The Mass Spectrometry of Some Bisbenzyltetrahydroisoquinoline Alkaloids

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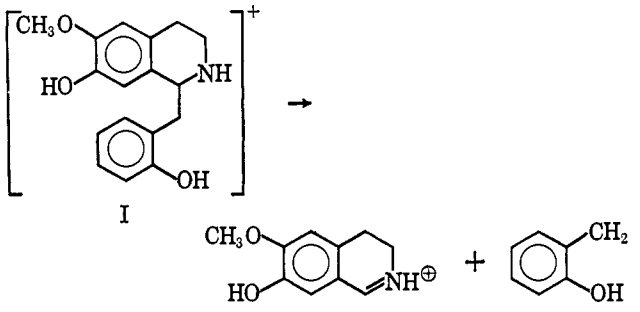
Abstract: The mass spectra of several alkaloids and alkaloid derivatives of the bisbenzyltetrahydroisoquinoline group have been determined. Interpretation of these spectra clearly indicates the value of mass spectrometry in the structure elucidation of bisbenzyltetrahydroisoquinolines.

Mass spectrometry has proved to be a very powerful tool in the determination of indole alkaloid structures.[1] In contrast, little has been reported concerning the application of this method to simple benzyltetrahydroisoquinoline bases. It is known, however, that benzyltetrahydroisoquinolines show a very characteristic fragmentation pattern in which cleavage occurs readily between the benzyl and the isoquinoline portions of the molecule. Thus, in the spectrum of 1-(2′-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (I), the molecular ion peak at *m/e* 285 has an intensity of only 0.2% of the base peak (a, *m/e* 178). The prominence of fragment a is due to its ease of formation by fission of a bond which is at the same time doubly benzylic and β to a basic nitrogen atom.[2]



I

a, *m/e* 178

A similar fragmentation pattern has been observed in the mass spectra of several cactus alkaloids containing the 1-isobutyltetrahydroisoquinoline grouping.[1,3]

The first use of mass spectrometry in bisbenzyltetrahydroisoquinoline chemistry was reported recently in conjunction with a revision of the structure of hernandezine.[4] The mass spectra of several bisbenzyltetrahydroisoquinoline bases now are described and interpreted. The examples chosen include one or more representatives of three different structural types, and the results clearly indicate the general utility of mass spectrometry in the structure determination of bisbenzyltetrahydroisoquinoline alkaloids.

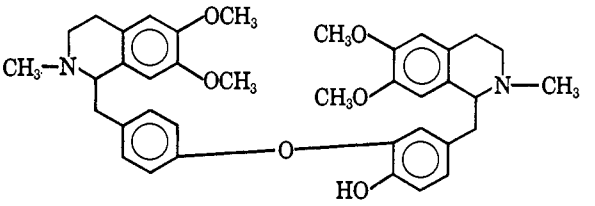
(1) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964.

(2) M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2807 (1963). In this paper the mass spectra of some *derived* benzyltetrahydroisoquinoline skeletal types (aporphines, cularines, and berbines) are also discussed.

(3) C. Djerassi, H. W. Brewer, C. Clarke, and L. J. Durham, *ibid.*, **84**, 3210 (1962).

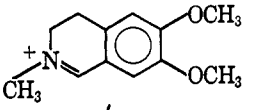
(4) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *Chem. Commun.*, 7 (1966).

Type I. One Diphenyl Ether Linkage, Tail to Tail. Dauricine (II) represents a type of compound which is a tail-to-tail dimer of the benzyltetrahydroisoquinoline bases. The fragmentation of this bisbenzyltetrahydroisoquinoline alkaloid is similar to that of compound I, cleavage of the carbon–carbon bond which is both β to nitrogen and β to two aromatic systems being



II

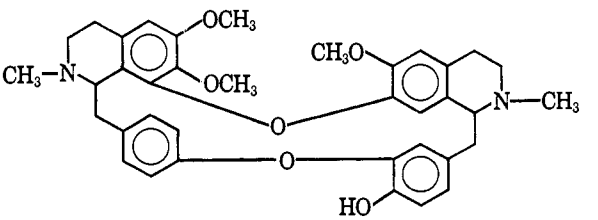
preferred. The base peak in the mass spectrum of dauricine (Figure 1) is found at *m/e* 206; a small



m/e 206

group of peaks around *m/e* 418 (0.15% of the base peak) results from charge retention on the remainder of the molecule. The molecular weight can be determined directly from a molecular ion peak of very low relative intensity (0.2%) at *m/e* 624.

