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LIMOGINE AND HIMALAYAMINE: A NEW CLASS OF ALKALOIDS

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Abstract: The novel alkaloids himalayamine (1) and limogine (2) have been obtained from Meconopsis villosa (Papaveraceae) and Corydalis claviculata (Fumariaceae), respectively.

In spite of the fact that some forty-two plant species fall within the ambit of the genus Meconopsis (Papaveraceae), only a few have had their rich alkaloidal content investigated.[1] We, therefore, initiated a study of Meconopsis villosa (Hook.f.) G. Taylor which was collected in the vicinity of Darjeeling, in northern India.[2] Fractionation of the alkaloids yielded himalayamine, $C_{20}H_{17}O_6N$, mp 218° ($CHCl_3$-petroleum ether), whose UV spectrum with λ max 293 nm denotes an isoquinoline alkaloid of a somewhat unusual nature since the UV maximum for most isoquinolines is in the 280-290 nm region. The two most important features of the mass spectrum are a molecular ion peak m/z 367, and a base peak m/z 350 formed by loss of hydroxide from the molecular ion.[3] It was thus logical to assume the presence of an alcohol function in the molecule.

Analysis of the ^1H NMR spectrum led to tentative structure 1 for himalayamine. Obvious features are an N-methyl singlet, two methylenedioxys, and four aromatic protons, two as singlets and two as doublets (see expression 1a). The section of the spectrum which was more difficult to interpret concerned the five core aliphatic protons located near the center of the molecule. Doublets at δ 2.73 and 3.61 could be assigned to the benzylic hydrogens at C-13. Another set of proton doublets centered at δ 3.26 and 4.80 could represent H-6 and 5, respectively. The relatively large vicinal coupling constant of 7.3 Hz is indicative of a dihedral angle of about 12°, as required by the assignment of relative stereochemistry in expression 1. Finally, the downfield δ 5.89 singlet must represent the benzylic hydrogen at C-8.

An NMR nuclear Overhauser enhancement difference study (NOEDS)[4] of himalayamine proved to be in agreement with the structural assignment (see expression 1b). Irradiation of H-5 (δ 4.80) led to a 7.9% NOE of H-4 (δ 6.94) and a 5.4% NOE of H-6 (δ 3.26). Alternatively, irradiation of H-6 produced a 7.4% NOE of H-5, as well as a 1% NOE of the N-methyl singlet (δ 2.40) and a 2.5% NOE of H-13 (δ 2.73). Significantly, acetylation of himalayamine with Ac_2O in pyridine led to amorphous O-acetylhimalayamine, $C_{22}H_{19}O_7N$, whose NMR spectrum shows H-5 downfield at δ 5.92.[5]

At this stage, a ^{13}C NMR study was required, but paucity of material precluded this since only 1.5 mg of himalayamine were available. By a felicitous coincidence, however, while investigating the structure of himalayamine, we were also analyzing the content of Corydalis claviculata (L.) DC (Fumariaceae), which had been collected near Limoges, France. It was noted that the new alkaloid limogine (2), $C_{20}H_{17}O_5N$, isolated from this source, differed in its composition from 1 only in having one less oxygen, while it exhibited an almost identical UV spectrum.[6,7] The mass spectrum of limogine (2) shows a strong molecular ion peak m/z 351, and base peak m/z 350.[7] The ^1H NMR spectrum (see expression 2) bears a similarity to that of himalayamine (1a). A conspicuous difference, however, is that the chemical shift of H-4 is now relatively upfield at δ 6.65, while H-5β is also shifted upfield to δ 3.14. The chemical shift assignments were confirmed by an NMR NOEDS (see expression 2a).[8,9] Additionally, resolution enhancement through gaussian multiplication (GM) showed that long range coupling obtains between H-12 and H-13, as well as between H-4 and H-5.[7]

