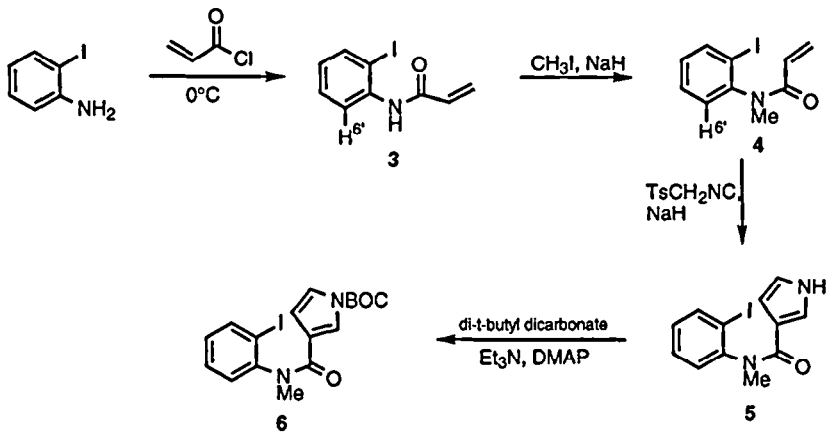


R = H 0% 70%
R = CHO 43% <10%

Scheme 2

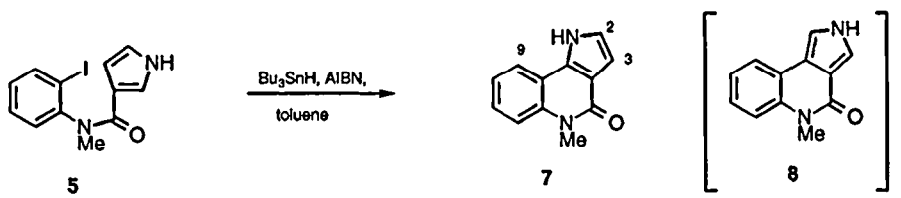
As a first stage in our synthetic endeavours, we decided to attempt the preparation of the simple unsubstituted pyrroloquinoline skeleton following the pathway shown in Scheme 3. Reaction of two equivalents of 2-iodoaniline with acryloyl chloride gave the N-arylacrylamide **3** in 96% yield. As we have previously demonstrated, a tertiary amide is required in order to attain the correct conformation around the amide bond for cyclisation to occur.[13] Thus **3** was methylated (NaH, CH_3I) to give tertiary amide **4** in 81% yield. The change in the shift of the H-6' proton from δ8.30 in **3** to δ7.27 in **4** clearly demonstrates the switch in conformation upon *N*-alkylation. Reaction of **4** with tosylmethylisocyanide (Tosmic®) gave the pyrrole-3-carboxamide **5** in 57% yield. With the radical cyclisation precursor in hand, substitution on the pyrrole nitrogen was explored in order to give substrates with differing electronic properties. All attempts at methylation of **5** failed to give any desired *N*-methyl compound and led instead to a extensive decomposition. However,

formation of the *N*-tBOC derivative was achieved in virtually quantitative yield by reaction at low temperature with di-t-butyl dicarbonate and triethylamine and catalytic dimethlaminopyridine.



Scheme 3

Pyrrole carboxamide **5** was then subjected to standard reductive radical cyclisation conditions [tributyltin hydride (0.02M) in refluxing toluene with catalytic AIBN]. The only product which could be isolated was assigned the pyrroloquinoline structure **7** (scheme 4).

