

CALAFATIMINE, A NEW IMINO BISBENZYLISOQUINOLINE ALKALOID

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Abstract — A new bisbenzylisoquinoline alkaloid from Berberis buxifolia was chemically correlated with calafatine. On this basis, and using spectrometric evidence, structure 1 is proposed for calafatimine. The stereochemistry of calafatine is discussed using its specific rotation and that of calafatimine.

The structure of calafatine, the unusually substituted major bisbenzylisoquinoline alkaloid from the roots of Berberis buxifolia Lam. ("calafate") was published recently.¹ Calafatine is also a component of the stem bark of this species, and it is found in both roots and stems together with berberine, argemonine, norargemonine, syringaresinol,² and the alkaloid described here under the name calafatimine (1).

Calafatimine crystallized from benzene-cyclohexane, mp 180-182 °C, $[\alpha]_D^{20} -141$ °(CHCl₃). Its UV spectrum showed $\lambda_{\text{max}}^{\text{MeOH}}$ (log ε) 235 (4.85 sh), 280 (4.40), and 292 nm (3.93 sh), with no shift on adding 0.1 M NaOH. The mass spectrum showed intense molecular and M-1 ions at m/e 636 (100 %, C₃₈H₄₀N₂O₇) and 635. An abundant double benzylic cleavage fragment was observed at m/e 381 (85 %), while the corresponding doubly charged species at m/e 190.5 was relatively unimportant (38 %). Other significant peaks came at m/e 606 (4 %), 590 (3 %), 575 (5 %), 469 (3 %), 367 (20 %), 318 (4 %), 184 (13 %), and 174 (14 %). These data agree with a head-to-head, tail-to-tail imino bisbenzylisoquinoline structure,³ with one N-methyl and three methoxyl groups in the isoquinolinoxy-isoquinoline portion, and two methoxyl groups in the benzylic half.

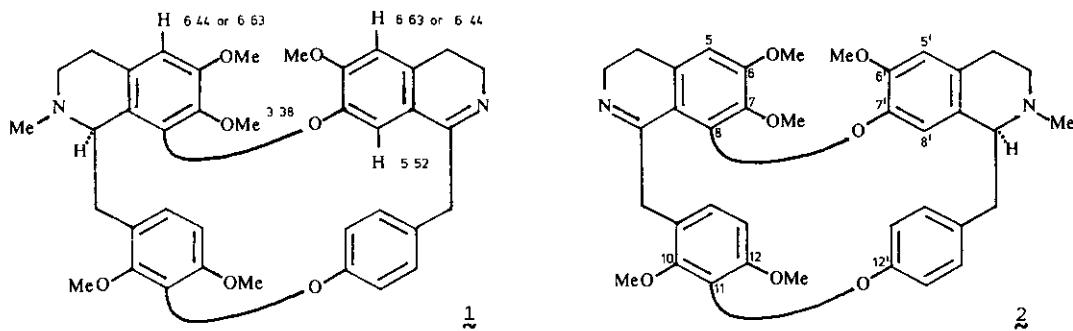
The PMR (CDCl₃) spectrum of calafatimine confirmed the presence of five methoxyl groups (three-proton singlets at 3.38, 3.74, 3.80, 3.82, and 3.90 ppm), a single N-methyl group (three-proton singlet at 2.40 ppm), and nine aromatic ring protons resonating between 5.52 and 7.23 ppm. The aromatic proton resonance pattern bears a striking resemblance to that recorded for calafatine, with a one-proton singlet at 5.52 ppm assignable to a hydrogen atom at C(8) or C(8'),⁴ and two more one-proton singlets at 6.44 and 6.63 ppm corresponding to hydrogen atoms at C(5) and C(5').

A two-proton AB system with an apparent coupling constant of about 8 Hz occurs at 6.80 and 7.02 ppm, and can be assigned to the hydrogen atoms at C(13) and C(14). Three one-proton doublets of doublets, apparent coupling constants of about 2 and 8 Hz, are centered at 5.98, 6.44, and 7.23 ppm; a fourth is partially obscured by the abovementioned signal at 7.02 ppm, and all four are assignable to the hydrogen atoms on ring F.

Sodium borohydride reduction of calafatimine and N-methylation of the mixture of products (using formaldehyde-NaBH₄) afforded two compounds, one of which exhibited the same chromatographic behavior as calafatine. This substance was isolated and identified as calafatine (mp, IR, tlc), showing that calafatimine has the same unusual oxygenation pattern, and that the single chiral carbon atom in calafatimine must have the same absolute configuration as one of the dissymmetric centers in calafatine.

The N-methyl resonance at 2.40 ppm can be considered indicative of a tertiary nitrogen atom in ring A, as the corresponding signal in the structurally related thalsimine and thalibrunimine^{5,6} also appears at relatively low δ values. In this case, C(1) should be the chiral atom in (-)-calafatimine, and as its moderately high specific rotation is opposite in sign to those of the (S,M) 8*,11^t-7*,12^t bisbenzylisoquinoline alkaloids (+)-thalsimidine, (+)-thalsimine, and (+)-thalibrunimine, its absolute configuration should be (R,M), and therefore (+)-calafatine should be (R,S).⁷ This stereochemical assignment fits into a regular pattern which may be of biogenetic and chemosystematic consequence: all the 8*,11^t-7*,12^t bisbenzylisoquinoline alkaloids isolated from Berberis species have the (R,S) configuration, although the (S,S) configuration is quite common for this ring system in Thalictrum and in the more distantly related Menispermaceae, Atherospermataceae (= Monimiaceae-Atherospermoideae), and Hernandiaceae. The (R) configuration at C(1) is present in calafatine and calafatimine despite the extra oxygen substituent at C(10), and the same is true for the (S) configuration at C(1) in thalibrunine, N'-norththalibrunine, thalibrunimine, oxothalibrunimine, thalictrinine, and dihydrothalictrinine, where C(14) is hydroxylated.⁶

Structure 1 is based in part on the position of the N-methyl resonance. As this cannot be taken as adequate proof of the location of the N-methyl group, an alternative structure (2) must be considered for calafatimine, with its chiral center in ring D. Since the ring D configuration of the stereochemically correlated calafatine should be (S),⁷ calafatimine would belong to the heretofore unknown (M,S) 8*,11^t-7*,12^t subgroup of bisbenzylisoquinoline alkaloids, a possibility that would seem less likely.



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References

1. V. Fajardo, A. Urzúa, and B. K. Cassels, *Heterocycles*, 1979, 12, 1559.
2. V. Fajardo, A. Urzúa, R. Torres, and B. K. Cassels, *Rev. Latinoam. Quím.*, 1979, 10, 131.
3. J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. Chem. Soc. Perkin Trans 1*, 1972, 592.
4. The numbering system used is that of M. Shamma and J. L. Moniot, *Heterocycles*, 1976, 4, 1817.
5. J. M. Saá, M. V. Lakshminikantham, M. J. Mitchell, M. P. Cava, and J. L. Beal, *Tetrahedron Lett.*, 1976, 513.
6. J. Wu, J. L. Beal, and R. W. Doskotch, *J. Org. Chem.*, 1980, 45, 213.
7. B. K. Cassels and M. Shamma, *Heterocycles*, 1980, 14, 211.

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