Synthesis of the Putative Structure of 5,6-Dihydrobicolorine

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SYNTHESIS OF THE PUTATIVE STRUCTURE OF 5,6-DIHYDROBICOLORINE

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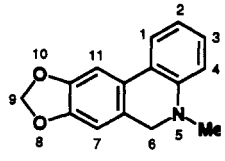
ABSTRACT.—A concise synthesis of the dihydrophenanthridine **1** has been developed and it has been shown that this material is spectroscopically different from the natural product characterized as 5,6-dihydrobicolorine. A comparison of published ^{1}H- and ^{13}C-nmr spectroscopic data obtained for 5,6-dihydrobicolorine and the alkaloid ismine [**2**] suggest that these compounds are identical.

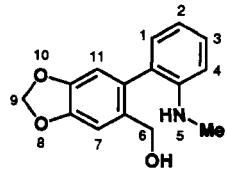
Several recent studies concerned with plants in the family Amaryllidaceae that grow on the Iberian Peninsula have resulted in the isolation of, *inter alia*, an allegedly new alkaloid that was named 5,6-dihydrobicolorine and assigned the phenanthridine structure **1** (1–3). Prior to these studies amine **1** had been synthesized on two separate occasions (4,5). In this earlier work (4) amine **1** was reported to be unstable and, in the more recent study, a derivative of the well-known alkaloid ismine [**2**], which has recently (6) been isolated from a Spanish Amaryllidaceae species, was shown to undergo efficient cyclization, affording compound **1**. On neither occasion were spectroscopic or physical data reported for the synthetic material thus precluding immediate comparisons with the natural product. Very recently, a third synthesis of the phenanthridine **1** has been reported (7) but, once again, no spectroscopic data were provided for this compound.

As a result of our interest in developing concise synthetic routes to various phenanthridine alkaloids (8), we were attracted to compound **1** as a simple target upon which to test our methodology. We now report a short preparation of this tertiary amine and demonstrate that it is spectroscopically different from the natural product 5,6-dihydrobicolorine. The initial step in our synthesis (Scheme 1) involved Suzuki cross-coupling (9) of boronic acid **3** (8) with the carbamate derivative, **4** (10), of *o*-bromoaniline. The resulting biaryl **5** (90%) was then subjected to Bischler-Napieralski cyclization (11) using neat $POCl_3$ at 160°. In this way the chlorophenanthridine **6** was obtained in 88% yield. Treatment of compound **6** with trimethyloxonium tetrafluoroborate (12) and reduction of the resulting methyliminium ion with $NaBH_4$ afforded the tertiary amine **1** (91% at 73% conversion). As reported earlier (4), compound **1** proved to be unstable and, upon heating, underwent ready air oxidation to give the known alkaloid **7** (6,7). In the mass spectrum of compound **1** there was always a prominent ion at *m/z* 253 which is attributed to the formation of phenanthridinone **7** (mol wt 253).

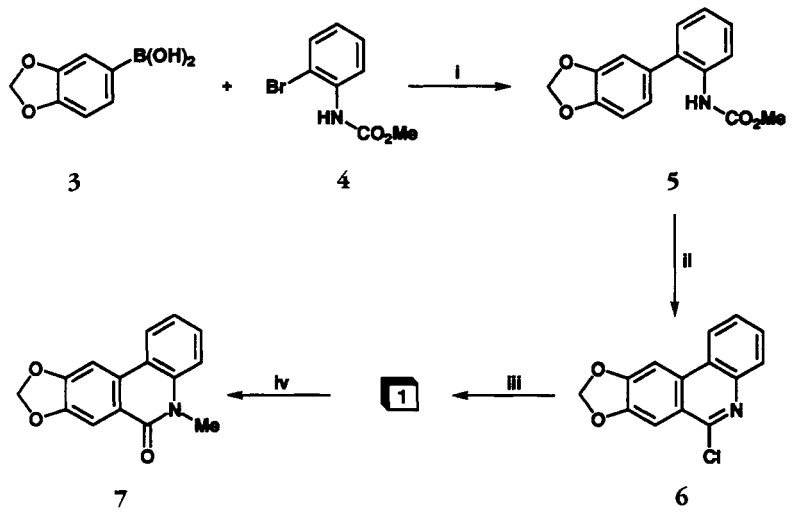
A comparison of the spectroscopic data obtained for 5,6-dihydrobicolorine with the analogous data derived from synthetic **1** revealed significant differ-