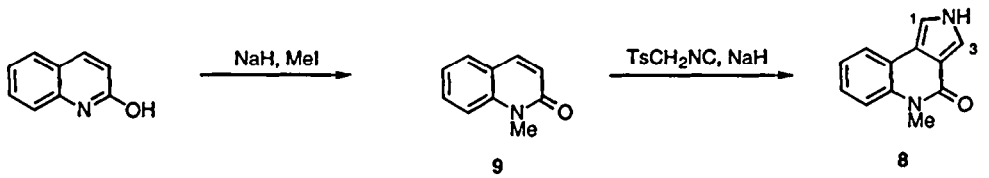


Scheme 4

This structure was assigned mainly on the basis of its nmr spectra and also on the independent synthesis of a regioisomer (see below). The ^{1}H nmr spectrum showed only resonances for only 6 protons (with the exception of the *N*-methyl group at δ3.88). A doublet at δ6.83 with a *J* value of 2.5 Hz was assigned to the β-pyrrole proton (H-3). The H-2 resonance was part of an overlapping multiplet at δ7.3. These features indicated that the pyrrole ring was intact and a 5-exo-trig cyclisation to give a spiropyrrolidinyloxindole had not occurred. In the light of Muchowski's cyclisation this rearomatisation of the pyrrole ring is unsurprising. However, the aryl radical could have added on to the pyrrole C-2 position to give a regioisomeric pyrroloquinoline **8**. It is rather difficult to distinguish between these possibilities based on the nmr data presented above as it is well known that coupling occurs between the α-pyrrole protons in 2,5-unsubstituted pyrroles.[14] An nOe experment on our isolated product proved inconclusive with no nOe being observed between H-9 and either H-2 or H-3. We came to the conclusion that the best way to resolve this regioisomer question was to unambiguously synthesise pyrrolo[4,3-*c*]quinolone **8**. This was achieved in two steps starting from 2-hydroxyquinoline (scheme 5).

Methylation using sodium hydride in THF with methyl iodide furnished the *N*-methylquinolone **9** in 76% yield. Reaction with tosylmethyl isocyanide using sodium hydride as base led to the regioisomeric pyrrolo[4,3-*c*]quinolone **8** in 56% yield. The ^{1}H and ^{13}C nmr spectra of this compound were completely different to those observed for our cyclisation product **7**. Thus H-1was part of a complex multiplet at δ7.3

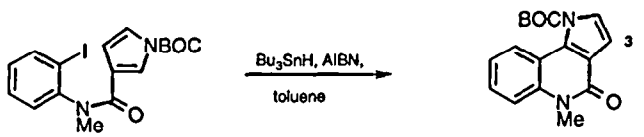
whilst H-3 appeared as a triplet (*J* 2.3 Hz) indicating coupling to the N-H in addition to 4-bond coupling. On this basis we assigned the structure **7** to the product of radical cyclisation of pyrrole carboxamide **5**.



9 **8**

Scheme 5

Finally, we reacted the *N*-tBOC pyrrole carboxamide **6** under the same radical cyclisation conditions (scheme 6). We were pleased to find that the sole isolable product in 52% yield was the pyrrolo[3,2-*c*]quinolone **10**. The structure was assigned using nmr spectra and by analogy with the spectra obtained for **7**. Again H-3 was clearly discernible as a doublet (*J* 3.5 Hz) at δ6.94. The higher yield obtained in this latter cyclisation is almost certainly caused by the electron-withdrawing effect of the BOC group although whether this exerts its influence via enhancement of the rate of addition of the nucleophilic aryl radical to C-2 of the pyrrole or whether it simply improves the stability of the product towards isolation is unclear.



6 **10**

Scheme 6

In summary, we have achieved a short, high-yielding synthesis of the novel tricyclic core of the martinelline alkaloids which has the potential to be extended into a total synthesis of these interesting natural products.

Acknowledgements

We should like to thank King's College London for a Research Studentship to TCTH. The ULIRS Mass Spectrometry Unit and NMR service at King's College London.