Since about 21 mg of limogine (2) were available to us, we were able to obtain a decoupled ^{13}C NMR spectrum (see expression 2b). We considered it imperative at this point, however, to employ off-resonance decoupling to determine the first-order multiplicities, and hence the number of protons bound to each carbon. But even 21 mg of material was an insufficient amount to carry out efficiently such an operation with the spectral equipment available to us. We, therefore, had recourse to the recently developed gated spin echo (GASPE) technique, in which one observes the evolution of a carbon spin with a time which is dependent upon the magnitude of the carbon-hydrogen coupling and the multiplicity. As a result, quaternary and methylene carbon signals appear above an arbitrary line, while methine and methyl carbon signals are found below that line.[10] The signal for C-8 (89.6 ppm) was found to lie below the base line and is thus due to a methine carbon, while that for C-14 (93.7 ppm) is above the line and represents a quaternary center. Likewise, the 35.2 ppm signal due to the N-methyl carbon is situated below the line and can be differentiated from the two above-the-line methylene carbon signals appearing near 37 ppm.

Turning now to the problem of the absolute configuration, both alkaloids possess the identical chirality since they are dextrorotatory and their CD curves are closely related. The two alkaloids show characteristic UV maxima at or near 293 ($A \rightarrow L_b$), 237 ($A \rightarrow L_a$) and 200 nm ($A \rightarrow B$). In spite of the rather strong UV absorptions in the $A \rightarrow L_b$ and $A \rightarrow L_a$ regions ($\log \varepsilon \approx 4.0$), chromophoric interactions leading to exciton coupling is not observed in the CD curves because of the relatively long distance between the two chromophores. In contrast, a Davydov splitting is seen in the allowed $A \rightarrow B$ transitions band ($\log \varepsilon \approx 4.5$).[11,12] The Cotton effect is positive in the short wavelength end of the CD spectrum, so that the two chromophores interact as depicted in expression 3 (positive chirality). Expression 3 possesses the same absolute configuration as 1 and 2.

The biogenesis of himalayamine (1) and limogine (2) cannot presently be ascertained. It should be noted, however, that protopine is one of the major alkaloids of C. claviculata, and that intramolecular 1,3-dipolar cycloaddition of the protopine ylid 4 would formally produce limogine.

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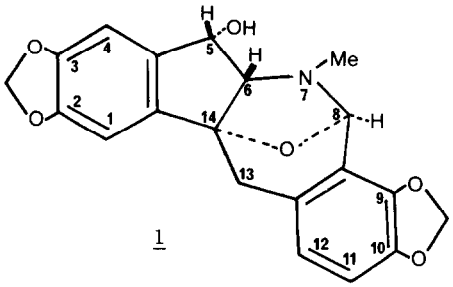

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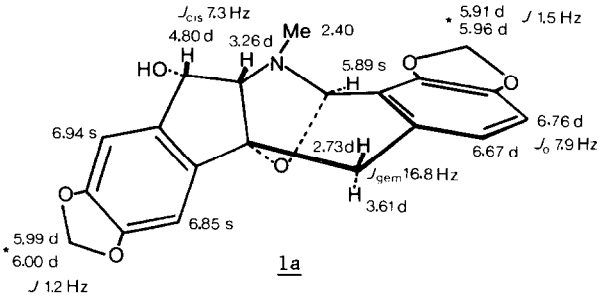

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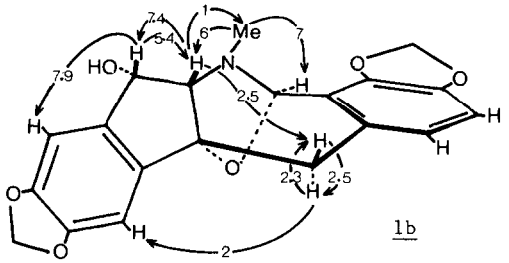
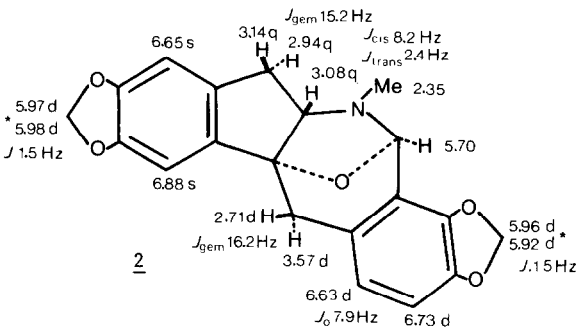


