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MAGALLANESINE: AN ISOINDOLOBENZAZOCINE ALKALOID

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Abstract: Berberis darwinii Hook. (Berberidaceae) has yielded magallanesine (1), the first known isoindolobenzazocine alkaloid.

South American members of the botanical genus Berberis (Berberidaceae) comprise more than 50 species,[1] each of which constitutes an abundant source of isoquinoline bases. We now describe the new alkaloid magallanesine (1), the first isoindolobenzazocine known to occur in nature, which has been found in Berberis darwinii Hook. collected in southern Chile.[2]

The yellow, optically inactive, magallanesine (1), $C_{21}H_{17}NO_6$, crystallizes readily from methanol, m.p. 254-256° C.

The 360 MHz $CDCl_3$ NMR spectrum has been summarized around expression 1.[3] Immediately striking is the one-proton vinylic singlet absorption at δ 6.33, which is accompanied by aromatic singlets at δ 6.65 and 7.24, and aromatic doublets at δ 7.13 and 7.45. Also present are two methoxyl singlets at δ 3.94 and 4.11, as well as a methylenedioxy singlet at δ 6.01.

The IR spectrum in chloroform solution includes a broad carbonyl peak at 1720 cm^{-1}. The UV spectrum indicates a highly conjugated system, λ max (MeOH) 246, 262 sh, 306, 377 sh nm (log ϵ 4.15, 4.02, 3.83, 4.33), and undergoes no significant change either in acid or in base.

The mass spectrum of magallanesine (1) shows molecular ion peak m/z 379 which is also the base peak. Other significant peaks are m/z 364 $(M - CH_3)^+$ (22%), and m/z 351 $(M - CO)^+$ (31%).[4]

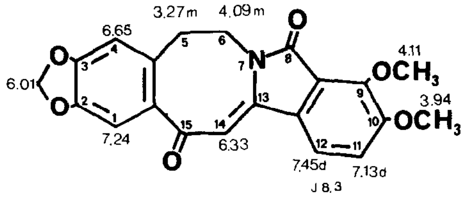
To gain further insight into the constitution of magallanesine, the alkaloid was subjected to an NMR NOEDS study,[5] the results of which have been summarized around expression 1-NOE. The commanding motifs of the NOE patterns consisted of two sets of interlocking enhancements, the first extending from H-4 (δ 6.65 s) to H-5 (δ 3.27 m) and then on to H-6 (δ 4.09 m), and the other from the C-10 methoxyl (δ 3.94 s) to H-14 (δ 6.33 s) through H-11 (δ 7.13 d) and H-12 (δ 7.45 d). Significantly, only H-1 (δ 7.24) among the aromatic protons did not show any nuclear Overhauser interactions. The $CDCl_3$ ^{13}C NMR spectrum of magallanesine was also in accord with the presence of two carbonyl functions in the molecule, with singlet peaks at δ 165.87 (C-8) and 192.52 (C-15).[4]

At this stage, it became necessary to eliminate from consideration alternate structure 2 for the alkaloid. This possibility was considered unlikely since it incorporates a pyridone system which would have shown an IR pyridone carbonyl absorption near 1670 cm^{-1}.[6] The pyridone ring proton (indicated in expression 2 by the symbol H) would also have been expected to show an ^1H NMR singlet in the vicinity of δ 7.33,[7] whereas in magallanesine (1) this singlet is seen one ppm more upfield at δ 6.33.

As further evidence against expression 2, the alkaloid was reduced with sodium borohydride in methanol at room temperature over a period of 3 h. Pyridones do not usually reduce under such conditions. Magallanesine, however, provided amorphous (±)-tetrahydromagallanesine (3), $C_{21}H_{21}NO_6$; ν max ($CHCl_3$) 1680 cm^{-1}; λ max (MeOH) 219, 263, 292 sh nm (log ϵ 4.48, 4.25, 3.96); whose ^1H NMR spectrum has been delineated around expression 3. All chemical shift assignments were confirmed by appropriate spin decoupling experiments.

The mass spectrum of tetrahydro derivative 3 exhibited an intense molecular ion peak m/z 383 (67%), and base peak m/z 206 most likely representing fragment 4.[8]

It is appropriate at this point to consider some of the related alkaloids also found among South American members of the Berberidaceae. These include the ever-present protoberberinium salt berberine (5), the highly oxidized protoberberine prechilenine (6),[7] the isoindolobenzazepines chilenine (7)[9] and lennoxamine (8),[7] the isoindoloisoquinoline nuevamine (9),[10] and the isoquinolinobenzazepine puntarenine (10).[11] The present addition of magallanesine (1) to this array of alkaloids makes it evident that the family Berberidaceae possesses a unique propensity for expansion as well as contraction of nitrogenous rings. The precursor alkaloid is most probably berberine (5) which may suffer oxidation to prechilenine (6). The latter can then rearrange to chilenine (7). A mechanism has been offered for the ring contraction incurred in the possible conversion of chilenine (7) into nuevamine (9).[10] It is wiser, however, to refrain from postulating biogenetic pathways which would culminate in the formation of the more complex puntarenine (10) and magallanesine (1).