Type II. Two Diphenyl Ether Linkages, Head to Head. Attachment of the two tetrahydroisoquinoline aromatic rings by an ether linkage and the benzylic rings by another ether linkage results in a cyclic, head-to-head bisbenzyltetrahydroisoquinoline base of which oxyacanthine (III) is an example. The greatly



III

increased intensity of the molecular ion peak in the mass spectrum (Figure 2) of oxyacanthine, compared with dauricine (Figure 1), results because oxyacanthine must cleave two bonds, except for C–H, in order to form an abundant fragment with mass less than the molecular weight.

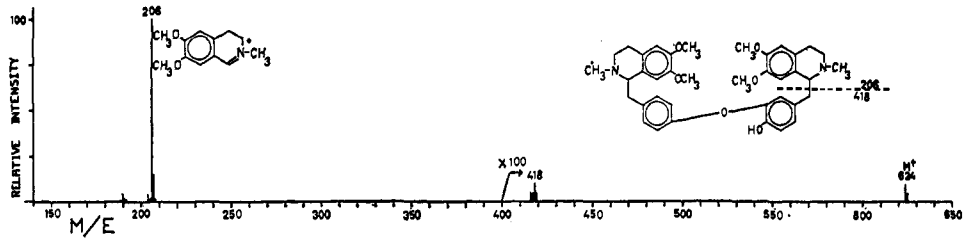


Figure 1. The mass spectrum of dauricine.

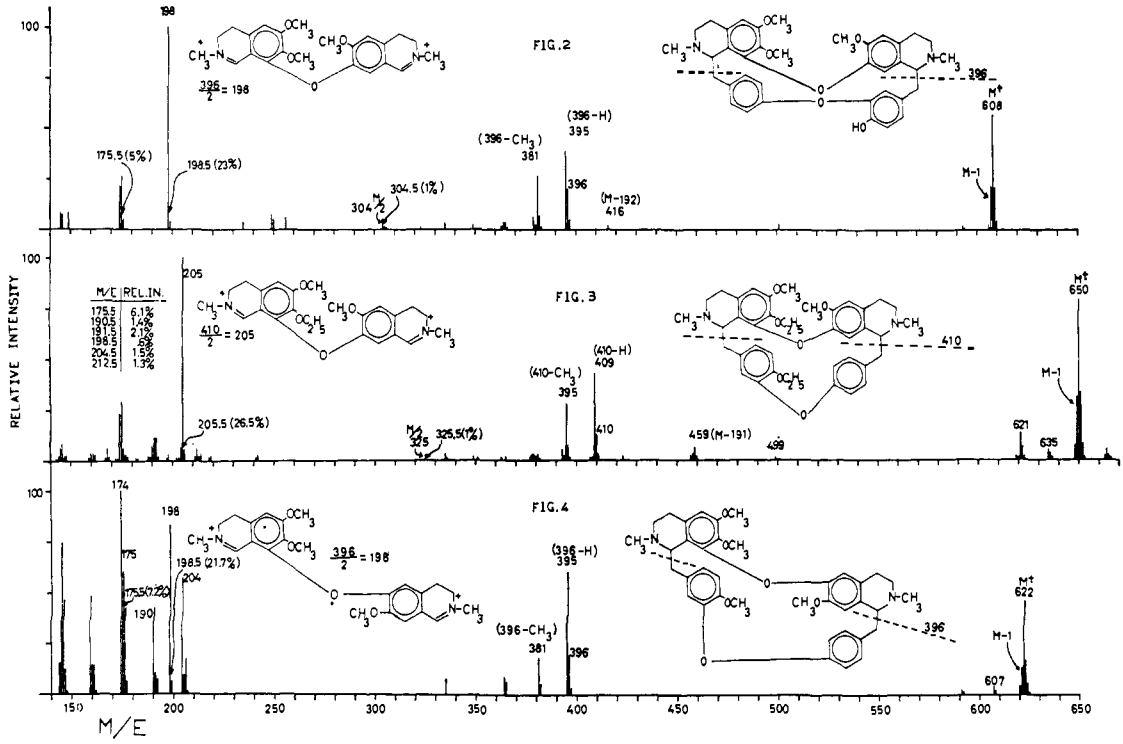
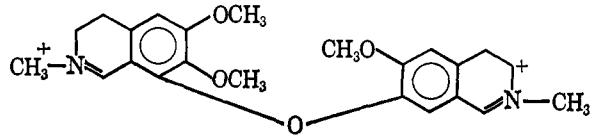