Experimental

General details

All reactions were carried out under argon and solutions dried with magnesium sulphate. Diethyl ether, tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl immediately before use. Acryloyl chloride and dimethyl sulphoxide were freshly distilled before use. Sodium hydride was washed with petrol or hexane at least 3 times before use. Column chromatography was performed with silica gel (Merck 7734) using the flash chromatography technique. Thin layer chromatographic analysis was performed using plastic-backed silica plates (Merck 5735). Components were visualised by either UV or phosphomolybdic acid dip. All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1605 FT-IR spectrophotometer. ^{1}H nmr spectra and ^{13}C NMR were recorded on a Bruker AM360 spectrometer operating at 360 MHz for proton and 90 MHz for carbon. Tetramethylsilane (TMS) was adopted as the internal standard for ^{1}H nmr spectra and the solvent peaks for ^{13}C nmr spectra. Chemical shifts (δ_H and δ_C) are quoted as downfield from tetramethylsilane. The multiplicity of a ^{1}H nmr signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, br = broad and m = multiplet. High resolution mass spectra were performed at the

Chemistry Department, King's College, London University. Elemental analysis of compounds were carried out at the Chemistry Department, University College, London University.

_N_1-(2-iodophenyl)acrylamide (3)

A solution of 2-iodoaniline (9.68 g, 44.2 mmol) in ether (15 ml) was added slowly, with stirring to a chilled solution of acryloyl chloride (2.0 g, 1.8 ml, 22.1 mmol) in ether (50 ml). The mixture was allowed to warm to room temperature and stirred for 1 hour. The solution was washed with HCl (50 ml of 0.05M), sodium bicarbonate solution (50 ml) and water (2 × 60 ml) dried over magnesium sulphate, filtered and solvent removed under reduced pressure giving a crude solid which was purified by recrystallisation (petrol/ether) to give the title compound as a white crystalline solid (5.8 g, 96%), m.p. 104-105°C; R_f (2:1 petrol:ethyl acetate) 0.46; (Found: M^+, 272.9649. C_9H_8INO requires M^+, 272.9651); δ_H(360 MHz; $CDCl_3$) 5.82 (1H, dd,*J* 10.1 and 1.0 Hz, -C(O)CH=CHH_{trans}), 6.31 (1H, dd, *J* 16.9 and 10.1 Hz, -C(O)CH_{gem}=CH_2), 6.46 (1H, dd, *J* 16.9 and 1.0 Hz, -C(O)CH=CHH_{cis}), 6.85 (1H, t, *J* 7.6 Hz, **H**-4'), 7.34 (1H, t, *J* 7.8 Hz, **H**-5'), 7.63 (1H, br. s, **NH**), 7.76 (1H, dd, *J* 7.9 and 1.2 Hz, **H**-3'), 8.30 (1H, d, *J* 7.0 Hz, **H**-6'); δ_C(90 MHz; $CDCl_3$) 90.23 (**C**-2'), 122.07 (**C**-6'), 126.10 (**C**-4'), 128.06 (-CH=CH_2), 129.17 (**C**-5'), 131.13 (-CH=CH_2), 137.89 (**C**-1'), 138.72 (**C**-3'), 163.38 (**C**=O); ν_{max} (NaCl)/cm^{-1} 3582 and 3181 (m, secondary amide N-H stretch), 3093 and 3018 (m, olefinic C-H stretch), 2924 (s, saturated C-H stretch), 1678 (m, secondary amide C=O), 1655 (s, C=C), 1628 (m, conjugated C=C with aromatic ring), 1572(w, N-H bending), 988 and 936 (s, C-H out of plane deformation in RCH=CH_2); **m/z** 273 (25.95%, M^+), 146 (100%, M^+–I), 70 (2.18%, M^+–C_6H_4I), 55 (19.38%, M^+–C_6H_5IN), 39 (2.28%, $C_3H_3^+$). (Found: C, 39.49; H, 2.78; N, 5.05. C_9H_8INO requires C, 39.56; H, 2.97; N, 5.13)

_N_1-(2-iodophenyl)-_N_1-methylacrylamide (4)

