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(±)-NUEVAMINE, AN ISOINDOLOISOQUINOLINE ALKALOID, AND (±)-LENNOXAMINE, AN ISOINDOLOBENZAZEPINE

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Abstract: Berberis darwinii Hook (Berberidaceae) has yielded the lactams (±)-nuevamine (7) and (±)-lennoxamine (8). Nuevamine is the first known isoindoloisoquinoline alkaloid, while lennoxamine is an isoindolobenzazepine structurally related to (±)-chilenine (3).

The study of the alkaloids of the Berberidaceae is facilitated by the fact that relatively large amounts of these plants can be collected. It, therefore, becomes possible to study the minor alkaloids present, i.e. those available only in small amounts, which often afford an insight into the catabolic pathways for the principal alkaloids.

The protoberberinium salt berberine (1) is present in large quantities in all Berberis species. An understanding of its catabolism was recently provided by the isolation of the minor alkaloid (±)-chilenine (3) from Berberis empetrifolia Lam. collected in southern Chile. (±)-Chilenine (3) is most probably formed in the plant by rearrangement of the reactive species 8,13-dioxo-14-hydroxycanadine (2), also named prechilenine, which is itself derived from oxidation of berberine (1).[1] The sequence berberine (1) ⟶ prechilenine (2) ⟶ chilenine (3) has also been carried out in vitro.[2]

We now wish to describe two minor alkaloids, (±)-nuevamine (7) and (±)-lennoxamine (8) which fulfill the useful function of describing for us some catabolic pathways from (±)-chilenine (3). Both compounds were obtained from B. darwinii Hook, gathered in southern Chile, in the vicinity of Ciudad Osorno.[3]

(±)-Nuevamine (7), $C_{19}H_{17}NO_5$, mp 212° C (MeOH), ν max $CHCl_3$ 1675 cm^{-1} (lactam carbonyl), has a mass spectrum with molecular ion peak m/z 339, which is also the base peak. Most of the remaining peaks can be accounted for either by loss of methyl or methoxyl groups, or by cleavage along the dotted lines in diagram 7 (Table). The NMR spectrum at 200 MHz in $CDCl_3$ was very informative, and has been summarized around expression 7A. The key feature is the one-proton singlet at δ 5.64 representing H-13 which is doubly benzylic and also alpha to the lactam nitrogen.

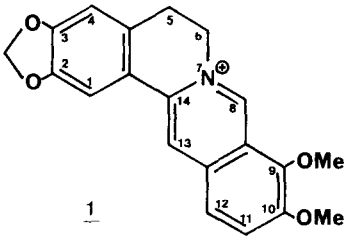
Following the structural elucidation of nuevamine (7) by spectral means, it was recalled that this compound had been prepared synthetically a few years ago by treatment of (±)-chilenine (3) with methanolic potassium hydroxide to afford imidol 4. Species 4 underwent acid catalyzed cyclization to the dienonium cation 6 via the deep red iminium salt 5. The unisolated cation 6 then suffered facile decarboxylation to the isoindoloisoquinoline 7.[2] Presently, spectral and tlc comparison of natural (±)-nuevamine with synthetic 7 proved the two materials to be identical.

The biogenesis of nuevamine (7) in all likelihood closely resembles the *in vitro* pathway followed for its semisynthesis from berberine and chilenine as delineated above. Nuevamine is thus the first recognized isoindoloisoquinoline alkaloid. To ascertain that nuevamine was not an artifact of isolation, chilenine (3) was treated with ammonium hydroxide, acidified with aq. HCl, and rebasified with ammonium hydroxide. This procedure, which parallels the isolation sequence, did not provide any nuevamine (7).

That chilenine (3) can also be metabolized through a different pathway is indicated by the isolation of our second alkaloid (±)-lennoxamine (8), which besides chilenine is the only natural isoindolobenzazepine known. (±)-Lennoxamine (8), $C_{20}H_{19}NO_5$, mp 225° C (MeOH), ν max $CHCl_3$ 1675 cm^{-1} (lactam carbonyl), has a mass spectrum where the molecular ion m/z 353 is the base peak. Some of the significant cleavages are along the dotted lines shown in expression 8 (Table).

The NMR spectrum of lennoxamine furnished nearly conclusive structural evidence, and has been outlined around expression 8A. H-13 which is alpha to the lactam nitrogen is now relatively upfield at δ 4.29 since it is mono rather than doubly benzylic. Additionally, it is split into a ddd system by the C-14 methylene protons as well as by long range coupling with H-12.

The racemic compound 8 had been reliably and conveniently prepared in the early 1970's by Brossi and coworkers.[4] In our hands, spectral and tlc comparison of (±)-lennoxamine with authentic 8 showed the two materials to be identical.