1b



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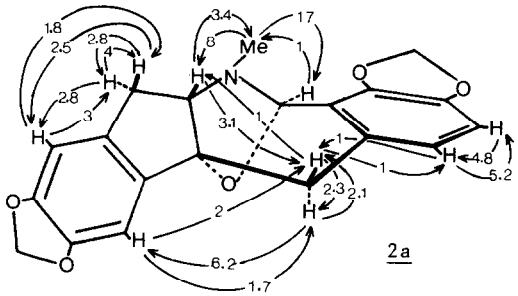
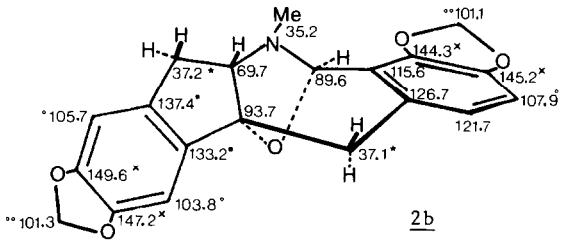
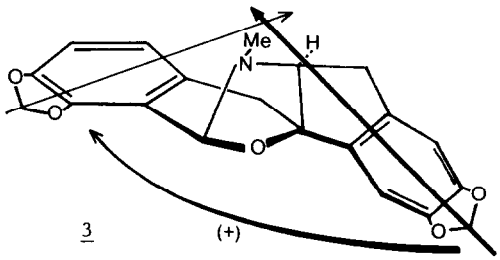


2a



2b



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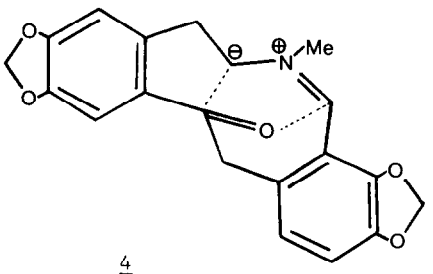

