Revised Structures of Hernandezine and Thalsimine. Mass Spectrometry of a Bisbenzylisoquinoline Alkaloid

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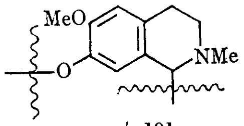
THE alkaloid (+)-hernandezine, isolated from *Thalictrum hernandezii,* was assigned the bisbenzylisoquinoline structure (I) on the basis of elemental analysis ($C_{39}H_{44}O_7N_2$), n.m.r. data, and its conversion on oxidation into the dibasic acid (II). Cleavage of the alkaloid with potassium in liquid ammonia afforded, as the sole product isolated, a phenolic base (m.p. 138—139°) which analyzed for $C_{39}H_{46}O_7N_2$ but was not further characterized.[1]

We have now isolated hernandezine from *T. fendleri*; and it also occurs in *T. rochebrunianum.*[2] Re-examination of the n.m.r. spectrum of hernandezine[1] confirmed the presence of a high-field aromatic proton at $\delta = 6{\cdot}02$. A signal in this region of a benzyltetrahydroisoquinoline spectrum is characteristic of a C-8 proton highly shielded by the atomatic ring of a benzyl group;[3] such a proton is not found in structure (I). The mass spectrum of hernandezine confirmed the molecular weight of 652 ($C_{39}H_{44}O_7N_2$) but offered further evidence against structure (I), and strong support for the isomeric formulation (IV).[4]

The base peak in the spectrum is a doubly charged fragment (III) at *m/e* 213 (isotope 213·5) derived from the two isoquinoline rings of the alkaloid. Most significant for the differentiation of structures (I) and (IV) is the fragment at *m/e* 461 corresponding to $M - 191$; fragments at *m/e* 190 and 192 form when the charge is retained on the monomethoxylated isoquinoline ring with hydrogen transfer.[5]

If (IV) is indeed the correct structure for hernandezine, it would be expected that the diphenolic base *N*-methylcoclaurine (VI) would be formed as a result of cleavage with sodium or potassium in liquid ammonia. Optically active (VI) has been reported to melt at 138—139°, corresponding exactly to the melting point of the sublimable crystalline phenol mentioned in the first paragraph.[6] In addition, the elemental analytical values found for this phenol fit the formula $C_{18}H_{21}O_8N$ required for *N*-methylcoclaurine (VI), as well as the previously assumed formula $C_{39}H_{46}O_7N_2$.


m/e 191

That the sublimable crystalline phenol from hernandezine is indeed *N*-methylcoclaurine became a virtual certainty from the results of a recent paper by Maekh and Yunusov concerning the structure of thalsimine, a new bisbenzylisoquinoline alkaloid from *T. simplex.* This base was shown to be identical with hernandezine, with the exception that one of the $\text{C–}\overset{|}{\text{N}}\text{–CH}_3$ functions of hernandezine is replaced by the imino-function $\text{–}\overset{|}{\text{C}}\text{=N–}$. When thalsimine or 1′,2′-dihydrothalsimine was cleaved with sodium in liquid ammonia, coclaurine was formed and characterized as such. In spite of this last fact, however, structure (Ia) was assigned to thalsimine.[7]

We have re-run the sodium in liquid ammonia cleavage of hernandezine with a view to isolating the non-phenolic component and thus settling conclusively the structure of this alkaloid. Instead of obtaining the expected tetramethoxybenzylisoquinoline (VII), we isolated the oily trimethoxy-derivative (VIII), $C_{20}H_{25}O_3N$. The n.m.r. spectrum