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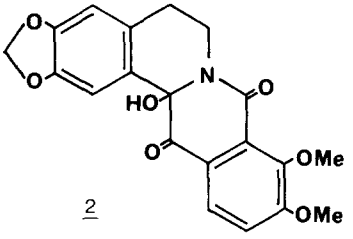

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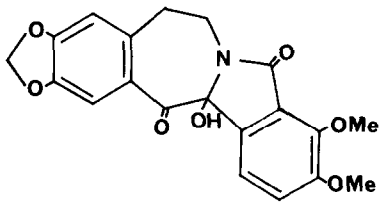

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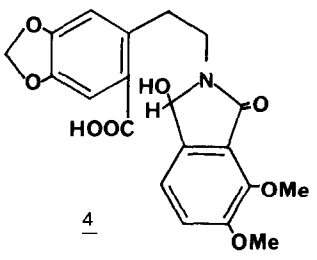

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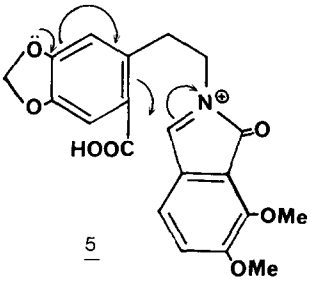

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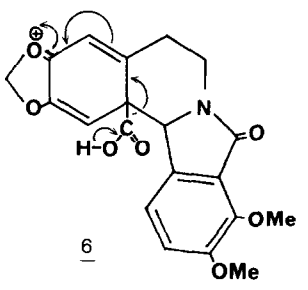

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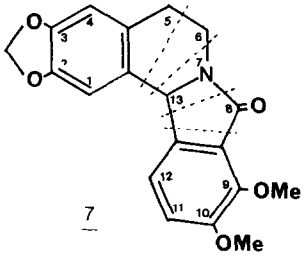
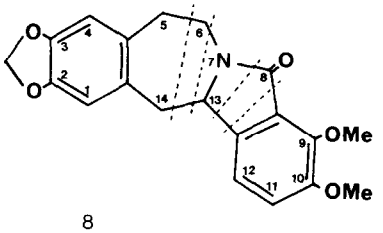


7



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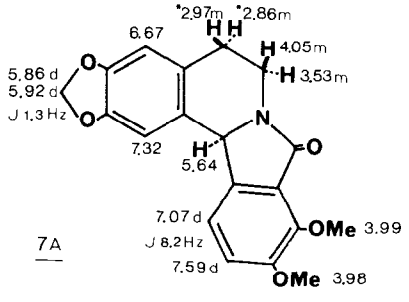
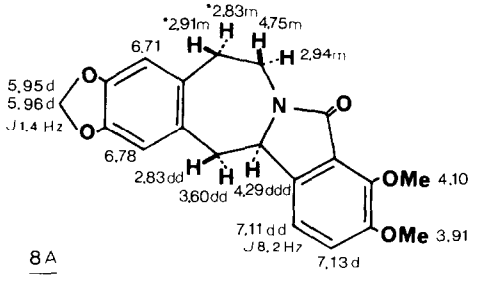


7A



8A

$J_{14\alpha,14\beta}$ 14,6 Hz ; $J_{3,14\alpha}$ 1,5 Hz

$J_{13,14\beta}$ 10,6 Hz ; $J_{12,13}$ 0,87 Hz

*Chemical shifts with identical superscripts are interchangeable.

The most rational hypothesis for the formation of (±)-lennoxamine (8) in nature is that it originates from a series of dehydrations and reductions of (±)-chilenine (3).

Two points are worth noting in conclusion. Firstly, since chilenine (3) is a racemate, it follows that nuevamine (7) and lennoxamine (8) are also racemic. Secondly, the C-14 ketonic center of chilenine (3) may undergo *in vivo* nucleophilic attack to supply eventually either nuevamine (7) or lennoxamine (8). Nature, however, does not provide for a facile reduction of an amide carbonyl, so that the lactam moiety of chilenine (3) is transferred intact into nuevamine (7) and lennoxamine (8).[5]

TABLE: Spectral Characteristics of the Alkaloids

Nuevamine (7): λ max (MeOH) 250 sh, 262, 276 sh nm (log ε 3.90, 4.09, 3.45); ms m/z 339 $(M)^+$ (100), 338 (67), 325 (11), 324 (44), 310 (13), 308 (38), 294 (13), 293 (7), 292 (6), 281 (8), 280 (7), 164 (6).

Lennoxamine (8): λ max (MeOH) 235 sh, 293 nm (log ε 4.11, 4.05); ms m/z 353 $(M)^+$ (100), 352 (17), 339 (10), 338 (47), 335 (28), 205 (14), 192 (18), 190 (18), 162 (56), 161 (79), 160 (29), 149 (22).

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References and Footnotes

1. Fajardo, V.; Elango, V.; Cassels, B.K.; Shamma, M. Tetrahedron Lett. 1982, 23, 39.
2. Moniot, J.L.; Hindenlang, D.M.; Shamma, M. J. Org. Chem. 1979, 44, 4347.
3. The plant (18 kg, dry) was collected during May-June 1982. The chromatographic fractions were further purified by recrystallization to yield 7 (1.3 mg) and 8 (2 mg).
4. Teitel, S.; Klötzer, W.; Borgese, J.; Brossi, A. Can. J. Chem. 1972, 50, 2022.
5. TLC R_f values on Merck Silica Gel F-254 glass plates are for nuevamine (7) 0.59, and for lennoxamine (8) 0.83, in the system $CHCl_3$-MeOH (97:3 v/v).

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