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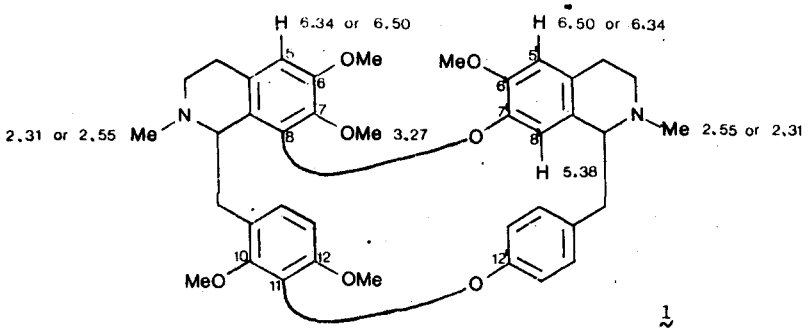
Abstract — Spectrometric and chemical evidence is presented that calafatine, an alkaloid from Berberis buxifolia, has structure 1. The substitution pattern on ring E is unique in isoquinoline alkaloids.

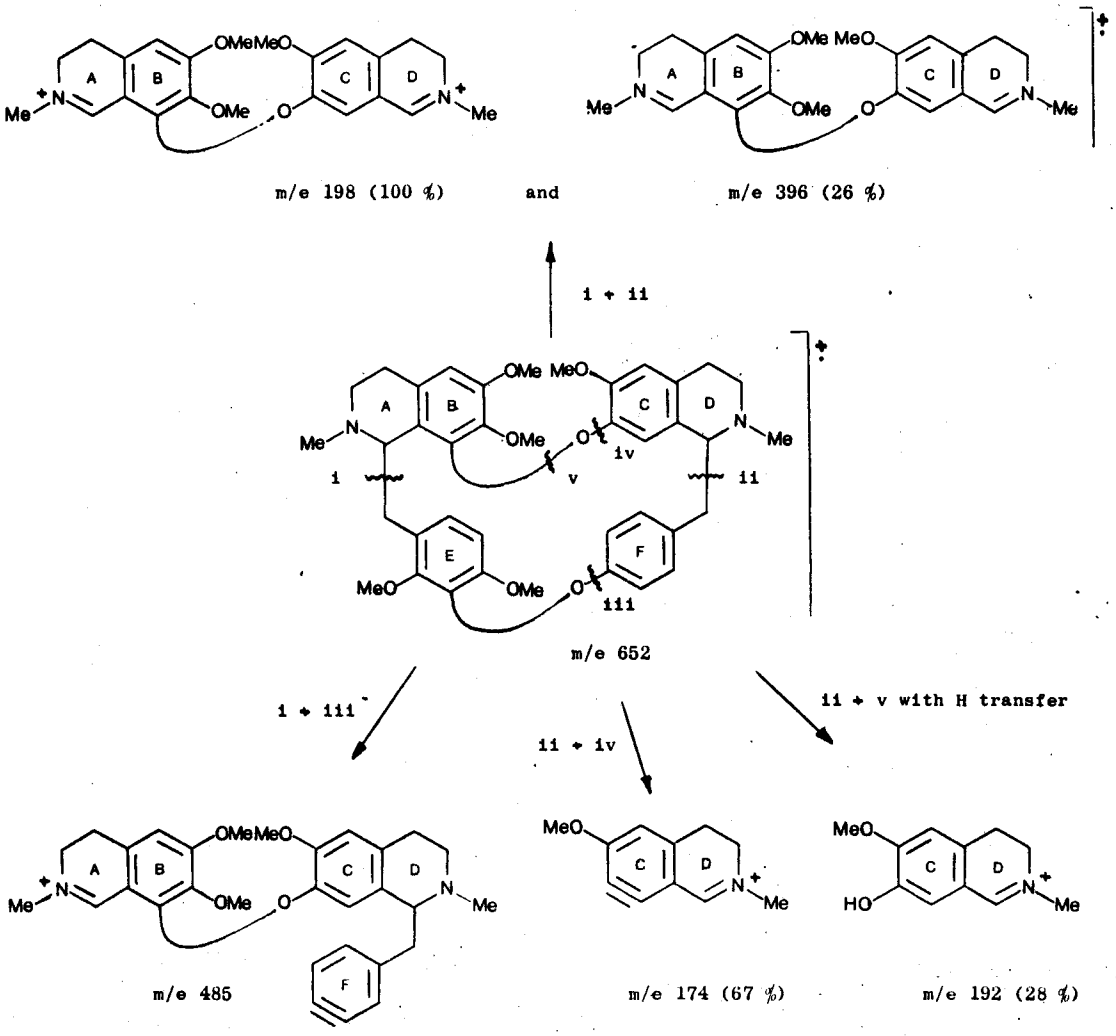
Berberis buxifolia Lam. ("calafate") has been shown to contain norargemonine, argemonine, and the lignan syringaresinol in addition to berberine.[1] In this communication the structure of calafatine (1), the major nonquaternary extractive of the roots, is discussed.