Figure 2. The mass spectrum of oxyacanthine. Doubly charged peaks at half-units are not drawn but their locations and relative intensities are indicated in the mass spectrum.
Figure 3. The mass spectrum of O,O-diethylobamegine. Doubly charged peaks at half-units are not drawn but their locations and relative intensities are indicated in the mass spectrum.
Figure 4. The mass spectrum of O-methylthalicberine. Doubly charged peaks at half-units are not drawn but their locations and relative intensities are indicated in the mass spectrum.

The most intense peak in the mass spectrum of oxyacanthine is found at *m/e* 198 with an isotope peak at *m/e* 198.5. This fragment is formed by two cleavages similar to the formation of *m/e* 206 from dauricine (II, Figure 1), with two charges retained on the tetrahydroisoquinoline groups.

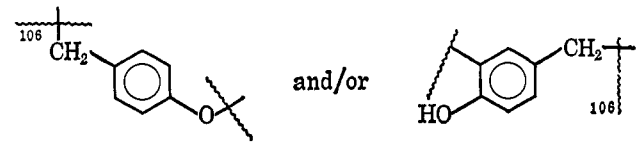


***m/e* 396/2 = *m/e* 198**

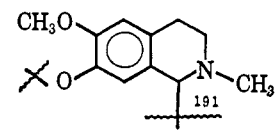
Isopilocerine, a bisisobutyltetrahydroisoquinoline alkaloid, forms an analogous doubly charged fragment.[1,3]

If only one charge is retained on the tetrahydroisoquinoline half of the molecule, the fragment is found at *m/e* 396 (approximately half of the peak at *m/e* 396 in Figure 2 is an isotope peak from *m/e* 395). Metastable ion peaks are present for the loss of a hydrogen atom and a methyl group from *m/e* 396 to form *m/e* 395 and 381, respectively.

Two peaks of low relative intensity which are found in the high-mass region of the spectrum are of structural significance. A fragment at *m/e* 501, loss of 107 mass units, corresponds to loss of one benzylic group plus a hydrogen atom.



A fragment at *m/e* 416 (M − 192) corresponds to loss of one tetrahydroisoquinoline unit plus a hydrogen atom.



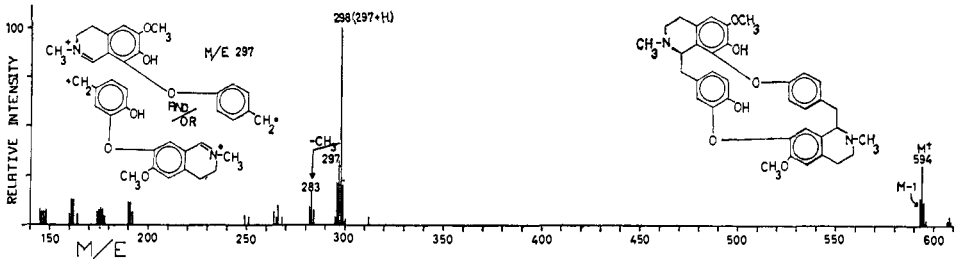
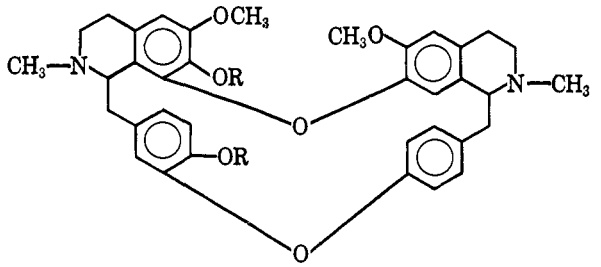


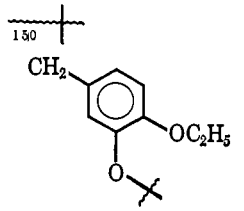
Figure 5. The mass spectrum of chondodendrine.

