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CHILENINE: AN ISOINDOLOBENZAZEPINE ALKALOID

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Abstract: *(±)-Chilenine (3), the first isoindolobenzazepine alkaloid, has been found in Berberis empetrifolia Lam. (Berberidaceae).*

Members of the plant family Berberidaceae are known to produce an array of unusual isoquinoline alkaloids. In particular, a study of four Berberidaceae of Pakistan has resulted in the isolation of pakistanamine, the sole proaporphine-benzylisoquinoline presently known,[3] as well as of a variety of aporphine-benzylisoquinoline dimers including chitraline, pakistanine, and 1-O-methylpakistanine, as well as khyberine and kalashine.[4] In an effort to locate a phenolic analog of pakistanamine which would help explain the biogenetic sequence leading to the aporphine-benzylisoquinolines, it was decided to undertake a study of the Berberidaceae of Chile, which number no less than fifty different species.[5]

Twenty kilograms of the stems and above ground wood of Berberis empetrifolia Lam. (Berberidaceae) were, therefore, collected in southernmost Chilean Patagonia, in the province of Magellan, 40 km west of Punta Arenas, in late February 1981. The powdered plant was extracted with cold methanol. Following evaporation of the solvent, the residue was extracted with dilute hydrochloric acid. The acid extract was then basified with ammonium hydroxide and extracted with chloroform to give 62 g of crude alkaloids. This fraction was placed on a chromatographic column of Merck Silica Gel 60 (2.5 Kg). Elution was with chloroform-methanol mixtures of increasing polarity. A total of more than 400 100-mL fractions were collected. The alkaloids readily characterized proved to be the known berberine (1), oxyberberine (2), protopine, (+)-isotetran-

drine, and (+)-pakistanine which is the major alkaloid of the plant (≈ 5 g). No pakistanamine or any of its unknown phenolic analogs could be obtained.

From fractions 41-49, however, chilenine, a colorless, optically inactive alkaloid was obtained (20 mg), λ_{max}^{MeOH} 211, 228 sh, 281 sh and 312 nm (log ε 4.39, 4.25, 3.68 and 3.72), whose molecular composition, $C_{20}H_{17}NO_7$, suggested a highly oxidized species. The 200 MHz (FT) $CDCl_3$ NMR spectrum supports structure 3, and has been summarized in expression 3a. A salient feature of this spectrum is the absence of any aliphatic protons beside the four assigned to ring B. Noteworthy also is the presence of one methylenedioxy absorption as a close doublet of doublets, two methoxyl singlets, as well as a total of four aromatic protons.

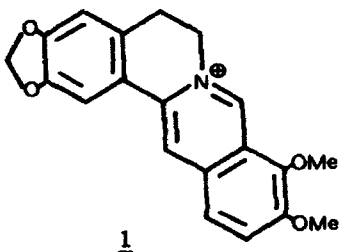
Consonant with this assignment, the IR spectrum of chilenine (3) in chloroform exhibits absorptions at 1690 (lactam), 1720 (conjugated ketone) and 3450 br (hydroxyl) cm^{-1}. The mass spectrum shows peaks m/z 383 (M^+) (17), 367 (36), 352 (18), 338 (40), 308 (15), 220 (59), 176 (86), 165 (33), and 148 (100).

Coincidentally, racemic 3 had actually been prepared recently in our laboratory in a sequence involving oxidation of berberine (1) with potassium ferricyanide. Following work-up, treatment of the isolable α-keto carbinolamide 4 with ammonium hydroxide had generated the stable isoindolobenzazepine 3,[6] a sample of which has now been found to be identical with natural chilenine.

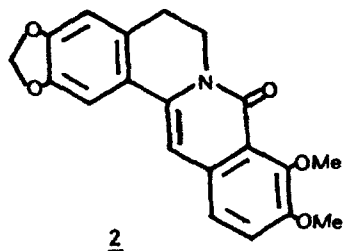
The most logical hypothesis for the formation of (±)-chilenine in nature is that this alkaloid is generated by a pathway paralleling the one followed inadvertently *in vitro*, *i.e.* by initial oxidation of berberine (1) to the intermediate 4 which can now be named prechilenine. Base catalyzed rearrangement of prechilenine in the plant would then yield chilenine (3).

Following the above findings, a fraction of the original methanol plant extracts that had not been treated with either acid or base was subjected to TLC, and the resulting spots compared with the spot due to an authentic sample of semi-synthetic prechilenine (4) obtained by oxidation of berberine, as well as to the spot due to authentic chilenine (3). Chilenine, but no prechilenine could be detected in this plant material.

It is known that the angular hydroxyl of prechilenine (4) is labile and can be readily substituted by a methoxyl group through the intermediacy of azaquinonium ion 5 to form stable species 6.[6] It was, therefore, considered possible that any prechilenine present in the plant



1



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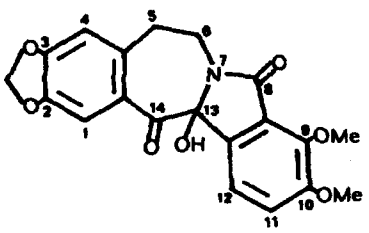
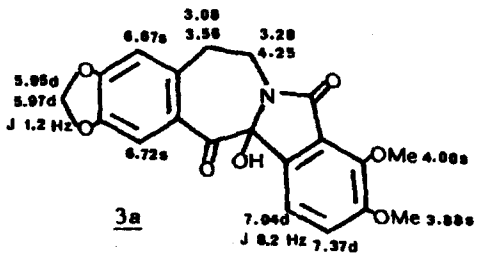


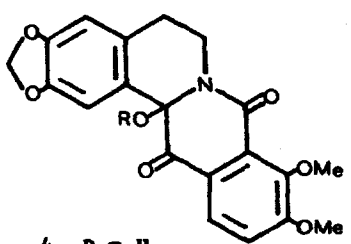
3



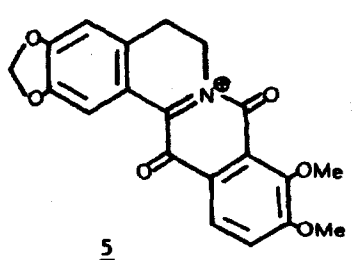
3a

H-5: qq, J_1 3.5, J_2 7.0, J_3 14 Hz.
H-6: qq, J_1 4.0, J_2 9.0, J_3 15 Hz.

The NMR chemical shift assignments for H-11 and 12 are interchangeable.



4, R = H
6, R = Me



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material could have been converted completely to 6 during the methanol extraction process. However, TLC comparisons of the plant extracts with authentic 6 in our possession could detect no such material in the extracts. We hope to collect additional samples of B. empetrifolia in the coming months in a continuing search for the chilenine biogenetic precursors. (±)-Chilenine (3) is the first isoindolobenzazepine known to occur in nature, and could thus be considered the lone representative of a new class of isoquinoline alkaloids.

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References and Footnotes

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