

## A Revision of the Structure of Sauvagnine

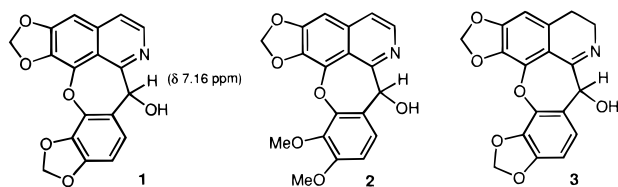
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The alkaloid sauvagnine is not the  $\alpha$ -hydroxytetrahydrocircularine **1**, but the phenolic benzoyl isoquinoline **4**.

The alkaloid sauvagnine, isolated from *Corydalis claviculata*,<sup>1</sup> was originally assigned the  $\alpha$ -hydroxytetrahydrocircularine structure **1** on the basis of its spectroscopic similarities to the alkaloid linnaresine, for which the structure **2** had been proposed.<sup>2</sup> The accompanying alkaloid dihydrosauvagnine was assigned the partially reduced structure **3**.



The recent findings<sup>3</sup> that linnaresine does not have structure **2**, and that  $\alpha$ -hydroxycircularines are easily oxidized by air, strongly suggested the necessity of reexamining the structure of sauvagnine.

Close inspection of the <sup>1</sup>H-NMR spectrum of sauvagnine suggested the possibility that the signal at 7.16 ppm might belong to an aromatic proton rather than to a benzylic one. On the other hand, the spectroscopic data for sauvagnine are, to our understanding, clearly in accordance with the presence of an isoquinoline unit: its <sup>1</sup>H-NMR spectrum shows two pyridinic doublets at 7.64 and 8.44 ppm with a coupling constant of 5.5 Hz and two aromatic singlets at 7.35 and 7.16 ppm; its UV spectrum undergoes a bathochromic shift in acidic media; and in the EIMS spectrum the molecular ion appears at 337 amu. In view of these data, we tentatively hypothesized the benzoyl isoquinoline structure (**4**), which is also supported by the similarity the <sup>1</sup>H-NMR data to those of other benzoyl isoquinolines.

To prove our hypothesis we undertook the total synthesis of compound **4** by the pathway shown in Figure 1.

The anion derived from the Reissert compound **5**<sup>4</sup> was alkylated with aldehyde **6**.<sup>5</sup> The crude condensation product (**7**) was hydrolyzed under basic conditions (NaOH, EtOH, ref), affording compound **8** in 68% overall yield. Oxidation of **8** (Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>, AcOH, 100 °C) followed by debenzoylation of the phenol group (Me<sub>3</sub>SiI, CHCl<sub>3</sub>, ref), afforded the desired compound **4**.

The <sup>1</sup>H-NMR, EIMS, and UV spectra of compound **4** were identical to those reported for sauvagnine. The IR spectrum (not provided by sauvagnine) showed the carbonyl band at 1652 cm<sup>-1</sup>.

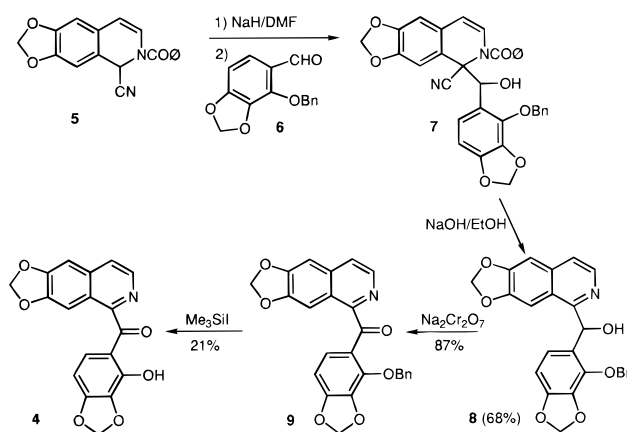


Figure 1. Synthesis of compound **4**.

In conclusion, we have shown that the alkaloid sauvagnine has the benzoyl isoquinoline structure **4**.

