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APPLICATION OF MASS SPECTROMETRY TO STRUCTURE PROBLEMS:[1] THE OCCURRENCE OF EBURNAMENINE AND RELATED ALKALOIDS IN RHAZYA STRICTA AND ASPIDOSPERMA QUEBRACHO BLANCO

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The leaves of Rhazya stricta Decaisne are reported[2] to contain akuammidine I (= rhazine)[3] and quebrachamine (II),[4] one of the major alkaloids of Aspidosperma quebracho blanco. Recently we had investigated the alkaloids of quebracho bark which led to the discovery of a number of new alkaloids.[5] It was thus of interest to search other quebrachamine-producing plants for these aspidosperma alkaloids and we therefore extracted a small sample (we had only 11 g. at out disposal) of the leaves of Rhazya stricta and examined the less polar base-fractions.

Gas chromatographic separation of the crude alkaloid mixture led to several fractions, the mass spectra of which indicated that there are, in

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[1] Part IX. For Part VIII see: K. Biemann and G. Spiteller, J. Amer. Chem. Soc. in press

[2] A. Chatterjee, C. R. Ghosal, N. Adityachaudhury, and S. Ghosal, Chem. and Ind. 1034 (1961).

[3a] J. Levy, J. LeMen and M.-M. Janot, Compt. rend. 253, 131 (1961); [b] S. Silvers and A. Tulensky, Tetrahedron Letters 339 (1962); [c] L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham and C. Djerassi, J. Amer. Chem. Soc. 84, 2161 (1962).

[4] K. Biemann and G. Spiteller, Tetrahedron Letters 299 (1961).

[5] K. Biemann, M. Friedmann-Spiteller and G. Spiteller, Tetrahedron Letters 485 (1961). Full paper to be published in J. Amer. Chem. Soc.

fact, at least four compounds present which also occur[5] in A. quebracho blanco, namely quebrachamine (II), 1,2-dehydroaspidospermidine (III),[6] aspidospermidine (IV), and a compound of mol. wt. 278 (mass spectrum Fig. 1a), a minor constituent of the quebracho bark. We could, however, not find as yet any fraction that contained aspidospermatine (V) or its derivatives, a group relatively abundant in A. quebracho blanco.

Pre-fractionation of the Rhazya-alkaloids on aluminum oxide followed by gas chromatography permitted in addition the isolation of a fifth compound which had a mol. wt. of 294 (mass spectrum Fig. 1b). This compound and the one of mol. wt. 278 were recognized as the Hunteria alkaloids eburnamonine (VI)[7] and eburnamenine (VIIa),[7] respectively, the mass spectra of which we had determined in connection with a study of the spectra of other indole alkaloids being carried out in our laboratory.

The identity of eburnamonine VI was further corroborated by reduction of that fraction with lithium aluminum deuteride; it yielded monodeuteroeburnamenine (VIIb) (via monodeuteroeburnamine followed by dehydration) as borne out by the spectrum which now showed peaks at m/e 279, 250, and 209.

Because of the ease with which eburnamine (VIII) is converted to VIIa, not only chemically[7] but also in the inlet system of the mass spectrometer and upon injection into the gas chromatograph (as evidenced by identical mass spectra and retention times), it was not possible a priori to conclude whether VIIa or VIII, or both, are actually present in these two plants. Nevertheless, this question was resolved when it was observed that the spectrum of VIIa is obtained from two different fractions, both earlier and later ones, of the aluminum oxide chromatogram. Reduction of the later