1

Calafatine crystallized from benzene-cyclohexane in needles, mp 135-137°C, $[\alpha]_D$ + 280° ($CHCl_3$). Its UV spectrum showed λ_{max}^{MeOH} (log ε) 281 (3.82), and 258 nm (3.32), unchanged upon addition of alkali, consistent with a non-phenolic oxygenated benzyltetrahydroisoquinoline chromophore. Its mass spectrum (Scheme 1) showed the molecular ion at m/e 652 corresponding to the molecular formula $C_{39}H_{44}N_2O_7$, indicating that the substance is a doubly coupled bisbenzyltetrahydroisoquinoline, as the UV spectrum rules out the possibility of any unsaturations besides the aromatic systems. The base peak came at m/e 198 and a fairly abundant ion was also observed at m/e 396, giving evidence that both isoquinoline portions are joined together.[2] It can therefore be concluded that calafatine is a head-to-head, tail-to-tail bisbenzyltetrahydroisoquinoline. Assuming that an ether bridge is involved in the coupling of the heterocyclic systems, the mass of the simply and doubly-charged benzylic cleavage (i + ii) products indicates that this part of the molecule should bear two N-methyl groups and three methoxyl groups, leaving two methoxyl groups in the benzylic portions of the molecule.

Scheme 1



The PMR ($CDCl_3$) spectrum of calafatine confirmed the presence of two N-methyl groups (three-proton singlets at δ 2.31 and 2.55 ppm) and five methoxyl groups (three-proton singlets at 3.27, 3.65, 3.71, 3.72, and 3.83 ppm). A one-proton singlet at 5.38 ppm could be assigned to a hydrogen atom at C-8 or C-8', and the absence of any other high-field aromatic proton suggested that either C-8 or C-8' is involved in the coupling of both halves of the molecule. Two further one-proton singlets at 6.34 and 6.50 ppm are assignable to hydrogen atoms at C-5 and C-5'. Three one-proton doublets at 5.88, 6.34, and 7.10 ppm with apparent coupling constants of about 2 and 10 Hz are clearly visible in the spectrum, while a fourth at 6.90 ppm is partly obscured by an asymmetrical doublet

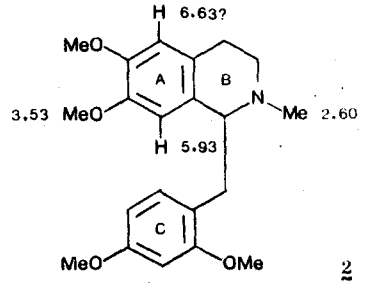
with the same frequency and an apparent coupling constant of about 10 Hz. These doublets of doublets can be assigned to the four non-equivalent hydrogen atoms of a 4-substituted benzyl group in a macrocycle. The wide doublet's companion occurs at 6.70 ppm, and both can be assigned to the hydrogen atoms on ring E, which is therefore substituted at C-10, C-11, and C-12.[3]

The high resonance field of one of the methoxyl groups (3.27 ppm) is characteristic of C-7 or C-7' substituents when C-8 or C-8', respectively, is involved in a diaryl ether bridge.[4] This, together with the aromatic singlet data, shows that the alkaloid is either C-8/C-7' or C-7/C-8' coupled. As one of the benzyl rings is 10,11,12-trisubstituted, C-10 or C-11 should be joined to the C-12' oxygen atom in the other half of the molecule if the concept of phenolic oxidative coupling is applicable. This would restrict the structural possibilities to only four, namely 6,7,8*,10†,11,12 - 6,7*,12†; 6,7*,10†,11,12 - 6,7,8*,12†; 6,7,8*,10,11†,12 - 6,7*,12†; and 6,7*,10,11†,12 - 6,7,8*,12† with all available oxygen atoms methylated.

