(+)-ROEMECARINE, A C-4 HYDROXYLATED TETRAHYDROBENZYLISOQUINOLINE ALKALOID

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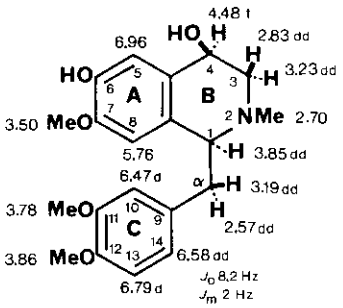
Abstract - Roemeria carica A. Baytop (Papaveraceae) of Turkish origin has supplied (+)-roemecarine (1), which is the first C-4 hydroxylated tetrahydrobenzylisoquinoline alkaloid. Species 1 is accompanied in the plant extract by its N-oxide, (+)-roemecarine 2-α-N-oxide (4).

Although more than sixty naturally occurring tetrahydrobenzylisoquinolines have been reported in the literature, none are hydroxylated at the benzylic C-4 position. On the other hand, several aporphines,[4] protoberberines,[5] and cularines[6,7] are known which bear a benzylic hydroxyl substituent at the corresponding site on ring B.

Since all aporphines, protoberberines and cularines originate biogenetically from tetrahydrobenzylisoquinoline precursors, it would be expected that tetrahydrobenzylisoquinolines hydroxylated at C-4 exist in nature. Indeed, it has been shown that the ring B benzylic hydroxyl in the protoberberine alkaloid berberastine is introduced at an early stage of the biogenetic sequence,[8] so that the intermediacy of a C-4 hydroxylated tetrahydrobenzylisoquinoline precursor could be contemplated.

We now describe the amorphous alkaloid (+)-roemecarine (1), $C_{20}H_{25}NO_5$, found in Roemeria carica A. Baytop (Papaveraceae), which is the first naturally occurring C-4 hydroxylated tetrahydrobenzylisoquinoline.[9]

The mass spectrum of roemecarine (1) shows a very weak $(M - 1)^+$ ion, m/z 358 (0.1%). The base peak, m/z 208, corresponds to species 2 which represents the upper half of the molecule. Additionally, 2 can lose the elements of water to form ion 3, m/z 190 (29%).[10]



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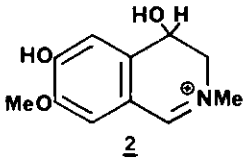

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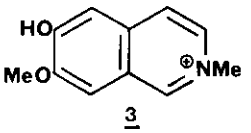

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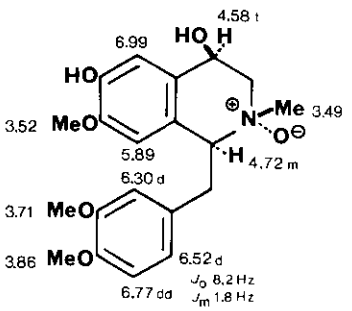

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Besides incorporating an alcoholic function, (+)-roemecarine (1) is phenolic since its UV spectrum shows a definite bathochromic shift in base.[10]

The 360 MHz ($CDCl_3$) NMR spectrum displays five aromatic proton absorptions, two as singlets and three as an ABX system. (+)-Roemecarine (1) thus bears four aromatic substituents, and has the same aromatic oxygenation pattern as the tetrahydrobenzylisoquinoline laudanosoline. Present also in the spectrum is an N-methyl signal at δ 2.70. Three methoxyl singlets are in evidence, one of which is upfield at δ 3.50 and is characteristic of a C-7 substituent.[11] The two remaining methoxyls which absorb at δ 3.78 and 3.86 must be attached to ring C. An interesting feature of the spectrum is the one-proton narrow triplet at δ 4.48 due to H-4 which is gem to the hydroxyl. This hydroxyl is also responsible for the downfield shift of H-5 to δ 6.96.

