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SANTIAGONAMINE: A NEW APORPHINOID ALKALOID INCORPORATING A PHENANTHRIDINE SKELETON

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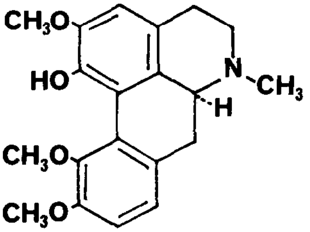
Abstract: Santiagonamine (6), the first phenanthridine alkaloid, has been isolated from Berberis darwinii Hook (Berberidaceae).

As part of a study of the alkaloidal content of Chilean barberries, it was recently established that Berberis buxifolia Lam. and B. actinacantha Mart. ex Schult. (Berberidaceae) produce the racemic γ-lactone chiloenamine (3).[2] This alkaloid may be considered to be the product of a catechol dioxygenase intradiol cleavage of the aporphine derivative 2.[2,3] Significantly, the known aporphine (+)-corydine (1) was also found in B. actinacantha.[2]



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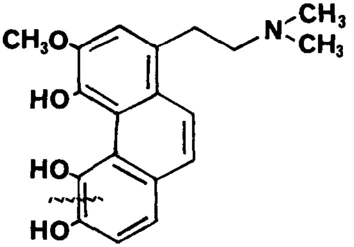

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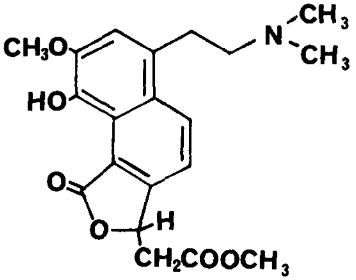

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Presently, we have found that chiloenamine (3) also occurs in B. darwinii Hook, where it is accompanied by the novel alkaloid santiagonamine (6), $C_{19}H_{18}N_2O_3$.[4] The 360 MHz ^{1}H NMR spectrum ($CDCl_3$) of santiagonamine has been summarized around expression 6. A telling feature of this spectrum is the set of aromatic doublets centered at δ 8.06 and 9.15 (J_o = 5.2 Hz) characteristic of the vicinal protons of a pyridine moiety, and the other set of aromatic doublets at δ 7.77 and 8.26 (J_o = 9.3 Hz) typical of H-9 and H-10 in a phenanthrene, or phenanthridine, system.[5]

A detailed NMR nuclear Overhauser difference study (NOEDS) was carried out on the alkaloid, the results of which are summarized in expression 6-NOE. All enhancements are inversely proportional to the sixth power of interproton distance.[6] Interestingly, a negative NOE of 4% was registered between the protons on the β carbon in the dimethylaminoethyl side chain and H-9 (δ 7.77). This negative indirect NOE is a counterpoint to the strong (22%) positive NOE of H-10 (δ 8.26) observed upon irradiation of the side chain β protons at δ 3.38.[7] A network of interproton connectivities was thus established, starting from the C-3 methoxyl protons, moving towards H-2 and H-α, and eventually terminating at H-7.

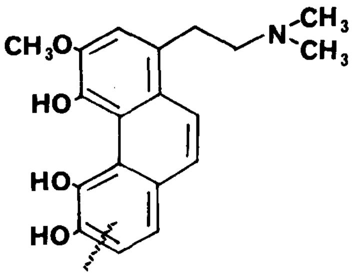
Significantly, santiagonamine (6) exhibits ν max $CHCl_3$ 1755 cm^{-1} (lactone carbonyl). The UV spectrum, λ max MeOH 225, 253, 273 sh, 300, 310, 366 nm (log ϵ 5.02, 5.03, 4.70, 4.60, 4.61, 4.45), undergoes a bathochromic shift in acid solution, λ max MeOH-H_3O^+ 229, 258, 267 sh, 278 sh, 298, 309, 329, 368, 391, 396, 400, 434 nm (log ϵ 5.03, 4.99, 4.94, 4.73, 4.39, 4.43, 4.32, 4.26, 4.28, 4.28, 4.27, 4.22). Furthermore, the methanolic solution of 6 turns yellow upon acidification.

The mass spectrum of santiagonamine (6) shows molecular ion peak m/z 322 (1). The dominating base peak is m/z 58 $(CH_2N(CH_3)_2)^+$. Other peaks are m/z 264 $(M - CH_2N(CH_3)_2)^+$ (0.35), 236 (0.75), 221 (0.16), 206 (0.53) and 193 (1.1).

