LIMOUSAMINE: A 4-HYDROXYLATED CULARINE ALKALOID

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Abstract: Limousamine (5), the first C-4 hydroxylated cularine alkaloid, has been obtained from Corydalis claviculata (L.) DC (Fumariaceae).

Although the isoquinoline alkaloids presently number more than one thousand members, there is a fundamental unity in diversity which helps to classify and rationalize the formation of these naturally occurring bases. Thus, one of the threads running through some of the aporphines is that they may be found bearing a hydroxyl at C-4, as in the alkaloids (+)-cataline (1) found in a plant belonging to the family Papaveraceae,[1] and (+)-4-hydroxydicentrine (2) produced by a member of the Lauraceae.[2] A variety of other C-4 hydroxylated aporphines have been obtained from the plant families Rhamnaceae, Monimiaceae, Annonaceae, Menispermaceae, and Atherospermataceae.[1]

Alongside this array of C-4 hydroxylated aporphines must be juxtaposed the berbines berberastine (3) and thalidastine (4) which incorporate a hydroxyl group at the corresponding C-5 site. These two salts have been found among plants of the family Berberidaceae.[3]

We now describe the new base limousamine (5) which is the first cularine alkaloid to be hydroxylated at C-4. Extensive chromatography of the alkaloidal extracts from 0.5 kg of dry Corydalis claviculata (L.) DC (Fumariaceae), collected near Limoges, yielded 13 mg of amorphous and colorless limousamine (5), $C_{19}H_{21}O_5N$, λ max MeOH 210, 230 sh, 283 and 292 sh nm (log ε 4.54, 4.14, 3.82 and 3.69) with a bathochromic shift in base.#

Limousamine (5), λ max MeOH-OH^- 211, 251 sh, 291 nm (log ε 4.60, 4.06, 3.92); nmr $CDCl_3$ at 200 MHz coupling constants H-3$\underline{\alpha}$ J_{gem} 11.6 Hz, $J_{3\underline{\alpha},4\underline{\alpha}}$ 2.4 Hz; H-3$\underline{\beta}$ J_{gem} 11.6 Hz, $J_{3\underline{\beta},4\underline{\alpha}}$ 3.8 Hz; H-1 $J_{1,\alpha\underline{\alpha}}$ 3.4 Hz, $J_{1,\alpha\underline{\beta}}$ 10.7 Hz; H-$\alpha\underline{\alpha}$ $J_{1,\alpha\underline{\alpha}}$ 3.4 Hz, J_{gem} 16.2 Hz, H-$\alpha\underline{\beta}$ $J_{1,\alpha\underline{\beta}}$ 10.7 Hz, J_{gem} 16.2 Hz. CD MeOH $\Delta\varepsilon$ (nm) for 5, 0 (296), +0.6 (291), -3.1 (273), -2.7 (237), 0 (231), positive tail at 217 nm. For (+)-cularidine (8a), CD $\Delta\varepsilon$ (nm) 0 (297), +0.3 (292), -2.9 (274), -3.5 (233), 0 (227), positive tail at 222 nm.

A telling feature of the ^{1}H nmr spectrum (see expression 5) is the broad one-proton singlet at δ 4.57, in reality a multiplet, representing H-4. In the spectra of the C-4 hydroxylated aporphines, there is a clear cut difference in the chemical shifts of H-4 for the syn series (H-4 and H-6a on the same side) as exemplified by cataline (1)[4] on the one hand, and the corresponding shifts in the anti series as shown by 4-hydroxydicentrine (2)[2] on the other. H-4 is found between δ 4.5 and 4.6 in the former case, and further downfield around 4.8 or 4.9 in the latter.[1] The same phenomenon has been observed in the berbine series where the nmr spectrum of the syn semi-synthetic base 6 shows the H-5 absorption at δ 4.51, while the corresponding peak for the anti compound 7 is at δ 4.86.[3] Limousamine thus incorporates the syn stereochemistry since H-4 appears at δ 4.56.

