A Short Synthesis of Hippadine

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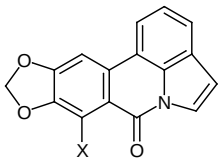
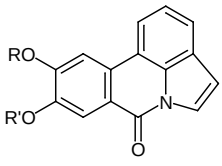
Abstract: A synthesis of the pyrrolophenanthridone alkaloid hippadine is described. The approach features the use of a low temperature Ullman type coupling reaction to effect construction of the pentacyclic skeleton and an unusual methylene oxidation promoted by barium manganate.

Key words: alkaloids, natural products, copper chemistry, oxidations, heterocycles

The use of extracts from various *Crinum* Amaryllidaceae species in the herbal treatment of rheumatism, piles and abscesses has prompted numerous investigations into their phytochemistry.[1,2] Of the compounds identified as natural products (e.g. **1** to **4**),[1–11] hippadine **(1)**, which reversibly inhibits fertility in male rats,[10] and kelbretorine **(2)**, which displays useful antitumour activity,[11,12] have gained greatest prominence. Indeed, several synthetic approaches to these pyrrolophenanthridone alkaloids have been reported.[13–23] In this paper we describe a new synthesis of hippadine **(1)** in which the pentacyclic skeleton is constructed using a copper(I)-mediated aryl to aryl coupling, akin to the Ziegler modified Ullman reaction.[24] In addition, an unusual methylene oxidation promoted by barium manganate is described.

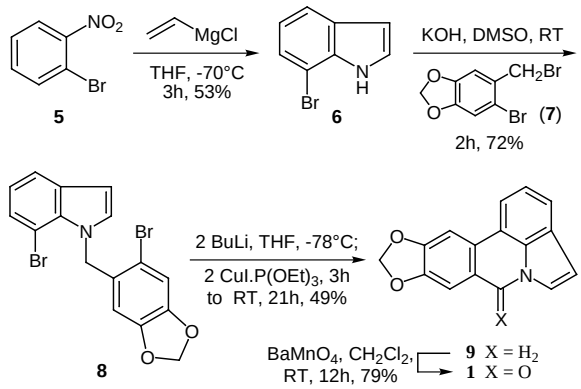


1 X =H, Hippadine
2 X = OH, Kalbretorine



3 R = H, R' = Me, Pratorinine
4 R = Me, R' = H, Pratorimine

Our synthesis of hippadine **(1)** began with the union of the known bromides **6** and **7** (each prepared in one step, from 2-bromonitrobenzene **(5)** and piperonyl alcohol, respectively).[25,26] Sequential transmetallation of the resulting dibromide **8** with 2 equivalents of butyllithium, then 2 equivalents of copper(I) iodide next promoted an intramolecular aryl–aryl coupling to give pentacycle **9** (itself a natural product found in the bulbs of *Pancratium biflorum*).[8,9,23,27,28] Attempts to effect the known aerial oxidation of **9** to hippadine gave only traces of the natural product.[23] However, simply stirring a dichloromethane solution of **9** with barium manganate provided hippadine **(1)** in good yield (Scheme).



Scheme

In conclusion, our synthesis of hippadine was accomplished in four steps from cheap, commercially available starting materials. It compares favourably with all previously published syntheses and has demonstrated further the utility of copper(I)-promoted aryl to aryl couplings in target synthesis. In addition, the use of barium manganate to effect the oxidation of a methylene to a ketone is noteworthy.

Melting points were obtained using a Reichert heated platform apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. IR spectra were recorded using a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR. NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) or a Bruker AM400 (operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C). Chemical shifts (δ) are reported as values in parts per million relative to TMS (δ_H, δ_C 0.00) or residual $CHCl_3$ (δ_H 7.27, δ_C 77.2). Low resolution mass spectra were recorded using atmospheric pressure chemical ionisation (APCI), positive ion on a Micromass platform quadropole mass analyser with an electrospray ion source. High resolution mass spectra were recorded on a variety of instruments either in house or at the EPSRC mass spectrometry centre, Swansea.

All reactions were magnetically stirred, conducted under a N_2 atmosphere using flame dried glassware and monitored by TLC, using Macherey-Nagel Alugram Sil G/UV_{254} precoated aluminum foil plates of layer thickness 0.25mm. Compounds were visualised firstly by UV irradiation, then by exposure to iodine vapour and finally by heating plates exposed to solutions of phosphomolybdic acid in EtOH. Column chromatography was performed on Sorbsil 60 silica gel (230–400 mesh), slurry packed and run under low pressure. THF was dried and degassed by refluxing over sodium wire using benzophenone ketyl as indicator. Petroleum ether used refers to the fraction boiling at 40–60 °C. All reagents were used as supplied.