### Experimental Section

**General Experimental Procedures.** <sup>1</sup>H-, and <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub>, at 250.13 and 62.83 MHz, respectively, on a Bruker WM-250 spectrometer; chemical shifts are reported in parts per million (ppm) downfield from internal Me<sub>4</sub>Si. Mass spectra were recorded at an ionization voltage of 70 eV. Melting points are uncorrected.

**1-[2-(Benzyloxy)-3,4-(methylenedioxy)phenyl]-1-[6,7-(methylenedioxy)isoquinolinyl]carbinol (**8**).** 80% NaH (0.03 g, 1.01 mmol) was suspended in 5 mL of anhydrous DMF under Ar. To the cooled suspension (−15 °C) was slowly added a solution of **5** (0.24 g, 0.78 mmol) in 4 mL of anhydrous DMF. After 10 min, **6** (0.20 g, 0.75 mmol, dissolved in 4 mL anhydrous DMF) was added, and the reaction mixture was allowed to warm to room temperature over 12 h. After addition of 5 mL of MeOH, the mixture was evaporated to dryness, leaving a residue that was dissolved in C<sub>6</sub>H<sub>6</sub> (20 mL) and washed with H<sub>2</sub>O (20 mL).

The yellowish solid obtained after evaporation of the C<sub>6</sub>H<sub>6</sub> was suspended in a solution of 10 mL of EtOH, 5.5 mL of H<sub>2</sub>O, and 0.1 g of KOH, and the mixture was refluxed for 3 h. Upon cooling, a precipitate appeared, which was filtered out and washed with a small volume of EtOH. The resulting solid (0.23 g, 68%) was identified as **8** and was recrystallized from EtOH: mp 189–191 °C; IR (KBr)  $\nu$  max 3358 (OH), 2894, 1623, 1586, 1495, 1459 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  8.31 (1H, d, *J* = 5.6, Ar-H), 7.55 (2H, d, *J* = 6.7, 2 × Ar-H), 7.43–7.33 (4H, m, 4 × Ar-H), 7.13 (1H, s, Ar-H), 7.03 (1H, s, Ar-H), 6.53 (1H, s, Ar-CH), 6.38 (1H, d, *J* = 8.2, Ar-H), 6.33 (1H, d, *J* = 8.2, Ar-H), 6.18 (1H, br s, OH), 6.04,

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5.99 (2H, 2 × s, ArO—CH<sub>2</sub>—OAr), 5.94 (2H, s, ArO—CH<sub>2</sub>—OAr), 5.47, 5.34 (2H, 2 × d, *J* = 11.3, ArCH<sub>2</sub>); <sup>13</sup>C NMR δ 158.0, 151.0, 149.2, 148.7, 140.6, 139.5 (CH), 137.6, 137.4, 135.3, 129.9, 128.9 (2 × CH), 128.6 (3 × CH), 122.7, 122.1 (CH), 120.7 (CH), 104.1 (CH), 103.4 (CH), 102.0 (CH<sub>2</sub>), 101.5 (CH<sub>2</sub>), 101.4 (CH), 74.7 (CH<sub>2</sub>), 66.3 (CH); EIMS *m/z* 429 [M]<sup>+</sup> (1), 322 (100), 172 (21), 91 (36). Anal. Calcd for C<sub>25</sub>H<sub>19</sub>NO<sub>6</sub>: C, 69.92; H, 4.46; N, 3.26. Found: C, 69.88; H, 4.42; N, 3.37.