1



2



3 4 5 6 7

SCHEME 1. Reagents and conditions: (i) $Pd(PPh_3)_4$ (3 mol. %), 2 M aqueous Na_2CO_3, (1:10) EtOH-C_6H_6, 80°, 8 h; (ii) $POCl_3$ (neat), 160° (sealed tube), 16 h; (iii) Me_3OBF_4 (5 mol. equiv.), CH_2Cl_2, 37°, 42 h then $NaBH_4$ (17 mol. equiv.), EtOH, 24 h, room temperature; (iv) aerial oxidation.

ences (see Table 1). In contrast, there are dramatic similarities between the nmr data sets for 5,6-dihydrobicolorine and ismine [**2**] (Table 1). Furthermore, the reported (1,6) ir data for these compounds are also very similar. In the eims (6) of **2**, the expected molecular ion is observed at *m/z* 257 (35%) and the base peak, which appears at *m/z* 238, corresponds to loss of the elements of H_2O and a hydrogen atom. Consequently, it is conceivable, even likely, that in the reported (1) mass spectrum of 5,6-dihydrobicolorine the true molecular ion was not observed and the ions appearing at *m/z* 239 (11%) and 238 (96%) are not the $[M]^+$ and $[M-1]^+$ ions, respectively, but derive from the same fragmentation processes seen for **2**.

The foregoing data and observations lead us to the conclusion that the structure of 5,6-dihydrobicolorine is not represented by compound **1** but, rather, by compound **2**. Thus the alkaloids ismine and 5,6-dihydrobicolorine are one and the same compound.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H- and ^{13}C-nmr spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution. Petroleum ether refers to the hydrocarbon fraction boiling between 40–60° unless otherwise stated.

Methyl o-bromophenylcarbamate [**4**].—*o*-Bromoaniline (19.4 g, 0.113 mol) was added cautiously to a cooled (0°) and magnetically stirred solution of methyl chloroformate (20 ml, 0.26 mol) in CH_2Cl_2 (200 ml) containing anhydrous K_2CO_3 (30 g, 0.22 mol). After 10 h the reaction mixture was filtered and the solids thus retained washed with CH_2Cl_2 (200 ml). The combined filtrates were washed with HCl (1×200 ml of a 2 M aqueous solution) and brine (1×200 ml), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Distillation of the resulting brown oil afforded the title compound (25.6 g, 98%) as a colorless oil, bp 141–142°/14 mm Hg. On standing under refrigeration this material solidified. A spectroscopically pure sample of compound **4** was obtained as fine colorless needles (aqueous MeOH): mp 32–33° [lit. (10) mp 31–33°]; hrms *m/z* M^+, 228.9736 (calcd for $C_8H_8{}^{79}BrNO_2$, 228.9738); ir (melt on NaCl) ν max 3400, 2950, 1739, 1591, 1577, 1523, 1439, 1302, 1214, 1072, 750, 668 cm^{-1}; ^{1}H nmr δ 8.13 (1H, br d, J=8 Hz), 7.50 (1H, dd, J=8 and 1 Hz), 7.30 (1H, t, with further coupling, J=8 Hz), 7.14 (1H, br s), 6.92 (1H, ddd, J=8, 8, and 1 Hz), 3.80 (s, 3H); ^{13}C nmr δ 153.6, 135.7, 132.2, 128.4, 124.2, 120.1, 112.5, 52.5; eims (70 eV) *m/z* $[M]^+$ 231 (20), 229 (20), $[M-CH_3OCO]^+$ 172 (7), 170 (7), $[M-Br]^+$ 150 (100), $[M-Br-CH_3]^+$ 135 (15), 91 (28).