Ring B in a tetrahydrobenzylisoquinoline such as (+)-roemecarine (1) possesses essentially the same conformation as ring B of an aporphine, and benzylic hydroxylation should have nearly the same effect in both instances. In order to establish the relative stereochemistry of (+)-roemecarine (1), the NMR spectrum of the alkaloid was, therefore, compared with those of aporphines hydroxylated at C-4 of established chirality. In such aporphines, H-4 appears near δ 4.50 as an apparent triplet when syn to the asymmetric H-6a, and at δ 4.90 as a doublet of doublets if anti to H-6a.[4,12] The δ 4.48 apparent triplet absorption in the NMR spectrum of (+)-roemecarine (1) is indicative of a syn relationship between H-1 and H-4.[13]

A detailed NMR NOEDS study of 1 showed that H-4 (δ 4.48) is proximate to H-5 (δ 6.96). Furthermore, the chemical shift assignments for the three methoxyls as well as for the remaining aromatic protons were also confirmed.[10]

The alkaloid is dextrorotatory, and its CD spectrum shows a strong maximum at 238 nm, with a negative tail below 232 nm. These data are consistent with the 1S configuration.[14] It follows that (+)-roemecarine is defined by expression 1.

Accompanying (+)-roemecarine (1) in the plant extracts was the corresponding N-oxide, (+)-roemecarine 2-α-N-oxide (4), $C_{20}H_{25}NO_6$, whose zinc in hydrochloric acid reduction furnished (+)-roemecarine (1).[15] The chemical shift for H-1 in a tetrahydrobenzylisoquinoline N-oxide is diagnostic of the relative stereochemistry.[16] When the N-oxide oxygen is syn to H-1, the latter appears downfield between δ 4.50 and 4.70. In the alternate anti configuration, H-1 falls between δ 4.00 and 4.30. The H-1 absorption in (+)-roemecarine 2-α-N-oxide is at δ 4.72, so that this N-oxide incorporates the syn arrangement as indicated in expression 4.[17]

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REFERENCES AND NOTES

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9. R. carica was collected between Marmaris and Bozburun, in Muğla Province, on March 31, 1985. A voucher specimen, No. 621, was deposited in the Herbarium of the Department of Pharmacognosy, Ege University. The powdered dry plant (1 kg) was extracted with cold EtOH. The extract was treated with 5% aq. HCl. The acidic soln. was basified with NH_4OH, and the alkaloids extracted with $CHCl_3$. The crude alkaloids (0.5 g) were placed on a silica gel chromatographic column. Elution was with $CHCl_3$ followed by $CHCl_3$ enriched with increasing amounts of MeOH. Alkaloids isolated were (+)-roemecarine (1), 4.2 mg; (+)-roemecarine 2-α-N-oxide (4), 3 mg; the aporphine (+)-isocorydine, 1 mg; and the phthalideisoquinoline (-)-α-narcotine, 3 mg.

10. (+)-Roemecarine (1): $C_{20}H_{25}NO_5$; m/z 358 $(M - 1)^+$ (0.1), 357 (0.2), 341 (0.1), 340 (0.2), 339 (0.5), 208 (100), 190 (29); λ max (MeOH) 229 sh, 282 nm (log ε 4.03, 3.66); λ max (MeOH + OH^-) 237 sh, 253 sh, 286, 305 sh nm (log ε 3.98, 3.83, 3.64, 3.53); Δε (nm) (MeOH)

0 (298), +1 (284), 0 (255), +5 (238), negative tail below 232 nm ; $[\alpha]_D$ +9° (c 0.07, MeOH). NMR aliphatic protons coupling constants $J_{3\alpha,4}$ 3.2 Hz, $J_{3\beta,4}$ 2.6 Hz, J_{3gem} 12.6 Hz, $J_{1,\alpha\alpha}$ 9.2 Hz, $J_{1,\alpha\beta}$ 3.5 Hz, $J_{\alpha gem}$ 13.2 Hz. Significant NMR NOE's are MeO-7 to H-8 (20%), H-8 to MeO-7 (12%), MeO-11 to H-10 (20%), H-10 to MeO-11 (14%), MeO-12 to H-13 (25%), H-13 to MeO-12 (14%), H-5 to H-4 (11%), H-4 to H-5 (9%), H-4 to H-3α (3%), H-3α to H-4 (9%), H-1 to H-10 (12%), H-10 to H-1 (4%), N-Me to H-1 (9%).

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15. (+)-Roemecarine 2-α-N-oxide (4): $C_{20}H_{25}NO_6$; m/z 375 $(M)^+$ (0.3), 373 (0.4), 359 (1), 357 (2), 341 (1), 224 (2), 208 (100), 190 (17); λ max (MeOH) 231, 282 nm (log ε 4.07, 3.70); Δε (nm) (MeOH) 0 (294), +1.2 (280), +0.5 (255), +6 (239), negative tail below 232 nm; $[\alpha]_D$ +18° (c 0.09, MeOH).

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