A solution of *N*1-(2-iodophenyl)acrylamide (5.0 g, 18.3 mmol) in dry THF (30 ml) was added to a stirred suspension of sodium hydride (1.0 g of 60% dispersion in mineral oil, 22 mmol) in THF (50 ml). The mixture was stirred for 1 hour after which methyl iodide (3.2 ml, 52 mmol) was added and the solution stirred overnight. Water (20 ml) was added to quench the reaction. The solvent was removed *in vacuo* and the residue was dissolved in ether (60 ml). The organic layer was washed with water (3 × 60 ml), dried over magnesium sulphate, filtered and the ether removed *in vacuo* giving a crude product which was purified by flash column chromatography (2:1 petrol:ethyl acetate) to give the title compound as a yellow oil (4.27 g, 81%); R_f (2:1 petrol:ethyl acetate) 0.38; (Found: M^+, 286.9861. $C_{10}H_{10}INO$ requires M^+, 286.9807); δ_H(360 MHz; $CDCl_3$) 3.25 (3H, s, N-CH_3), 5.52 (1H, dd,*J* 10.4 and 2.0 Hz, -C(O)CH=CHH_{trans}), 5.84 (1H, dd, *J* 16.7 and 10.4 Hz, -C(O)CH_{gem}=CH_2), 6.39 (1H, dd, *J* 16.7 and 2.0 Hz, -C(O)CH=CHH_{cis}), 7.11 (1H, td, *J* 7.7 and 1.6 Hz, **H**-4'), 7.27 (1H, dd, *J* 7.8 and 1.6 Hz, **H**-6'), 7.44 (1H, td, *J* 7.6 and 1.4 Hz, **H**-5'), 7.94 (1H, dd, *J* 7.9 and 1.4 Hz, **H**-3'); δ_C(90 MHz; $CDCl_3$) 35.99 (N-CH_3), 99.52 (**C**-2'), 127.8 (**C**-6'), 127.98 (-CH=CH_2), 129.21 (**C**-4'), 129.77 (**C**-5'), 129.89 (-CH=CH_2), 140.0 (**C**-3'), 145.278 (**C**-1'), 165.26 (**C**=O); ν_{max} (NaCl)/cm^{-1} 3055 (m, olefinic C-H stretch), 2928 (s, C-H stretch), 1661 (s, tertiary amide C=O), 1617 (s, C=C), 1577 (m, aromatic ring), 1470 (s, C-H deformation), 1398 (s, -CH_3 symmetrical deformation), 978 and 913 (s, C-H out of plane deformation in R-CH=CH_2), 768 and 726 (s, C-H out of plane deformation of a 1,2 disubstituted benzene ring); **m/z** 287 (0.33%, M^+), 286 (1.23%, M^+–H), 203 (2.65%, M^+–C_4H_6NO), 160 (100%, M^+–I), 105 (5.04%, $C_7H_7N^+$), 84 (8.18%, M^+–C_6H_4I), 55 (13.73%, M^+–C_7H_7IN).

_N_3-(2-iodophenyl)-_N_3-methyl-1_H_-3-pyrrolecarboxamide (5)

A solution of *N*1-(2-iodophenyl)-*N*1-methylacrylamide (2.2 g, 7.7 mmol) and tosylmethylisocyanide (1.50 g, 7.7 mmol) in ether (50 ml) and dimethylsulphoxide (18 ml) was added slowly to a stirred suspension of sodium