Methyl o-(3',4'-methylenedioxyphenyl)phenylcarbamate [**5**].—A mixture of 3,4-methylenedioxyphenylboronic acid [**3**] (7.90 g, 47.6 mmol),

Table 1. Comparison of ^{13}C- and ^{1}H-Nmr Spectral Data Derived from Compound **1**, 5,6-Dihydrobicolorine and Compound **2** (Ismine) (All spectral data obtained using $CDCl_3$ as solvent.)

1	5,6-Dihydrobicolorine	**2**
δ_C	δ_C[a]	δ_C[b]
147.5 (arom. C)	147.5 (arom. C)	147.7 (arom. C)
146.8 (arom. C)	147.4 (arom. C)	147.5 (arom. C)
146.5 (arom. C)	146.6 (arom. C)	146.7 (arom. C)
128.4 (arom. CH)	133.9 (arom. C)	134.0 (arom. C)
127.2 (arom. C)	131.0 (arom. C)	131.1 (arom. C)
126.2 (arom. C)	130.0 (arom. CH)	130.0 (arom. CH)
123.6 (arom. C)	129.0 (arom. CH)	129.1 (arom. CH)
123.0 (arom. CH)	127.2 (arom. C)	127.3 (arom. C)
118.7 (arom. CH)	117.9 (arom. CH)	118.1 (arom. CH)
112.2 (arom. CH)	110.7 (arom. CH)	110.9 (arom. CH)
106.1 (arom. CH)	110.2 (arom. CH)	110.3 (arom. CH)
103.2 (arom. CH)	109.7 (arom. CH)	109.9 (arom. CH)
101.0 (C-9)	101.2 (C-9)	101.3 (C-9)
55.1 (C-6)	63.5 (C-6)	63.7 (C-6)
38.6 (Me)	30.8 (Me)	30.9 (Me)
δ_H	δ_H[a]	δ_H[c]
7.54 (H-1)	7.30 (H-3)	7.28 (H-3)
(dd, J=8 and 1 Hz)	(ddd, J=9, 8, and 2 Hz)	(ddd, J=8, 7, and 2 Hz)
7.20 (H-11) (s)	7.02 (H-11) (s)	7.00 (H-11) (s)
7.20 (H-3)	7.00 (H-1)	6.98 (H-1)
(td, J=8 and 1 Hz)	(dd, J=7 and 2 Hz)	(dd, J=7 and 2 Hz)
6.86 (H-2)	6.83 (H-2)	6.81 (H-2)
(td, J=8 and 1 Hz)	(ddd, J=9, 7, and 1 Hz)	(ddd, J=7, 7, and 1 Hz)
6.73 (H-4)	6.75 (H-4)	6.73 (H-4)
(dd, J=8 and 1 Hz)	(dd, J=8 and 1 Hz)	(dd, J=8 and 1 Hz)
6.64 (H-7) (s)	6.68 (H-7) (s)	6.67 (H-7) (s)
5.96 (H-9) (s)	6.00 (H-9) (s)	5.99 (H-9) (s)
4.08 (H-6) (s)	4.27 (H-6)[d]	4.26 (H-6)[d]
	(d, J=12 Hz)	(d, J=12 Hz)
2.90 (Me) (s)	4.19 (H-6)[d]	4.20 (H-6)[d]
	(d, J=12 Hz)	(d, J=12 Hz)
	2.74 (Me) (s)	2.73 (Me) (s)
	OH and NH resonances not reported	OH and NH resonances not reported

[a]Data obtained from ref. 1.

[b]Data provided by Dr. M. Wicki, Dr. M.A. Siddiqui, and Professor V. Snieckus.