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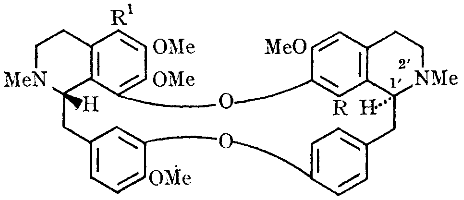
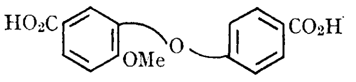
of (VIII) showed three methoxy-groups at $\delta = 3{\cdot}72$ (6H) and 3·53 (3H), and one *N*-methyl group at $\delta = 2{\cdot}44$. The A_2B_2 pattern for the aromatic protons in the bottom ring is clearly visible as four peaks centred at $\delta = 6{\cdot}82$ and 7·05 (apparent $J = 9$ c./sec.). Two additional aromatic protons, corresponding to those at C-6 and C-8 appeared as doublets at $\delta = 6{\cdot}27$ and 5·85, with characteristic *meta*-splittings of $J = 3$ c./sec. Both the C-7 methoxy (at $\delta = 3{\cdot}53$) and the C-8 proton are shifted upfield, commensurate with shielding by the bottom aromatic ring.[3] Since hindered aromatic methoxy-groups tend to cleave upon reduction with sodium in liquid ammonia, the formation of (VIII) could still be rationalized in terms of structure (IV) for hernandezine. In line with this result, sodium in liquid ammonia cleavage of authentic *O*-methylthalifendlerine (VII)[8] was then found to yield the same trimethoxy-base (VIII). It follows that structure (IV) must be that of hernandezine, and (IVa) that of thalsimine. Both structures incorporate the 18-membered ring characteristic of most bisbenzylisoquinolines possessing two diphenyl ether linkages.

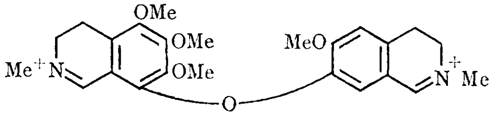


(I) R=OMe; R^1=H

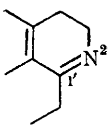
(IV) R=H; R^1=OMe



(II)

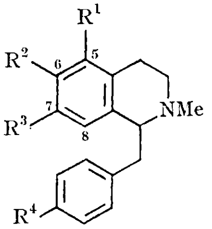


(III) *m/e* 213



(Ia) rest of molecule as in (I)

(IVa) rest of molecule as in (IV)



(V) $R^1=R^2=R^3=$OMe; $R^4=$OH

(VI) $R^2=$OMe; $R^3=R^4=$OH; $R^1=$H

(VII) $R^1=R^2=R^3=R^4=$OMe

(VIII) $R^1=R^3=R^4=$OMe; $R^2=$H

Hernandezine and thalsimine are novel structures in that they represent the first bisbenzylisoquinoline bases having an oxygenated function at C-5. It is biogenetically significant that hernandezine occurs in *T. fendleri* along with thalifendlerine (V),[8] which clearly represents one-half of the hernandezine molecule.

The present work illustrates the first use of mass spectrometry in the assignment of a bisbenzylisoquinoline structure. In a later paper we will describe in detail the mass-spectral behaviour of several bisbenzylisoquinolines, and the general utility of mass spectrometry in the structure determination of this group of alkaloids.

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[1] J. Padilla and J. Herran, *Tetrahedron*, 1962, **18**, 427.

[2] J. L. Beal and H. H. Fong, unpublished results.

[3] D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Letters*, 1965, 2687.

[4] The (*SS*)-configuration was recently assigned to hernandezine on the basis of optical rotatory dispersion data: A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J. Chem. Soc.*, 1965, 2239. Revision of structure (I) to structure (IV) does not change the validity of the stereochemical arguments presented in the English paper.

[5] The loss of a single isoquinoline unit by the specific rupture of the ether bridge joining it to a second isoquinoline ring is observed in the mass spectra of other bisbenzylisoquinoline bases, and appears to be a general cracking pattern in this series.

[6] M. Tomita and F. Kusuda, *J. Pharm. Soc. Japan*, 1952, **72**, 280.

[7] S. Kh. Maekh and S. Yu. Yunusov, *Doklady Akad. Nauk Uzbek. S.S.R.*, 1964, **21** (9), 27; (*Chem. Abs.*, 1965, **62**, 13191).

[8] M. Shamma, M. A. Greenberg, and B. S. Dudock, *Tetrahedron Letters*, 1965, 3595.