Obamegine (IV) and O,O-diethylobamegine (V) are other examples of type II. They differ from oxyacanthine (III) by the reversal of the ether linkage between the two benzylic groups.



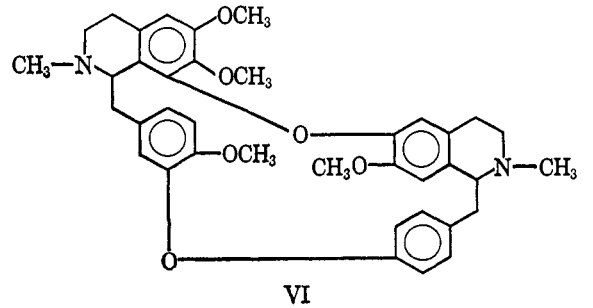
IV, R = H
V, R = C_2H_5

The mass spectrum (Figure 3) of O,O-diethylobamegine (V) shows the same major fragmentations as described for oxyacanthine (II, Figure 2). A minor fragment for M − 191 is present, but not for M − 107. The fragment of very low intensity at *m/e* 499 corresponds to the loss of 151 mass units.



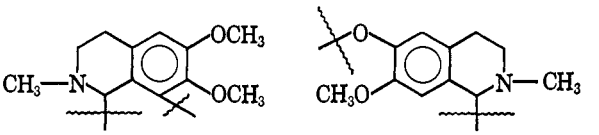
Obamegine (IV) fragments similarly except there is no peak at *m/e* 471 corresponding to the low-intensity M − 151 fragment discussed for compound V. Also, a peak of relative intensity 50% is found at *m/e* 192. This fragment may correspond to the M − 191 fragmentation discussed above, except with the charge retained on the tetrahydroisoquinoline fragment and with hydrogen transfer.

Another example of a type II compound is O-methylthalicberine (VI), which differs from compounds IV and V in the position of the ether linkage between the two tetrahydroisoquinoline units. By comparing the mass spectrum of compound VI (Figure 4) with the mass spectrum of oxyacanthine (III, Figure 2), it is possible to recognize from the peaks at *m/e* 395, 381, 198, and 198.5 that the tetrahydroisoquinoline half of O-methylthalicberine (VI) is similar to oxyacanthine (III). This similarity and the difference in molecular weights (622 *vs.* 608, 14 mass units) are characteristic of the fact that O-methylthalicberine has a methoxyl group in the benzyl half of the molecule rather than a hydroxyl group as in oxyacanthine.

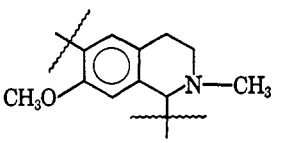


VI

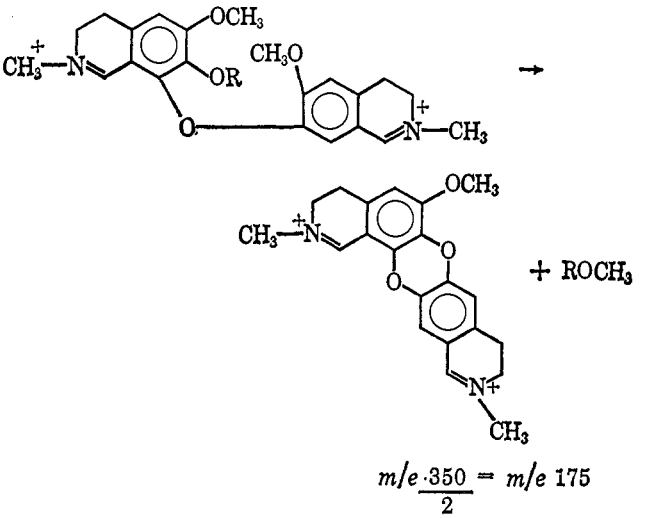
The absence of an M − 191 peak in Figure 4 may be characteristic of the 6,8-ether linkage between the two tetrahydroisoquinoline units, but this fact cannot be generalized until more examples are studied. The fragments at *m/e* 204, 190, and 174 may be due to the dehydro analogs of the following parts of the original molecule.