[c]Data obtained from Suau *et al.* (6).

[d]The magnetic non-equivalence of these benzylic protons can be attributed to restricted rotation about the biaryl axis within **2**, see Meyer & Meyer (13).

carbamate **4** (10.0 g, 43.5 mmol), $Pd(PPh_3)_4$ (1.50 g, 1.30 mmol), EtOH (20 ml), C_6H_6 (200 ml), and Na_2CO_3 (100 ml of a 2 M aqueous solution) was heated at reflux under N_2 for 8 h. Upon cooling, the organic layer was separated and the aqueous phase then extracted with CH_2Cl_2 (2×100 ml) and the combined organic phases were washed with brine (1×100 ml), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oil was subjected to chromatographic filtration (Si gel; 2:1:7, CH_2Cl_2-Et_2O-petroleum ether) and concentration of the appropriate fractions (R_f 0.3) gave a cream solid. Biaryl **5** (10.6 g, 90%) was obtained as colorless prisms [CH_2Cl_2-petroleum ether (60–80°)]: mp 109–110°; *anal.*, C, 66.4, H, 4.7, N, 5.2, $C_{15}H_{13}NO_4$ requires C, 66.4, H, 4.8, N, 5.2%; ir (KBr) ν max 3388, 2952, 2897, 1582, 1464, 1444, 1337, 767 cm^{-1}; ^{1}H nmr δ 8.11 (1H, br d, J=8 Hz), 7.34 (1H, t with further coupling, J=8 Hz), 7.18 (1H, dd, J=8 and 2 Hz), 7.09 (1H, dt, J=8 and 2 Hz), 6.91 (1H, dd, J=8 and 1 Hz), 6.82 (1H, m), 6.80 (1H, dd, J=8

and 2 Hz), 6.69 (1H, s), 6.03 (2H, s), 3.73 (3H, s); ^{13}C nmr δ 153.9, 148.2, 147.4, 135.0, 131.6, 130.9, 130.1, 128.3, 123.2, 122.6, 119.3, 109.7, 108.8, 101.3, 52.2; eims (70 eV) *m/z* [M]$^+$ 271 (100), [M−CH_3OH]$^+$ 239 (29), 182 (15), 154 (21).

6-Chloro[1,3]dioxolo[4,5-j]phenanthridine [**6**].—A solution of the carbamate **5** (200 mg, 0.74 mmol) in freshly distilled $POCl_3$ (2.0 ml, 22 mmol) was heated in a sealed tube at 160° for 16 h. Upon cooling the excess $POCl_3$ was removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (30 ml) and the solution thus obtained poured into Na_2CO_3 (30 ml of a saturated aqueous solution). After shaking well, the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (1×20 ml). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a light yellow solid which was sublimed (150°/0.3 mm Hg) to afford the title compound [**6**] (168 mg, 88%) as a colorless solid. A portion of this material was dissolved in CH_2Cl_2 and the resulting solution filtered through a 1-cm deep plug of neutral tlc-grade Al_2O_3 (CH_2Cl_2 elution). The filtrate was concentrated under reduced pressure to give a white solid. An analytically pure sample of compound **6** was obtained as colorless prisms (CH_2Cl_2): mp 196–197° (partial sublimation from 140° onwards); *anal.*, found, C, 65.2, H, 2.8, Cl, 14.3, N, 5.7, $C_{14}H_8ClNO_2$ requires C, 65.3, H, 3.1, Cl, 13.8, N, 5.4%; uv ($CHCl_3$) λ max (log ε) 354 (3.47), 337 (3.47), 310 (3.77), 281 (4.24), 256 (4.65) nm; ir (KBr) ν max 1481, 1460, 1288, 1237, 1039, 949, 845, 756 cm^{-1}; ^{1}H nmr δ 8.26 (1H, dd, *J*=9 and 1 Hz, H-1), 8.02 (1H, dd, *J*=9 and 1 Hz, H-4), 7.82 (1H, s, H-11), 7.73 (1H, s, H-7), 7.66 (1H, ddd, *J*=9, 8, and 1 Hz, H-3), 7.60 (1H, ddd, *J*=9, 8, and 1 Hz, H-2), 6.18 (2H, s); ^{13}C nmr δ 151.9, 150.0, 148.7, 142.9, 132.3, 129.1, 128.7, 127.0, 124.0, 121.9, 121.3, 104.9, 102.3, 100.1; eims (70 eV) *m/z* [M]$^+$ 259 (34), 257 (100), [M−Cl]$^+$ 222 (11), 164 (49).