hydride (1.0 g of 60% dispersion in mineral oil, 21 mmol) in ether (18 ml). Stirring was continued for 30 minutes after which water (90 ml) was carefully added followed by potassium hydroxide solution (90 ml of 1M). Extraction with ether (3 × 40 ml), drying of the organic layer with magnesium sulphate and removal of solvent *in vacuo* gave a crude product which was purified by flash column chromatography (3:4 petrol:ethyl acetate) to give the title compound as a white solid (1.43 g, 57%), m.p. 167-168°C. R_f (3:4, petrol: ethyl acetate) 0.23; (Found: M^+, 325.9905. $C_{12}H_{11}IN_2O$ requires M^+, 325.9916); δ_H(360 MHz; $CDCl_3$) 3.31 (3H, s, NCH_3), 5.71 (1H, br. s, H-4), 6.46 (1H, br. s, H-5), 6.59 (1H, br. s, H-2), 7.07 (1H, td, *J* 7.6 and 1.7 Hz, H-4'), 7.29 (1H, dd, *J* 7.8 and 1.7 Hz, H-6'), 7.38 (1H, td, *J* 7.6 and 1.4 Hz, H-5'), 7.91 (1H, dd, *J* 7.9 and 1.4 Hz, H-3'); 9.08 (1H, br. s, NH); δ_C(90 MHz; $CDCl_3$) 37.26 (N-CH_3), 100.07 (C-2'), 109.80 (C-4), 117.76 (C-5), 118.78 (C-3), 123.04 (C-2), 129.52 (C-6'), 129.68 (C-4'), 129.84 (C-5'), 139.99 (C-3'), 147.24 (C-1'), 165.51 (C=O); ν_{max} (NaCl)/cm^{-1} 3582 (w, pyrrole N-H stretch), 3228 (m, N-H), 2925 (s, C-H stretch), 2853 (w, N-CH_3), 1595 (s, amide C=O), 1540 (w, pyrrole C-C, C-N stretch), 1501 (w, aromatic ring), 1462 (s, pyrrole C-C, C-N stretch), 1377 (m, pyrrole C-H, C-N stretch), 1162 (w, pyrrole C-C, C-N stretch), 1059 (w, pyrrole C-H deformation), 722 (w, pyrrole C-H wag); **m/z** 326 (2.73%, M^+), 233 (94.89%, M^+–C_5H_4NO), 199.1 (100%, M^+–I), 94.0 (84.03%, M^+–C_7H_7IN). (Found: C, 44.51; H, 3.27; N, 8.39. $C_{12}H_{11}IN_2O$ requires C, 44.19; H, 3.40; N, 8.59)

tert-butyl 3-(2-iodophenyl(methyl)carbamoyl)-1*H*-1-pyrrolecarboxylate (6)

N -(2'-Iodophenyl), *N*3-(2-iodophenyl)-*N*3-methyl-1*H*-3-pyrrolecarboxamide (281.1 mg, 0.66 mmol) was dissolved in THF (25 ml), and cooled to -78°C in a dry ice-acetone bath. Triethylamine (100 mg, 0.13 ml, 1.0 mmol) was added followed immediately by addition of di-*tert*-butyl dicarbonate (216 mg, 1.0 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) (ca. 10 mg). The reaction mixture was stirred overnight, while it was allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (50 ml), washed with water (4 × 100 ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the title compound as a white crystalline solid (363 mg, 99%), m.p. 126-128 °C; R_f (3:4 petrol:ethyl acetate) 0.66; (Found: M^+, 425.9275. $C_{17}H_{19}IN_2O_3$ requires M^+, 426.0440); δ_H(360 MHz; $CDCl_3$) 1.52 (9H, s, $OC(CH_3)_3$), 3.33 (3H, s, NCH_3), 5.87 (1H, br. s, H-4), 6.86 (1H, br. s, H-5), 6.86 (1H, br. s, H-2), 7.10 (1H, dd, *J* 7.6 and 1.6 Hz, H-4'), 7.31 (1H, dd, *J* 7.9 and 1.6 Hz, H-6'), 7.41 (1H, td, *J* 7.6 and 1.4 Hz, H-5'), 7.93 (1H, dd, *J* 7.9 and 1.3 Hz, H-3'); δ_C(90 MHz; $CDCl_3$) 27.80 ($C(CH_3)_3$), 37.19 (N-CH_3), 84.38 ($OC(CH_3)_3$), 99.92 (C-2'), 112.71 (C-4), 117.44 (C-5), 119.26 (C-2), 122.12 (C-3), 123.59 (C-6'), 129.74 (C-4'), 129.8 (C-5'), 140.12 (C-3'), 146.69 (C-1'), 148.05 (^{t}BOC C=O), 164.09 (-NCH_3C=O); ν_{max} (NaCl)/cm^{-1} 2977.4 (w, C-H stretch), 1750.1 (s, BOC C=O), 1634.4 (s, amide C=O); **m/z** 426 (0.27%, M^+), 369 (5.06%, M^+–C_4H_9), 353 (2.55%, M^+–C_4H_9O), 325 (2.21%, M^+–$C_5H_9O_2$), 299 (5.35%, M^+–I), 260 (1.9%, M^+–$C_9H_{12}NO_2^+$), 199 (100%, M^+–$C_5H_8O_2$+I), 198 (5.53%, M^+–$C_5H_9O_2$+I), 57 (30.24%, $C_4H_9^+$ and M^+–$C_{13}H_{10}IN_2O_3$). (Found: C, 48.18; H, 4.52; N, 6.36. $C_{17}H_{19}IN_2O_3$ requires C, 47.90; H, 4.49; N, 6.57%)