5-Bromo-6-(bromomethyl)-1,3-benzodioxole **(7)** was prepared in 54% yield by the procedure of Barthel et al.[26] Physical [mp 91–93 °C (petroleum ether/Et_2O); Lit.[29] mp 94°C (petroleum ether); Lit.[26] mp 92–93 °C (MeOH)] and spectral characteristics were identical to those data previously reported.

7-Bromoindole (6)

Following the general procedure reported by Bartoli et al.,[25] vinylmagnesium chloride (86.3 mL of a 1.72 M solution in THF, 148.5 mmol) was added over 30 min to cooled solution (–70 °C) of 2-bromonitrobenzene (**5**; 10.0 g, 49.5 mmol) in THF (150 mL). After 3 h the mixture was warmed to r.t. and poured onto satd aq NH_4Cl solution (300 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (200 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to a brown oil (13.9 g). Purification by column chromatography (silica gel, petroleum ether) gave a yellow solid (5.4 g) which was recrystallised from pentane to give the title compound **6** (5.1 g, 53%) as colourless crystals; mp 42–44°C [Lit.[30] mp 42–43 °C; Lit.[26] mp 43–44°C].

IR: ν = 3398s, 1671w, 1560m, 1533w, 1426m, 1329s, 1189s, 1133s, 1094s, 919s cm^{-1}.

UV (MeOH): λ (ε) = 273 (4400) nm.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.34 (1 H, br s, NH), 7.62 (1H, d, *J* = 7.9 Hz, ArH), 7.39 (1 H, d, *J* = 7.6 Hz, ArH), 7.27 (1 H, app. t, *J* = 2.8 Hz, NCH), 7.05 (1 H, app t, *J* = 7.8 Hz, ArH), 6.66 (1 H, dd, *J* = 2.8, 2.0 Hz, NCHC*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.7 (C), 129.2 (C), 124.9 (CH), 124.5 (CH), 121.2 (CH), 120.1 (CH), 104.8 (C), 104.0 (CH).

MS (APCI+ve): m/z (%) = 197 ($[M+2]^+$, 100), 195 (M^+, 80).

1-(5-Bromobenzo[1,3]dioxol-6-yl)-methyl-7-bromo-1*H*-indole (8)

The general procedure for *N*-alkylation of indoles described by Heaney and Ley[31] was followed. Thus, to a stirred solution of powdered KOH (2.29 g, 40.8 mmol) in DMSO (20 mL) under N_2 and at r.t. was added 7-bromoindole (**6**; 2.00 g, 10.2 mmol). After 30 min the dibromide **7** (6.00g, 20.4 mmol) was added in a single portion. After a further 2 h H_2O (25 mL) was added and the resultant mixture extracted with Et_2O (3 × 30 mL). The organic phases were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow solid (7.09 g). Purification by column chromatography (silica gel, 5 to 10% ether in petroleum ether) and recrystallisation from Et_2O/petroleum ether gave the title compound (2.97 g, 72%) as a pale brown solid; mp 138–140°C.

IR: ν = 3104w, 2904w, 1557w, 1515w, 1479s, 1392m, 1318s, 1235s, 1033s, 927s cm^{-1}.

UV (MeOH): λ (ε) = 289 (7600), 272 (9400) nm.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (1 H, d, *J* = 7.9 Hz, ArH), 7.36 (1 H, d, *J* = 7.5 Hz, ArH), 7.09 (1 H, d, *J* = 3.1 Hz, NCH), 7.07 (1 H, s, ArH), 6.98 (1 H, app t, *J* = 7.7 Hz, ArH), 6.61 (1 H, d, *J* = 3.1 Hz, NCHC*H*), 5.90 (2 H, s, OCH_2O), 5.82 (1 H, s, ArH), 5.71 (2 H, s, NCH_2).

^1H NMR (300 MHz, DMSO-d_6): δ = 7.64 (1 H, d, *J* = 7.9 Hz, ArH), 7.50 (1 H, d, *J* = 3.1 Hz, NCH), 7.36 (1 H, d, *J* = 7.5 Hz, ArH), 7.29 (1 H, s, ArH), 6.98 (1 H, app t, *J* = 7.7 Hz, ArH), 6.65 (1 H, d, *J* = 3.1 Hz, NCHCH), 5.96 (2 H, s, OCH_2O), 5.68 (2 H, s, NCH_2), 5.43 (1 H, s, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 147.6 (C), 147.4 (C), 132.6 (C), 131.9 (C), 131.7 (C), 126.7 (CH), 121.2 (CH), 120.8 (CH), 112.7 (CH), 110.6 (C), 106.2 (CH), 103.1 (C), 102.4 (CH), 102.1 (CH_2), 52.3 (CH_2).