The biogenesis of santiagonamine can best be explained as proceeding by catechol dioxygenase distal extradiol cleavage[3] of aporphine derivative 2. The resulting aldehydo acid 4 can readily lactonize to 5. Species 5 can then be converted to santiagonamine (6) through ammonia capture, followed by dehydrative cyclization.

At this stage, we considered the possibility that the trapping of ammonia and the subsequent cyclization could have occurred during the isolation process, since treatment of the plant extracts with ammonium hydroxide is a standard procedure during initial fractionation. If this were to be the case, then the true alkaloid would be the δ-lactone 5. In our hands, TLC of the crude ethanolic extracts from B. darwinii prior to treatment with ammonium hydroxide showed such a complex mixture of compounds that it was not possible to tell with certainty that santiagonamine was present as an "original" alkaloid.

A very recent report, however, throws light on this matter. A study of the alkaloids in the seeds of Erythrina melanacantha (Leguminosae) resulted in the isolation of the new type Erythrina base erymelanthine (9). This substituted pyridine was recognized as the product of an extradiol cleavage of the accompanying alkaloid erysovine (7), through the intermediacy of the aldehydo



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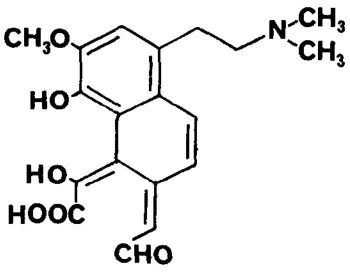

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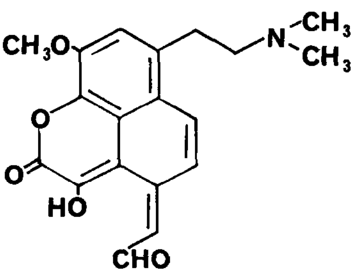

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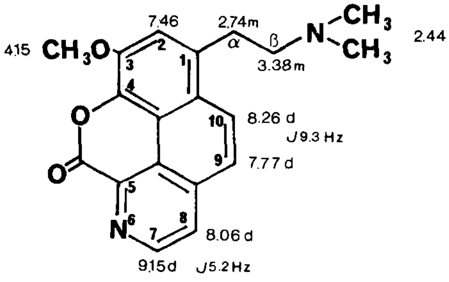

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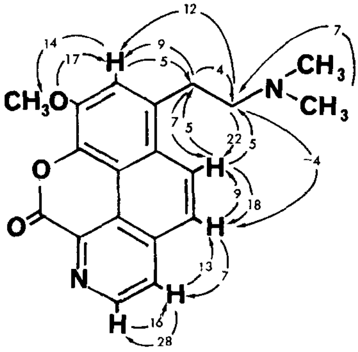
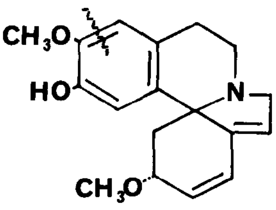


6 - NOE



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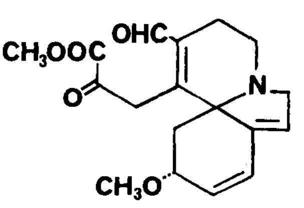

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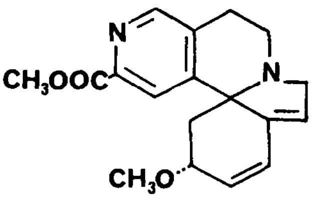

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ketoester 8.[8] In this instance, the number of natural products present in the seed was small enough that it was possible to reisolate erymelanthine (9) by a procedure omitting ammonium hydroxide during extraction. This effectively excluded the possibility that erymelanthine was an artifact of isolation.[8] It is a fair assumption, therefore, that by analogy santiagonamine is also a true natural product, and is thus the first known phenanthridine alkaloid.

The characterization of santiagonamine (6) furnishes us with a fresh insight into the catabolism of aporphines. It also indicates that catechol dioxygenase intradiol and distal extradiol cleavages may be operative within the same plant.

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References and Footnotes

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4. B. darwinii was collected in southern Chile, in the vicinity of Ciudad Osorno. The stems and branches of the plant (18 kg, dry) were collected during May-June 1982, and yielded 8.3 mg of santiagonamine (6) and 8.5 mg of chiloenamine (3). The molecular composition of santiagonamine, $C_{19}H_{18}N_2O_3$, was confirmed by high resolution mass spectroscopy.
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