5-methyl-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one (7)

Tri-*n*-butyltin hydride (0.14 ml, 0.52 mmol) was added dropwise to a solution of *N*3-(2-iodophenyl)-*N*3-methyl-1*H*-3-pyrrolecarboxamide (156 mg, 0.48 mmol) in dry toluene (20 ml). The solution was heated to 80°C when catalytic amounts of azo-iso-butyronitrile (AIBN) (ca. 5 mg) was added. The solution was refluxed for 4 hours, allowed to cool and the solvent was removed under reduced pressure. The residue was dissolved in ether (50 ml), washed with ammonia solution (6 × 50 ml of 10% solution), dried over magnesium sulphate and filtered. Removal of ether *in vacuo* yielded a crude product which was purified by flash column chromatography (1:2, petrol:ethyl acetate) to give the title compound as a pale pink oily residue (37.2 mg, 39%); R_f (1:2, petrol:ethyl acetate) 0.31; (Found M^+, 198.0775. $C_{12}H_{10}N_2O$ requires M^+, 198.0793);

δ_H(360 MHz; $CDCl_3$) 3.88 (3H, s, N-CH_3), 6.83 (1H, t, *J* 2.5 Hz, H-3), 7.30-7.35 (2H, m, H-2 and H-7), 7.46-7.48 (2H, m, H-6 and H-8), 7.96 (1H, dd, *J* 7.7 and 1.0 Hz, H-9), 10.87 (1H, br. s, pyrrole NH); δ_C(90 MHz; $CDCl_3$) 29.20 (N-CH_3), 102.35 (C-3), 115.18 (C-2), 118.90 (C-3a), 122.32 (C-6), 122.59 (C-9a), 123.74 (C-8), 126.22 (C-7), 126.84 (C-9), 126.97 (C-9b), 136.60 (C-6a), 155.87 (C-4, C=O). ν_{max} (NaCl)/cm^{-1} 3447 (m, pyrrole N-H), 2926 (m, C-H), 1637.5 (s, amide C=O), 1377 (w, pyrrole C-H and C-N stretch); **m/z** 199 (13.93%, M^++1), 198 (100%, M^+), 197 (31.17%, M^+-H), 169 (16.68%, $C_{11}H_9N_2^+$). A COSYspectrum was used to aid the assignments of the ^{1}H NMR spectral data and an nOe spectrum was used to determine the regiochemistry of the structure.

