A Revision of the Structure of Sauvagnine

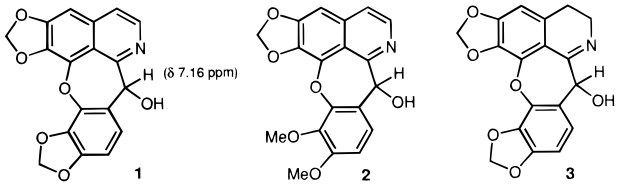
Alberto García, Luis Castedo,* and Domingo Domínguez*

Departamento de Química Orgánica, Facultad de Química y Sección de Alcaloides del C.S.I.C., 15706 Santiago de Compostela, Spain

Received January 29, 1996[⊗]

The alkaloid sauvagnine is not the α-hydroxytetradehydrocularine **1**, but the phenolic benzoyl isoquinoline **4**.

The alkaloid sauvagnine, isolated from *Corydalis claviculata*,[1] was originally assigned the α-hydroxytetradehydrocularine structure **1** on the basis of its spectroscopic similarities to the alkaloid linaresine, for which the structure **2** had been proposed.[2] The accompanying alkaloid dihydrosauvagnine was assigned the partially reduced structure **3**.



The recent findings[3] that linaresine does not have structure **2**, and that α-hydroxycularines are easily oxidized by air, strongly suggested the necessity of reexamining the structure of sauvagnine.

Close inspection of the ^{1}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 ^{1}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 ^{1}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**[4] was alkylated with aldehyde **6**.[5] The crude condensation product (**7**) was hydrolyzed under basic conditions (NaOH, EtOH, ref), affording compound **8** in 68% overall yield. Oxidation of **8** ($Na_2Cr_2O_7$, AcOH, 100 °C) followed by debenzylation of the phenol group (Me_3SiI, $CHCl_3$, ref), afforded the desired compound **4**.

The ^{1}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^{-1}.

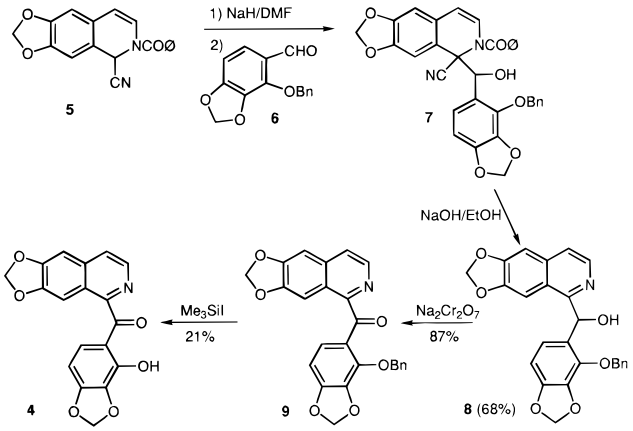


Figure 1. Synthesis of compound **4**.

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

Experimental Section

General Experimental Procedures. ^{1}H-, and ^{13}C-NMR spectra were recorded in $CDCl_3$, 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_4Si. 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_6H_6 (20 mL) and washed with H_2O (20 mL).

The yellowish solid obtained after evaporation of the C_6H_6 was suspended in a solution of 10 mL of EtOH, 5.5 mL of H_2O, 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) ν max 3358 (OH), 2894, 1623, 1586, 1495, 1459 cm^{-1}; ^{1}H NMR δ 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,

* To whom correspondence should be addressed. Phone: 34-9-81/59-10-85. FAX: 34-9-81/59 50 12.

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

S0163-3864(96)00209-1 CCC: $12.00

5.99 (2H, 2 × s, ArO−CH_2−OAr), 5.94 (2H, s, ArO−CH_2−OAr), 5.47, 5.34 (2H, 2 × d, J = 11.3, ArCH_2); ^{13}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_2), 101.5 (CH_2), 101.4 (CH), 74.7 (CH_2), 66.3 (CH); EIMS m/z 429 $[M]^+$ (1), 322 (100), 172 (21), 91 (36). Anal. Calcd for $C_{25}H_{19}NO_6$: 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 $Na_2Cr_2O_7$ (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_2O, basified with a saturated solution of NH_4Cl, and extracted with Et_2O (3 × 20 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and dried (Na_2SO_4). The residue left by evaporation of the solvents was purified on an SiO_2 column (97:3, CH_2Cl_2−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^{-1}; ^{1}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_2 − OAr), 6.02 (2H, s, ArO − CH_2 − OAr), 4.90 (2H, s, ArCH_2); ^{13}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_2), 102.0 (CH_2), 73.7 (CH_2); EIMS m/z 398 (5), 321 (21), 320 (100), 172 (14), 91 (48); UV (MeOH) λ max 296, 234, 208 nm. Anal. Calcd for $C_{25}H_{17}NO_6$: 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_3SiI (0.2 mL) was added to a solution of compound **9** (0.035 g, 0.08 mmol) in 5 mL of anhydrous $CHCl_3$, and the mixture was refluxed for 90 min. Because TLC showed the continued presence of starting material, more Me_3SiI (0.2 mL) was added and reflux was continued for a further 3 h. After cooling, the reaction mixture was washed with H_2O (10 mL), and a saturated solution of $NaHCO_3$ (10 mL), and was dried (Na_2SO_4). The residue left by evaporation of the solvents was purified by preparative TLC on SiO_2 (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^{-1}; ^{1}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_2), 6.11 (2H, s, CH_2); EIMS m/z 337 $[M]^+$ (73), 320 (39), 308 (39), 279 (100), 172 (46); UV (MeOH) λ max 332, 306, 238, 212, nm; λ max (MeOH + H^+) 345, 316, 242 nm; HREIMS calcd for $C_{18}H_{11}NO_6$ 337.0586, found 337.0577.

Acknowledgment. We thank the DGICYT for financial support under project SAF 93-0607. A. García thanks the CICYT for a fellowship.

References and Notes

(1) Allais, D.; Guinaudeau, H. *J. Nat. Prod.* **1990**, *53*, 1280−1286.
(2) Firdous, S.; Freyer, A. J.; Shamma, M.; Urzúa, A. *J. Am. Chem. Soc.* **1984**, *106*, 6099.
(3) García, A.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1993**, *34*, 1797.
(4) Chantimakorn, V.; Nimgirawath, S. *Aust. J. Chem.* **1989**, *42*, 209.
(5) García, A.; Castedo, L.; Domínguez, D. *Tetrahedron* **1995**, *51*, 8585.

NP960209J