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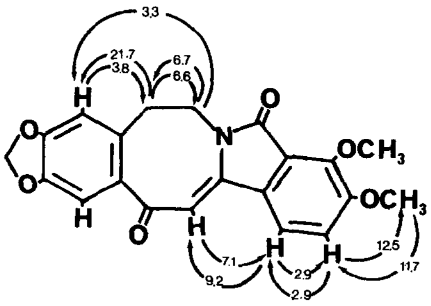
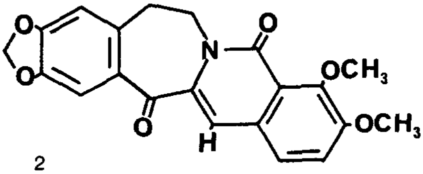


1-NOE



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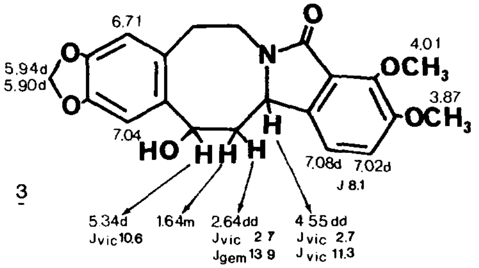

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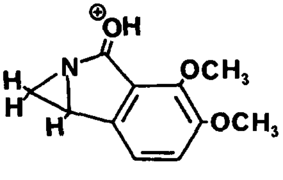

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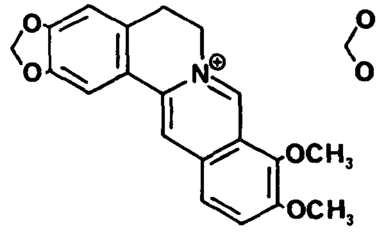

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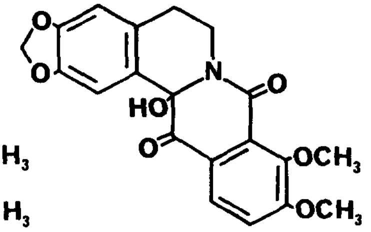

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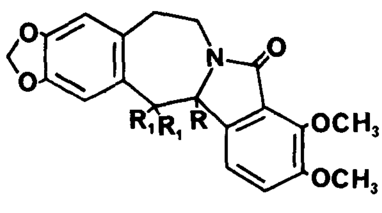
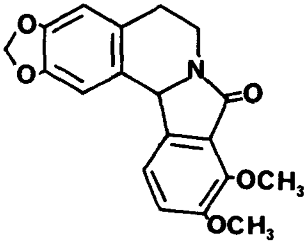


7 R = OH , $R_1 + R_1 = O$

8 $R = R_1 = H$



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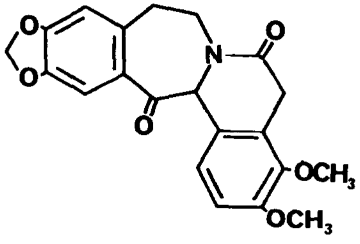

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References and Footnotes

1. L.W. Ahrendt, *J. Linn. Soc.* (London), Botany, **1961**, *57* (369), 1-410.
2. *B. darwinii* was gathered in the vicinity of Ciudad Osorno. The stems and branches (18 kg, dry) were collected during May-June, 1982, and yielded 12.5 mg of magallanesine (1), as well as 4 mg of prechilenine (6) as the O-methyl ether, 22 mg of chilenine (7), 3 mg of lennoxamine (8), 2 mg of nuevamine (9), 152 mg of puntarenine (10), in addition to gram quantities of berberine (5). The plant was identified by Ms. Mélica Muñoz Schick of the Museo Nacional de Historia Natural, Santiago.
3. In diagrams 1 and 3, J values are in Hz units.
4. Magallanesine (1), *m/z* 379 (100), 378 (18), 364 (22), 351 (31), 350 (42), 337 (33), 336 (45), 323 (79), 175 (94), 147 (45); ^{13}C NMR ($CDCl_3$) δ 33.24, 43.91, 56.61, 62.47, 101.77, 104.51, 109.17, 110.38, 116.09, 116.31, 119.68, 130.89, 132.64, 134.69, 138.96, 147.04, 147.39, 150.47, 154.69, 165.87, 192.52.
5. L.D. Hall and J.K.M. Sanders, *J. Am. Chem. Soc.*, **1980**, *102*, 5703.
6. K. Nakanishi and P.H. Solomon, "Infrared Absorption Spectroscopy", 2nd ed.; Holden-Day, Inc.: San Francisco, 1977; p. 47.
7. E. Valencia, I. Weiss, S. Firdous, A.J. Freyer, M. Shamma, A. Urzúa and V. Fajardo, *Tetrahedron*, in press. Prechilenine (6) was isolated as its methyl ether.
8. (±)-Tetrahydromagallanesine (3), *m/z* 383 (67), 354 (26), 218 (27), 206 (100), 193 (45), 192 (72), 177 (44), 163 (29).
9. V. Fajardo, V. Elango, B.K. Cassels and M. Shamma, *Tetrahedron Lett.*, **1982**, *23*, 39.
10. E. Valencia, A.J. Freyer, M. Shamma and V. Fajardo, *Tetrahedron Lett.*, **1984**, *25*, 599.
11. V. Fajardo, V. Elango, S. Chattopadhyay, L.M. Jackman and M. Shamma, *Tetrahedron Lett.*, **1983**, *24*, 155 (1983).

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