1-Methyl-2(*1H*)-quinolinone (9)

2-Hydroxyquinoline (1.08 g, 6.88 mmol) in dry THF (10 ml) was added to a stirred suspension of sodium hydride (0.4 g of 50% dispersion in mineral oil, 8.27 mmol) in dry THF (10 ml) at 0°C under argon. The mixture was allowed to warm to room temperature, once the evolution of hydrogen had ceased, methyl iodide (1.96 g, 0.86 ml, 13.8 mmol) was added dropwise and the solution stirred overnight, water (10 ml) was added to quench the reaction. The solvent was removed in vacuo and the residue dissolved in ether (50 ml). The solution was washed with water (2 × 50 ml), dried with magnesium sulphate, filtered and the solvent was removed in vacuo giving a crude product which was purified by recrystallisation (dichloromethane/hexane) yielding (**116**) as a white solid (836 mg, 76%), m.p. (72-73°C); R_f (2:3 hexane:ethyl acetate) 0.21; (Found M^+, 159.0674. $C_{10}H_9NO$ requires M^+, 159.0684); δ_H(360 MHz; $CDCl_3$) 3.61 (3H, s, N-CH_3), 6.61 (1H, d, *J* 9.5 Hz, H-3), 7.14 (1H, t, *J* 8.0 Hz, H-6), 7.25 (1H, d, *J* 8.4 Hz, H-5), 7.47 (2H, m, H-7 and H-8), 7.56 (1H, d, *J* 9.5 Hz, H-4); δ_C(90 MHz; $CDCl_3$) 29.07 (N-CH_3), 113.83 (C-3), 120.29 (C-4a), 121.33 (C-6), 121.80 (C-5), 128.43 (C-8), 130.33 (C-7), 138.66 (C-4), 139.64 (C-8a), 161.96 (C=O); ν_{max} (NaCl)/cm^{-1} 3048 (w, olefinic C-H stretch), 2942 (s, C-H stretch), 1647 (s, C=O), 1583 (m, aromatic ring), 1500 (w, aromatic ring), 1460 (s, C-H deformation), 1421 (s, C-C, C-N stretch), 1039 (w, C-O stretch); **m/z** 160 (37.11%, M^++H), 159 (100%, M^+), 158 (17.44%, M^+–H), 144 (1.6%, M^+–CH_3), 131 (39.52%, M^+–CO), 130 (M^+–CH_3N), 103 (11.04%, $C_7H_5N^+$), 102 (5.02%, $C_7H_4N^+$), 89 (12.79%, $C_7H_5^+$), 77 (14.46%, $C_6H_5^+$).

5-methyl-4,5-dihydro-2H-pyrrolo[4,3-*c*]quinolin-4-one (8)

A solution of 1-Methyl-2(*1H*)-quinolinone (602.1 mg, 3.78 mmol) and tosylmethyl isocyanide (886 mg, 4.54 mmol) in ether (30 ml) and dimethylsulphoxide (10 ml) was added slowly to a stirred suspension of sodium hydride (454 mg of 60% dispersion in mineral oil, 5.83 mmol) in ether (10 ml) at 0 °C. Stirring was continued for 30 minutes after which water (40 ml) was carefully added followed by potassium hydroxide solution (40 ml of 1M). Extraction with ether (3 × 40 ml), drying of the organic layer with magnesium sulphate and removal of solvent *in vacuo* gave a crude product which was recrystallised (dichloromethane/hexane) to give the title compound as an orange solid (418 mg, 55.8%) m.p. decomposes at 205°C; R_f (2:3 hexane:ethyl acetate) 0.21 ; (Found M^+, 198.0791. $C_{12}H_{10}N_2O$ requires M^+, 198.0793); δ_H(360 MHz; $CDCl_3$) 3.72 (3H, s, N-CH_3), 7.19 (1H, td, *J* 6.75 and 1.6 Hz, H-8), 7.31-7.39 (3H, overlapping signals, H-7, H-6 and H-1), 7.66 (1H, t, *J* 2.33 Hz, H-3), 7.81 (1H, dd, J 7.73 and 1.0 Hz, H-9), 10.47 (1H, br. s, N-H); δ_C(90 MHz; $CDCl_3$) 29.08 (N-CH_3), 110.62 (C-1), 114.56 (C-4a), 115.35 (C-6), 118.76 (C-3), 121.3 (C-9a), 122.24 (C-8), 123.16 (C-9), 126.76 (C-7), 137.51 (C-9b), 139.0 (C-5a), 160.94 (C=O); ν_{max} (NaCl)/cm^{-1} 3212 (m, N-H stretch), 1626 (s, tertiary amide C=O), 1522 (w, N-H bending), 1462 (s, C-H deformation); **m/z** 199 (100%, M^++1), 198 (100%, M^+), 197 (100%, M^+-H), 169 (19.2%, $C_{11}H_9N_2^+$), 168 (6.3%, $C_{11}H_8N_2$), 167 (9.3%, $C_{11}H_7N_2^+$), 143 (15.1%, $C_{10}H_9N$), 77 (3.1%, $C_6H_5^+$). A COSYand a ^{13}C-^{1}H correlation spectra were used to aid the assignments of the ^{1}H and ^{13}C NMR spectral data.