5-Methyl-5,6-dihydro[1,3]dioxolo[4,5-j]phenanthridine [**1**].—A solution of compound **6** (79 mg, 0.31 mmol) and trimethyloxonium tetrafluoroborate (Aldrich) (230 mg, 1.55 mmol) in CH_2Cl_2 (10 ml) was heated at reflux for 42 h. Upon cooling a further aliquot of CH_2Cl_2 (10 ml) was added and this was followed by the addition of a solution of $NaBH_4$ (200 mg, 5.3 mmol) in EtOH (5 ml). The resulting white reaction mixture was stirred at room temperature for 24 h then CH_2Cl_2 (20 ml) and $NaHCO_3$ (20 ml of a saturated aqueous solution) were added and the two phases separated. The aqueous phase was extracted with CH_2Cl_2 (1×20 ml) and the combined organic phases were then dried (K_2CO_3), filtered and concentrated under reduced pressure to a cream solid (73 mg). This material was dissolved in CH_2Cl_2-Et_2O (35 ml of a 1:6 mixture) and the resulting solution extracted with HCl (15 ml of a 2 M aqueous solution). Concentration of the organic phase afforded starting material **6** (21 mg, 27% recovery). Addition of Na_2CO_3 (50 ml of a saturated aqueous solution) to the separated aqueous phase obtained above resulted in a mixture which was extracted with CH_2Cl_2 (3×20 ml). The combined organic phases were dried (K_2CO_3), then filtered and concentrated under reduced pressure to afford compound **1** (48 mg, 91% at 73% conversion) as a cream solid: mp 77–81° [1]; hrms *m/z* found M$^+$ 239.0946, calcd for $C_{15}H_{13}NO_2$, M$^+$ 239.0946; ^{1}H nmr, see Table 1; ^{13}C nmr, see Table 1; ir (KBr) ν max 2793, 1502, 1473, 1286, 1236, 1206, 1034, 753 cm^{-1}; eims (70 eV) *m/z* [M]$^+$ 239 (49), [M−H]$^+$ 238 (100), 223 (28), 180 (19), 166 (16), 152 (13), 139 (25).

5-Methyl[1,3]dioxolo[4,5-j]phenanthridin-6-one [**7**].—A small sample of compound **1** was placed on a microscope slide which was then heated on a Kofler hot-stage melting point apparatus. Upon melting (at 77–81°) the sample immediately began to recrystallize and a second and final melting was observed in the range 237–244° [lit. (7) mp [for **7**] 245–247°]. Upon cooling this melt the title compound [**7**] was obtained as a white crystalline solid: ir (KBr) ν max 2921, 1641, 1481, 1311, 1239, 1033, 931, 750 cm^{-1}; ^{1}H nmr δ 8.08 (1H, dd, *J*=8 and 1 Hz, H-1), 7.90 (1H, s, H-7), 7.61 (1H, s, H-11), 7.51 (1H, ddd, *J*=8, 7, and 1 Hz, H-3), 7.39 (1H, dd, *J*=8 and 1 Hz, H-4), 7.29 (1H, ddd, *J*=8, 7, and 1 Hz, H-2), 6.12 (2H, s), 3.80 (3H, s). This material was identical with an authentic sample (14) of compound **7**.

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