4

References and Footnotes

1. J. Slavík and I. Slavíkova, Collect. Czech. Chem. Commun., 40, 3206 (1975); F. Šantavy in The Alkaloids, Vol. XVII, ed. by R.H.F. Manske and R. Rodrigo, Academic Press, N.Y. (1979), pp. 385-544; and J.D. Phillipson, Phytochemistry, 21, 2441 (1982).
2. M. villosa was gathered at an altitude of about 2,800 m, in view of Mt. Kanchenjunga.
3. Himalayamine (1), λ max 210, 235 sh, 293 nm (log ε 4.49, 3.98, 4.02), λ max MeOH-H^+ 210, 238, 295 nm (log ε 4.53, 3.96, 4.04); ms m/z 367 (M^+, 20), 351 (25), 350 (100), 336 (3), 334 (4), 320 (10), 292 (3), 188 (10), 163 (8); CD MeOH Δε(nm) -0.4 (298), +2 (281), +0.5 sh (260), -3 (243), 0 (236), +23 (215) positive tail; $[\alpha]_D^{25}$+137° (0.185, MeOH). NMR spectrum in $CDCl_3$.
4. L.D. Hall and J.K.M. Sanders, J. Am. Chem. Soc., 102, 5703 (1980).
5. O-Acetylhimalayamine, λ max MeOH 209, 239 sh, 293 nm (log ε 4.55, 3.91, 3.85); λ max MeOH-H^+ 210, 242 294 nm (log ε 4.58, 3.85, 3.89); ms m/z 409 (M^+, 4), 366 (1), 351 (19), 350 (100), 320 (4), 292 (2), 188 (9), 163 (6); NMR in $CDCl_3$ at 360 MHz δ 2.18 (s, $OCOCH_3$), 2.29 (s, NCH_3), 2.71 (d, J_{gem} = 16.5 Hz, H-13β), 3.24 (d, J_{cis} = 7.0 Hz, H-6), 3.60 (d, J_{gem} = 16.5 Hz, H-13α), 5.79 (s, H-8), 5.90d and 5.98d (J_{gem} = 1.2 Hz, OCH_2O), 5.92 (d, J_{cis} = 7 Hz, H-5β), 6.00d and 6.02d (J = 1.5 Hz, OCH_2O), 6.65 (d, J_o = 7.9 Hz), 6.73 (d, J_o = 7.9 Hz, H-11), 6.79 (s, H-1), 6.91 (s, H-4).
6. Five hundred grams of dried C. claviculata afforded 21 mg of limogine (2).
7. Limogine (2), amorphous, λ max MeOH 209, 238 sh, 293 nm (log ε 4.45, 3.98, 3.93); λ max MeOH-H^+ 210, 240, 297 nm (log ε 4.49, 3.96, 3.96); ν max $CHCl_3$ 3680, 3050-3150, 2380, 1520 cm^{-1}, ms m/z 351 (M^+, 64), 350 (100), 336 (6), 322 (12), 320 (15), 292 (12), 188 (60), 174 (11), 147 (2); CD MeOH Δε (nm) -0.48 (298), +2.15 (283), +0.24 sh (260), -2.15 (243), 0 (234), +17.2 (214) positive tail; $[\alpha]_D^{25}$+113° (0.108, MeOH). NMR spectrum in $CDCl_3$. NMR spin-spin splittings by GM are as follows: H-12 δ 6.63m, J_o = 7.94 Hz, $J_{12,13\alpha}$ = 1.21 Hz, $J_{12,13\beta}$ = 0.91 Hz; H-13α δ 3.57m, J_{gem} = 16.17 Hz, $J_{12,13\alpha}$ = 1.21 Hz; H-13β δ 2.72m, J_{gem} = 16.17 Hz, $J_{12,13\beta}$ = 0.91 Hz; H-4 δ 6.65m, $J_{4,5\alpha}$ = 0.91 Hz, $J_{4,5\beta}$ = 0.91 Hz; H-5α δ 2.94m, J_{gem} = 15 Hz, $J_{4,5\alpha}$ = 0.91 Hz; H-5β δ 3.14m, J_{gem} = 15 Hz, $J_{5\beta,6}$ = 8.24 Hz, $J_{4,5\beta}$ = 0.91 Hz.
8. Limogine is recovered unchanged following treatment with either sodium borohydride in methanol or lithium aluminum hydride in ether.
9. No NMR NOE between H-5 and H-6 of limogine (2) could be measured because the chemical shift values are too close to each other. Also, the difference in the chemical shifts between H-11 and H-12 is not large enough to allow for an exact quantitation of their respective NOE's.
10. D.J. Cookson and B.E. Smith, Org. Magn. Reson., 16, 111 (1981). In the ^{13}C GASPE NMR spectrum of limogine (2), the peaks above the base line were at 37.1, 37.2, 93.7, 101.1, 101.3, 115.6, 126.7, 133.2, 137.4, 144.3, 145.2, 147.2, and 149.6 ppm. The peaks below the base line were at 35.2, 69.7, 89.6, 103.8, 105.7, 107.9, and 121.7 ppm. In diagrams 1a, 2 and 2b, chemical shifts with identical superscripts are interchangeable.
11. For a discussion of the aromatic chirality method, see N. Harada, K. Nakanishi and S. Tatsuoka, J. Am. Chem. Soc., 91, 5896 (1969); and N. Harada and K. Nakanishi, Circular Dichroic Spectroscopy, Exciton Coupling in Organic Stereochemistry, University Science Books, Mill Valley, CA (1983).
12. M. Shamma, J.L. Moniot, W.K. Chan and K. Nakanishi, Tetrahedron Lett., 4207 (1971).

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