The absolute configuration of limousamine (5) can be derived from the fact that it is strongly dextrorotatory, $[\alpha]_D^{25}$ +185° (0.074, MeOH), like all other known cularine bases of established stereochemistry, so that it too must possess the S chirality at C-1. Additionally, the CD curve of limousamine (5) bears a distinct similarity to that of (+)-cularine (8) and of (+)-cularidine (8a).[5#]

The mass spectrum of limousamine (5) incorporates ion m/z 343. The base peak is m/z 328 due to ion 9 formed by facile loss of the methyl group from the methoxyl para to the oxepine oxygen.[5] There is also a peak m/z 310 representing the ion formed by loss of water from species 9. Significantly present also are peaks m/z 177 and 159 due to ions 10 and 11, respectively.

As expected, diazomethane O-methylation of limousamine (5) provided O-methyllimousamine whose ^{1}H nmr spectrum shows an extra O-methyl singlet.*

Ring B hydroxylated alkaloids may thus be encountered among the aporphines, berbines and cularines, and will undoubtedly be found among other groups of isoquinoline bases. They are also found within a broad range of botanical families.

It has been previously demonstrated, using in vivo experiments with labeled precursors, that the C-5 hydroxyl group of berberastine (3) is not derived by oxidation of berberine (12).[6] Rather, the alcohol function is formed at an early stage in the biogenetic chain, prior to formation of the required 4-hydroxylated benzylisoquinoline precursor. There is a possibility, therefore, that limousamine is also formed through intramolecular phenolic oxidative coupling of a 4-hydrolated tetrahydrobenzylisoquinoline.

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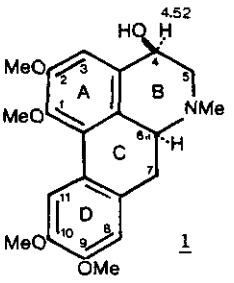
* O-Methyllimousamine, $C_{20}H_{22}O_5N$, nmr $CDCl_3$ at 360 MHz δ 2.66 s (NCH_3), 3.81 s, 3.87 s, 3.89 s (3 OCH_3), 4.30 q (H-1), 4.60 br s (H-4), 6.51 s (H-5), 6.83 s (H-2), 6.83 d (J_o 8.54 Hz, H-6), 7.13 d (J_o 8.54 Hz, H-5); ms m/z 357 (M^+, 31), 342 (100), 324 (47), 172 (6).



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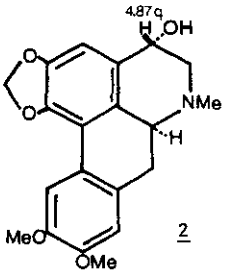

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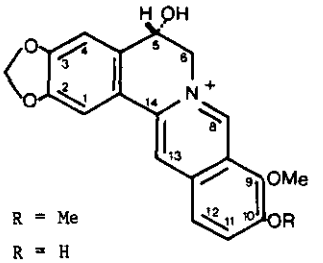
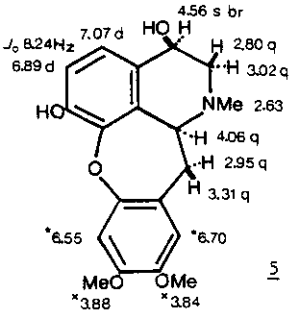


3, R = Me

4, R = H

12, R = Me, with H instead of OH at C-5.



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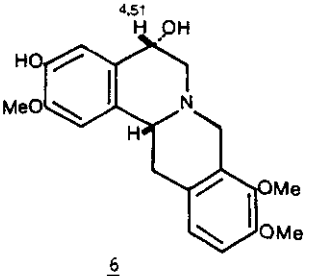

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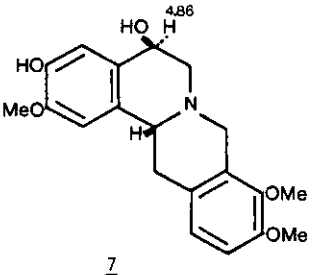

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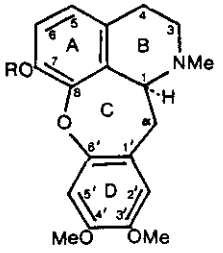
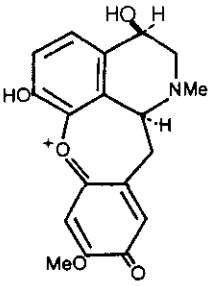


8, R = Me

8a, R = H



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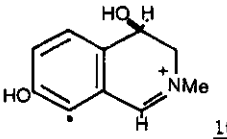

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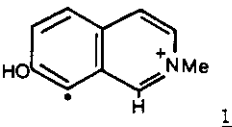

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