**1-[2-(Benzyloxy)-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)isoquinoline (9).** A solution of compound **8** (0.15 g, 0.35 mmol) in 1.5 mL of glacial HOAc was treated with Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (0.11 g, 0.36 mmol) in 1.5 mL of glacial HOAc. After being heated at 100 °C for 3 min, the mixture was poured on H<sub>2</sub>O, basified with a saturated solution of NH<sub>4</sub>Cl, and extracted with Et<sub>2</sub>O (3 × 20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). The combined organic extracts were washed with H<sub>2</sub>O (10 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue left by evaporation of the solvents was purified on an SiO<sub>2</sub> column (97:3, CH<sub>2</sub>Cl<sub>2</sub>—MeOH), affording 0.13 g (87%) of **9**: mp 137–139 °C (EtOH); IR (KBr) *ν* max 3060–2914, 1670 (CO), 1618, 1464, 1267 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 8.23 (1H, d, *J* = 5.5, Ar — H), 7.59 (1H, s, Ar — H), 7.47 (1H, d, *J* = 8.2, Ar — H), 7.36 (1H, d, *J* = 5.5, Ar — H), 7.10 (1H, t, *J* = 7.4, Ar — H), 6.99 (3H, m, 3 × Ar — H), 6.70 (1H, d, *J* = 8.2, Ar — H), 6.63 (2H, d, *J* = 7.4, 2 × Ar — H), 6.08 (2H, s, ArO — CH<sub>2</sub> — OAr), 6.02 (2H, s, ArO — CH<sub>2</sub> — OAr), 4.90 (2H, s, ArCH<sub>2</sub>); <sup>13</sup>C NMR δ 195.4 (CO), 156.3, 153.7, 151.0, 149.5, 142.7, 140.6, (CH), 137.2, 136.4, 135.8, 128.2 (2 × CH), 127.8 (CH), 127.4 (2 × CH), 126.8, 126.6 (CH), 123.5, 122.3 (CH), 104.0 (CH), 103.0 (CH), 102.8 (CH), 102.1 (CH<sub>2</sub>), 102.0 (CH<sub>2</sub>), 73.7 (CH<sub>2</sub>); EIMS *m/z* 398 (5), 321 (21), 320 (100), 172 (14), 91 (48); UV (MeOH) λ max 296, 234, 208 nm. Anal. Calcd for C<sub>25</sub>H<sub>17</sub>NO<sub>6</sub>: C, 70.25; H, 4.01; N, 3.27. Found: C, 70.62; H, 4.08; N, 3.37.

**1-[2-Hydroxy-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)isoquinoline (4).** Me<sub>3</sub>SiI (0.2 mL) was added to a solution of compound **9** (0.035 g, 0.08 mmol) in 5 mL of anhydrous CHCl<sub>3</sub>, and the mixture was refluxed for 90 min. Because TLC showed the continued presence of starting material, more Me<sub>3</sub>SiI (0.2 mL) was added and reflux was continued for a further 3 h. After cooling, the reaction mixture was washed with H<sub>2</sub>O (10 mL), and a saturated solution of NaHCO<sub>3</sub> (10 mL), and was dried (Na<sub>2</sub>SO<sub>4</sub>). The residue left by evaporation of the solvents was purified by preparative TLC on SiO<sub>2</sub> (3:7, EtOAc—hexane), affording 6 mg (21%) of **4** as a yellowish solid, mp 215–217 °C; IR (KBr) *ν* max 2920, 2853, 1652 (CO), 1610, 1578, 1497, 1460 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 12.1 (1H, br s, OH), 8.43 (1H, d, *J* = 5.5, Ar — H), 7.62 (1H, d, *J* = 5.5, Ar — H), 7.33 (1H, s, Ar — H), 7.15 (1H, s, Ar — H), 7.08 (1H, d, *J* = 8.5, Ar — H), 6.39 (1H, d, *J* = 8.5, Ar — H), 6.12 (2H, s, CH<sub>2</sub>), 6.11 (2H, s, CH<sub>2</sub>); EIMS *m/z* 337 [M]<sup>+</sup> (73), 320 (39), 308 (39), 279 (100), 172 (46); UV (MeOH) λ max 332, 306, 238, 212, nm; λ max (MeOH + H<sup>+</sup>) 345, 316, 242 nm; HREIMS calcd for C<sub>18</sub>H<sub>11</sub>NO<sub>6</sub> 337.0586, found 337.0577.

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## References and Notes

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