***tert*-butyl 5-methyl-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-1-carboxylate. (10)**
Tri-*n*-butyltin hydride (0.1 ml, 0.37 mmol) was added dropwise to a solution of *tert*-butyl 3-(2-iodophenyl(methyl)carbamoyl)-1*H*-1-pyrrolecarboxylate (150 mg, 0.35 mmol) in dry toluene (18 ml). The solution was heated to 80°C when catalytic amounts of azo-iso-butyronitrile (AIBN) (ca. 5 mg) was added. The solution was refluxed for 4 hours, allowed to cool and the solvent was removed under reduced pressure. The residue was dissolved in ether (50 ml), washed with ammonia solution (6 × 50 ml of 10% solution), dried over magnesium sulphate and filtered. Removal of ether *in vacuo* yielded a crude product which was purified by flash column chromatography (3:4 petrol:ethyl acetate) to give the title compound as a colourless oil (54.9 mg, 52%); R_f (1:2, petrol:ethyl acetate) 0.47; (Found M^+, 298.1335. $C_{17}H_{18}N_2O_3$ requires M^+, 298.1317); δ_H(360 MHz; $CDCl_3$) 1.69 (9H, s, $C(CH_3)_3$), 3.81 (3H, s, $N\text{-}CH_3$), 6.94 (1H, d, *J* 3.5 Hz, H-3), 7.26-7.30 (2H, m, H-7 and H-8), 7.50 (1H, d, *J* 3.6 Hz, H-2), 7.45-7.53 (1H, m, H-6), 8.68 (1H, dd, *J* 8.2 and 1.4 Hz, H-9); δ_C(90 MHz; $CDCl_3$) 28.01 (3×C, $C(CH_3)_3$), 29.79 ($N\text{-}CH_3$), 85.55 ($OC(CH_3)_3$), 108.5 (C-3), 114.53 (C-3a), 115.13 (C-2), 120.71 (C-9a), 121.52 (C-6), 125.73 (C-8), 126.94 (C-7), 128.49 (C-9), 134.73 (C-9b), 138.43 (C-6a), 149.66 (^{t}BOC C=O), 159.48 (C-4, C=O); ν_{max} (NaCl)/cm^{-1} 3053.8 (s, Aromatic C-H stretch), 2927.1 (aliphatic C-H stretch), 1710 (m, ^{t}BOC C=O), 1649.2 (m, amide C=O), 1370.1 (s, tertiary butyl C-H); **m/z** 299 (18.6%, M^++1), 298 (57.22%, M^+), 198 (85.06%, $C_{12}H_{10}N_2O$), 197 (23.87%, M^+- $C_5H_9O_2$), 57 (100%, $C_4H_9^+$). A COSYspectrum was used to aid the assignments of the ^{1}H NMR spectral data.

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