Closer inspection of the mass spectrum showed the presence of a low-abundance ion at m/e 485 attributable to the loss of ring E (i → iii) with hydrogen transfer, while no similar loss of ring F could be discerned. This fragmentation is characteristic of 6,7,8*,11†,12 - 6,7*,12† bisbenzyltetrahydroisoquinolines.[2] Furthermore, an intense (67 %) peak at m/e 174 can be explained by a cleavage (ii → iv) involving the isolation of rings C and D in this same type of alkaloids,[2] and another at m/e 192 should result from a related process (ii → v). These facts support the 6,7,8*,10,11†,12 - 6,7*,12† alternative for the structure of calafatine. Further evidence in favor of this structure comes from the N-methyl resonances, which are separated by more than 0.2 ppm in berbamine and related compounds, while both appear close together around 2.5 ppm in oxyacanthine and its congeners.[4]

In order to find some chemical support for this novel and unusual structure, a sodium - liquid ammonia cleavage was carried out. Only one non-phenolic product melting at 86°C (ligroin) was isolated in sufficient quantity to obtain its PMR ($CDCl_3$) spectrum, which showed the presence of one N-methyl group resonating at 2.60 ppm and four methoxyl groups at 3.53, 3.78, and 3.83 (6 H) ppm. The higher shielding of the 3.53 ppm methoxyl group shows that it represents the C-7 substituent in fragment (2). The C-8 and C-5 protons give singlets at 5.93 and (probably) 6.63 ppm, respectively, and the remaining three aromatic protons give a compex pattern between 6.35 and 6.85 ppm which was not investigated further due to lack of material. To test the possibility that this substance was laudanosine (3), originating from a C-10/C-12' dimer, the racemic base was prepared by borohydride reduction of papaverine methiodide. The PMR ($CDCl_3$) spectrum of laudanosine showed the N-methyl resonance at 2.50 ppm, methoxyl resonances at 3.54, 3.74, and 3.80 (6 H) ppm, and aromatic singlets

at 6.06 and (probably) 6.70 ppm, and a complex pattern due to the ring C hydrogen atoms, between 6.35 and 6.85 ppm, which clearly differed from that given by the reduction product of calafatine.



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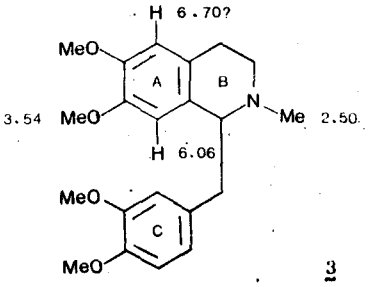

3

This is the first known example of a 6,7,8',10,11',12 - 6,7',12' bisbenzylisoquinoline alkaloid. Trisubstitution in ring E is unusual, but two meta methoxyl groups with an aryl ether function in between constitute a pattern which is so far unique in isoquinoline alkaloids. On biogenetic grounds one would expect this structure to arise from the coupling of two coclaurine units with C-10 oxidation at a later stage, or by coupling of a coclaurine moiety with a 6,7,10,12-tetraoxygenated benzyltetrahydroisoquinoline, a possibility which would seem less likely. Still, the existence of the structurally related 6,8-disubstituted aristolochic acids and aristolactams suggests that 6,7,10,12-tetrasubstituted benzylisoquinoline precursors, whatever their origin, may have to be considered in biogenetic theory.[5]

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References

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5. We are presently going through the process of reisolation, so as to obtain enough calafatine to establish its absolute configuration.

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