MS (APCI+ve): m/z (%) = 411 ($[M+4]^+$, 60), 409 ($[M+2]^+$, 90), 407 ($[M]^+$, 30), 215 (90), 213 (100).

Anal. calcd. C, 46.98; Br, 39.07; H, 2.71; N, 3.42. Found C 47.14; Br, 39.10; H, 2.61; N, 3.42.

7*H*-1,3-Dioxolo-4,5-*j*-pyrrolo-3,2,1-*de*-phenanthridine (9)

To a stirred solution of the dibromide **8** (0.60 g, 1.47 mmol) in THF (10 mL) at –78°C and under N_2 was added over 30 seconds BuLi (2.65 mL of a 1.3 M solution in hexane, 3.45 mmol). After 20 min copper(I) iodide triethylphosphite complex (1.57 g, 4.40 mmol) was added in a single portion. The mixture was allowed to warm to r.t. over 3 h, then stirred for 21 h. The mixture was diluted with Et_2O (40 mL), then washed with concd ammonia solution (10 x 40 mL), H_2O (50 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to a pink solid (0.79g). Purification by column chromatography (silica gel, 0 to 4% Et_2O in petroleum ether) gave a white solid (0.179 g, 0.72 mmol, 49%); mp partial sublimation above 151 °C, melting at 158–161 °C [Lit.[23] mp 159–161 °C (MeOH); Lit.[9] mp 154–156 °C].

IR: ν = 3097w, 2897w, 1496m, 1483m, 1335s, 1236s, 1038s, 938w, 790s cm^{-1}.

UV (CH_2Cl_2): λ (ε) = 355 (11300), 344 (12250) nm.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.59 (1 H, s, ArH), 7.44 (1 H, d, *J* = 7.2 Hz, ArH), 7.40–7.30 (2 H, m, NCH+ArH), 6.96 (1 H, app t, *J* = 7.6 Hz, ArH), 6.88 (1 H, s, ArH), 6.46 (1 H, d, *J* = 2.9 Hz, NCHC*H*), 6.07 (2 H, s, OCH_2O), 5.48 (2 H, s, NCH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 147.4 (C), 147.3 (C), 132.5 (C), 127.0 (CH), 125.3 (C), 124.3 (C), 123.3 (C), 120.2 (CH), 119.7 (CH), 118.4 (C), 113.0 (CH), 107.5 (CH), 102.9 (CH), 101.9 (CH), 101.4 (CH_2), 47.4 (CH_2).

MS (APCI+ve): m/z (%) = 250 (MH^+, 100), 249 (M^+, 40), 111 (30), 101 (20)

HRMS (EI): m/z (%) = Found 249.0768. $C_{16}H_{11}NO_2$ requires 249.0789.

1,3-Dioxolo-4,5-*j*-pyrrolo-3,2,1-*de*-phenanthridin-7-one (Hippadine, 1)

A solution of pentacycle **9** (0.091 g, 0.36 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. with $BaMnO_4$ (0.93 g, 3.6 mmol) for 12 h. The mixture was then filtered through a pad of Celite and the cake washed with CH_2Cl_2 (50 mL). Removal of the solvent in vacuo gave a white solid (0.101 g) which was recrystallised from acetone/petroleum ether to give hippadine (0.075 g, 0.29 mmol, 79%) as a white powder; mp 216–218°C (acetone/petroleum ether) [Lit.[23] mp 217–218°C (MeOH); Lit.[9] mp 207–209°C].

IR: ν = 3020w, 2920w, 1658m, 1602m, 1490m, 1440m, 1359w, 1253s, 1091m, 1037m cm^{-1}.

UV (CH_2Cl_2): λ (ε) = 360 inf (6050), 350 (7900), 300 (17100) nm.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.18 (1 H, d, *J* = 8.0 Hz, ArH), 8.10 (1 H, d, *J* = 3.6 Hz, NCH), 7.96 (1 H, s, ArH), 7.89 (1 H, s, ArH), 7.87 (1 H, d, *J* = 7.7 Hz, ArH), 7.56 (1 H, app t, *J* = 7.7 Hz, ArH), 7.06 (1 H, d, *J* = 3.6 Hz, NCHC*H*), 6.29 (2 H, s, OCH_2O).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8 (C), 151.2 (C), 147.0 (C), 129.9 (C), 129.1 (C), 126.5 (C), 122.4 (CH), 121.6 (CH), 121.1 (CH), 120.4 (C), 117.4 (CH), 114.9 (C), 109.3 (CH), 105.5 (CH), 101.0 (CH_2), 100.7 (CH).

MS (APCI+ve): m/z (%) = 264 (MH^+, 15), 146 (5), 127 (70), 125 (100).

Anal. calc. C, 73.00; H, 3.45; N, 5.32. Found C, 72.80; H 3.29; N, 5.02.

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