205 191



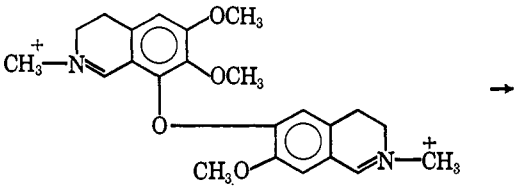
175



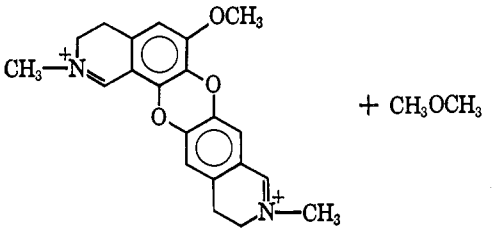
$m/e \frac{350}{2} = m/e$ 175

Compound	R
III	CH_3
IV	H
V	C_2H_5

Type II compounds III–VI show a doubly charged peak at 175 (isotope 175.5) in their mass spectra. This can be interpreted in terms of ether elimination from the doubly charged tetrahydroisoquinoline half of the molecule to form a dioxane ring.



from compound VI

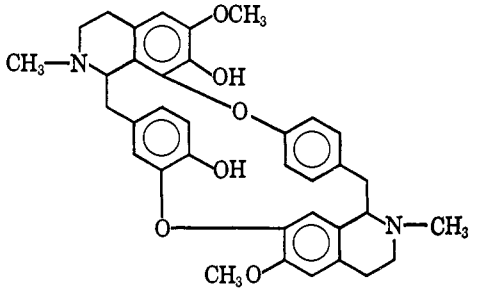


+ CH_3OCH_3

$$m/e\ \frac{350}{2} = m/e\ 175$$

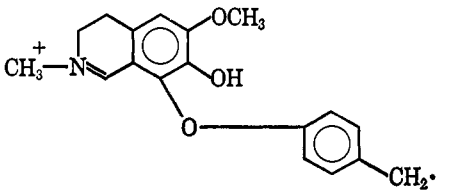
Metastable ion peaks in the mass spectra of compounds IV and V support this transition. This fragmentation can be useful for recognizing the nature of substitution at the positions involved.

Type III. Two Diphenyl Ether Linkages, Head to Tail. Chondodendrine (VII, Figure 5) is an isomer of obamegine (IV), having a head-to-tail structure rather than a head-to-head one. This variation in structure

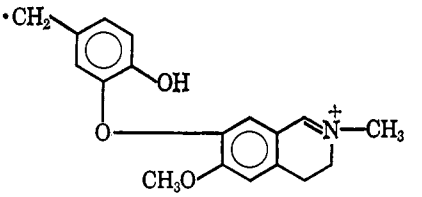


VII

produces extensive differences in the mass spectra of the two molecules. Both molecules cleave the bonds β to nitrogen and β to two aromatic systems. Unlike obamegine, chondodendrine does not form a doubly charged species but forms a singly charged species, *m/e* 297, and a singly charged species plus a transferred hydrogen atom, *m/e* 298. The absence of a peak



and/or



m/e 297

at *m/e* 297.5 from a doubly charged isotope of the molecular ion excludes the possibility that *m/e* 297 is a doubly charged molecular ion peak.

Summary. The mass spectra of these bisbenzyltetrahydroisoquinoline alkaloids demonstrate how readily mass spectrometry can be used to recognize types I–III. Mass spectrometry also can be used to determine whether substituents are in the tetrahydroisoquinoline part of the molecule or in the benzyl part.

In the type II compounds which give an M − 191 peak or its equivalent, it is even possible to determine which of the two tetrahydroisoquinoline units may bear a substituent.[4] Mass spectrometry is less sensitive to the differences in attachment such as exist in oxyacanthine, obamegine, and O-methylthalicberine.

Experimental Section

Mass Spectra. The mass spectra were determined with an Atlas Werke CH4 mass spectrometer, ionizing potential 70 ev, ionizing current 18 μa. The compounds were ionized by electron bombardment after sublimation directly into the electron beam from a small furnace heated by a tungsten coil.

In some of the mass spectra, a peak exists 14 mass units above the molecular ion peak. This is most likely due to a small amount of further methylated impurity.

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