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THE USE OF NUCLEAR MAGNETIC RESONANCE NUCLEAR OVERHAUSER ENHANCEMENTS IN THE STRUCTURAL ELUCIDATION OF BISBENZYLISOQUINOLINE ALKALOIDS

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Abstract: The new bisbenzylisoquinoline alkaloid (+)-temuconine (1) has been found in Berberis valdiviana Phil. (Berberidaceae). Its structure was confirmed by an NMR NOE study.

As part of a continuing study of Chilean members of the Berberidaceae family, we have isolated and characterized the new diphenolic bisbenzylisoquinoline alkaloid (+)-temuconine (1) obtained from Berberis valdiviana Phil. collected near the town of Temuco, in central Chile.[3]

The mass spectrum of (+)-temuconine (1), $C_{37}H_{42}O_6N_2$, shows peaks m/z 609 $(M - 1)^+$ (0.2), 206 (94) and 192 (100) (Table I). The latter two peaks represent the two different dihydroisoquinolinium cations which can result from cleavage of the central doubly benzylic bonds in species 1. The 200 MHz FT NMR spectrum in $CDCl_3$ has been summarized around expression 1 and includes three methoxyl and two N-methyl singlets. This spectrum bears a distinct similarity to that for the known triphenolic alkaloid (+)-berbamunine (2), which occurs in B. lycium Royle[4] and other Berberis species,[5] and which has been outlined in expression 2. The UV spectrum of 1 (Table I) has a maximum at 282 nm, typical of many bisbenzylisoquinoline alkaloids.

The circular dichroism (CD) curves and specific rotations for (+)-temuconine (1) and (+)-berbamunine (2) are also very similar (Table I), indicating that the two alkaloids possess the identical absolute configuration.

In order to eliminate the alternate diphenolic structure 3 as a possibility for (+)-temuconine (1), the alkaloid was subjected to an NMR nuclear Overhauser enhancement (NOE) study at 360 MHz. Irradiation of H-10 (δ6.46) gave a 6.8% NOE of the H-11',13' doublet (δ6.84), and a 1% NOE of the C-7 methoxyl (δ3.60). Alternatively, irradiation of the C-7 methoxyl led to a 43.7% NOE of H-8 (δ6.12) and a 12.5% NOE of H-10 (δ6.46). Finally, irradiation of H-8 (δ6.12) caused a 12.5% area increase of the C-7 methoxyl signal (δ3.60).[6] These data, summarized in expression 1A, show that structure 3 cannot apply to temuconine which must, therefore, be represented by expression 1. NOE measurements are thus a superior alternative to sodium in liquid ammonia cleavage in the structural elucidation of bisbenzylisoquinolines, particularly when only small quantities of the dimer are available for investigation.[7]

It is interesting at this stage to compare the structure of (+)-temuconine (1) with that of the related (+)-berbamunine (2). Alkaloid 2, being hydroxylated at both C-7 and C-12, may act in the plant as a biogenetic precursor to a proaporphine-benzylisoquinoline dimer. (+)-Temuconine (1), on the other hand, cannot undergo intramolecular oxidative coupling, so that it is not the immediate precursor of any proaporphine-benzylisoquinoline dimer.

TABLE I. Spectral and Physical Data for Bisbenzylisoquinolines

Temuconine (1): MS m/z 609 $(M - 1)^+$ (0.2), 417 (0.6), 386 (0.5), 355 (0.2), 206 (94), 192 (100), 177 (23); λ max (MeOH) 211, 227, 282 nm (log ε 4.74, 4.57, 4.09); CD (MeOH) $\Delta\varepsilon$(nm) +3.4(278), +0.34(255), +9.8(234), +5.3(221), +18.3(210), $[\alpha]_D^{25}$ +68° (c 0.24, MeOH).

Berbamunine (2): CD (MeOH) $\Delta\varepsilon$(nm) +4.1(284), 0(260), +13(227), +12(222), +19(210), $[\alpha]_D^{25}$ +77° (c 0.17, MeOH).

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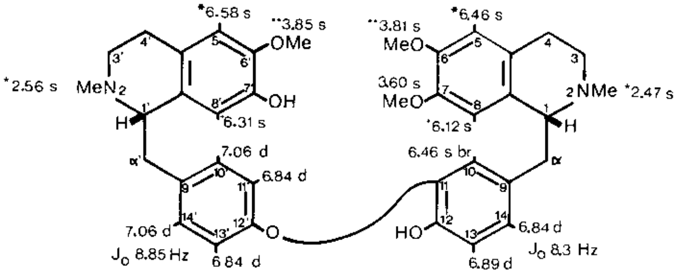
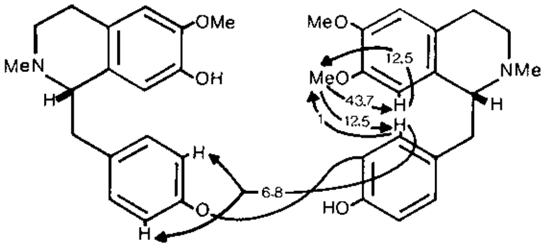
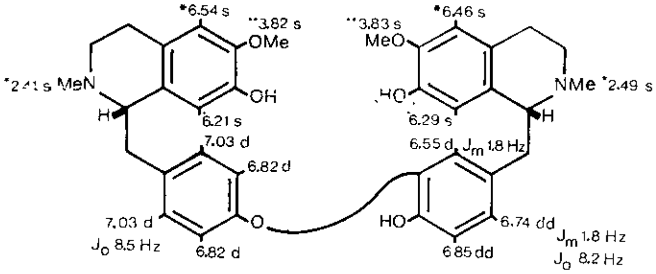


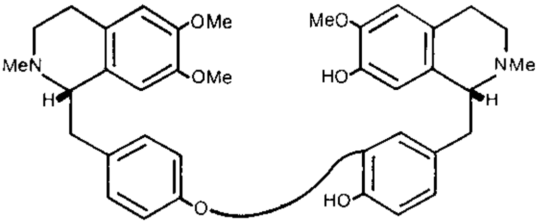
1



1A



2



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Chemical shifts with identical superscripts are interchangeable.

References and Footnotes

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3. Ten kg of dry B. valdiviana whole plant were extracted with cold ethanol. The extracts were chromatographed on a silica gel column, elution being with chloroform containing increasing amounts of methanol. Further purification was by TLC on Merck Silica Gel F-254 glass plates, using the system $CHCl_3$-MeOH-NH_4OH (90:10:1 v/v). A total of 10 mg of 1 was obtained.
4. V. Fajardo, J.E. Leet, V. Elango, S.F. Hussain, H. Guinaudeau and M. Shamma, unpublished results.
5. M. Tomita and T. Kugo, J. Pharm. Soc. Japan, 1957, 77, 1075.
6. The NOE experiments were carried out by FT NOE difference spectroscopy which allows even enhancements as low as 0.5% to be observed. A 16 sec equilibration time was used, which corresponds to at least ten times T_1. All samples were degassed prior to the measurements.
7. NMR NOE studies were also useful in the structural elucidation of the bisbenzylisoquinoline alkaloid tiliamosine, in which the lower half of the molecule consists of a biphenyl system rather than a diaryl ether, see K.P. Guha, P.C. Das, B. Mukherjee, R. Mukherjee, G.P. Juneau and N.S. Bhacca, Tetrahedron Lett., 1976, 4241; as well as in the study of the alkaloidal derivative dihydrodaphnine diacetate, see D. Neuhaus, H.S. Rzepa, R.N. Sheppard and I.R.C. Bick, Tetrahedron Lett., 1981, 22, 2933.

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