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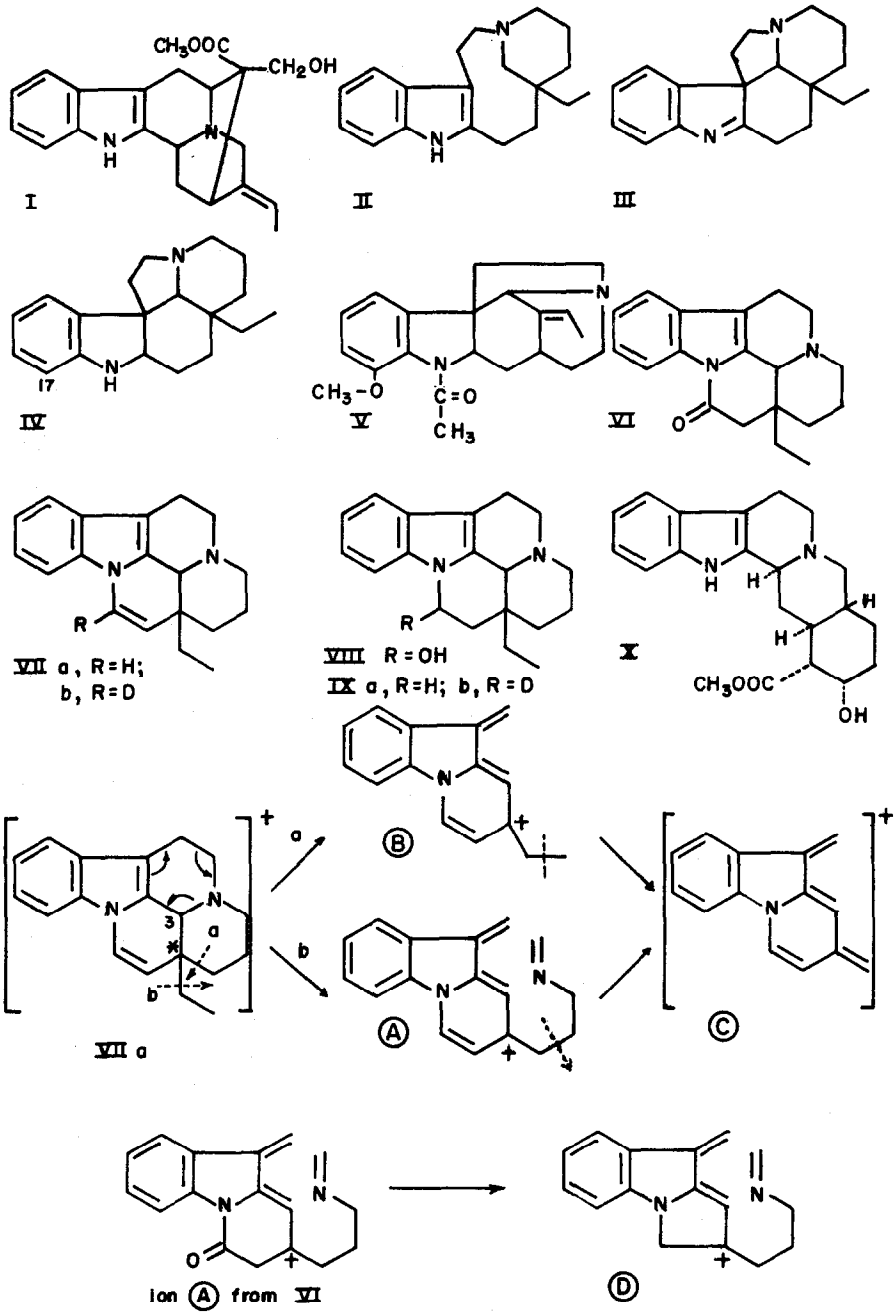
[6] Dr. G. F. Smith has informed us that he too has isolated III from Rhazya stricta.

[7] M. F. Bartlett and W. I. Taylor, J. Amer. Chem. Soc. 82, 5941 (1960). We are indebted to these authors for authentic samples of these alkaloids.


CH3OOC
CH2OH
I
II
III
IV
V
VI
VII a, R=H;
b, R=D
VIII R=OH
IX a, R=H; b, R=D
X
CH3OOC
OH
VII a
Ion (A) from VI

fraction with $LiAlD_4$ led to monodeuterodihydroeburnamenine IXb as evidenced by the mass spectrum which corresponded to the nondeuterated analog IXa (Fig. 1c) except for the shift by one mass number of certain peaks (see below). This experiment is considered conclusive evidence for the occurrence of both eburnamine (VIII) and eburnamenine (VII), in Rhazya stricta. From the aluminum oxide chromatogram of the quebracho alkaloids[5] it is concluded that VII rather than VIII is present in the bark of A. quebracho blanco.

The electron-impact induced fragmentation of this ring system (outlined on the previous page using VII as an example) seems to involve retro-Diels-Alder cleavage of ring C, a process common to six-membered rings containing a double bond.[8] Loss of either one of the chains attached to the starred carbon atom gives rise to the major peaks A (M-29) and B (M-70). The two processes required for the formation of fragments A and B can, in principle, take place in two different sequences. We would like to picture it as initiated by cleavage of bond a or b, respectively, followed by opening of ring C, rather than the reverse sequence, since the spectrum of VII indicates that the allylic nature of the quaternary carbon atom highly favors formation of fragments A and B, but supresses the loss of hydrogen, most probably from C-3, observed in the spectra of VI and IX. Loss of an alkyl radical from A or B leads to C, a significant process only in the spectrum of VII, presumably because only in this case is ion C that highly conjugated.

The spectra of the deuterated molecules VIIb (major peaks shift to m/e 194, 209, 250 and 279) and IXb (major peaks shift to m/e 196, 211, 252 and 281) are in agreement with these mechanisms.

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[8] K. Biemann, Angew. Chemie 74, 102 (1962). Intern. ed. 1, 98 (1962).

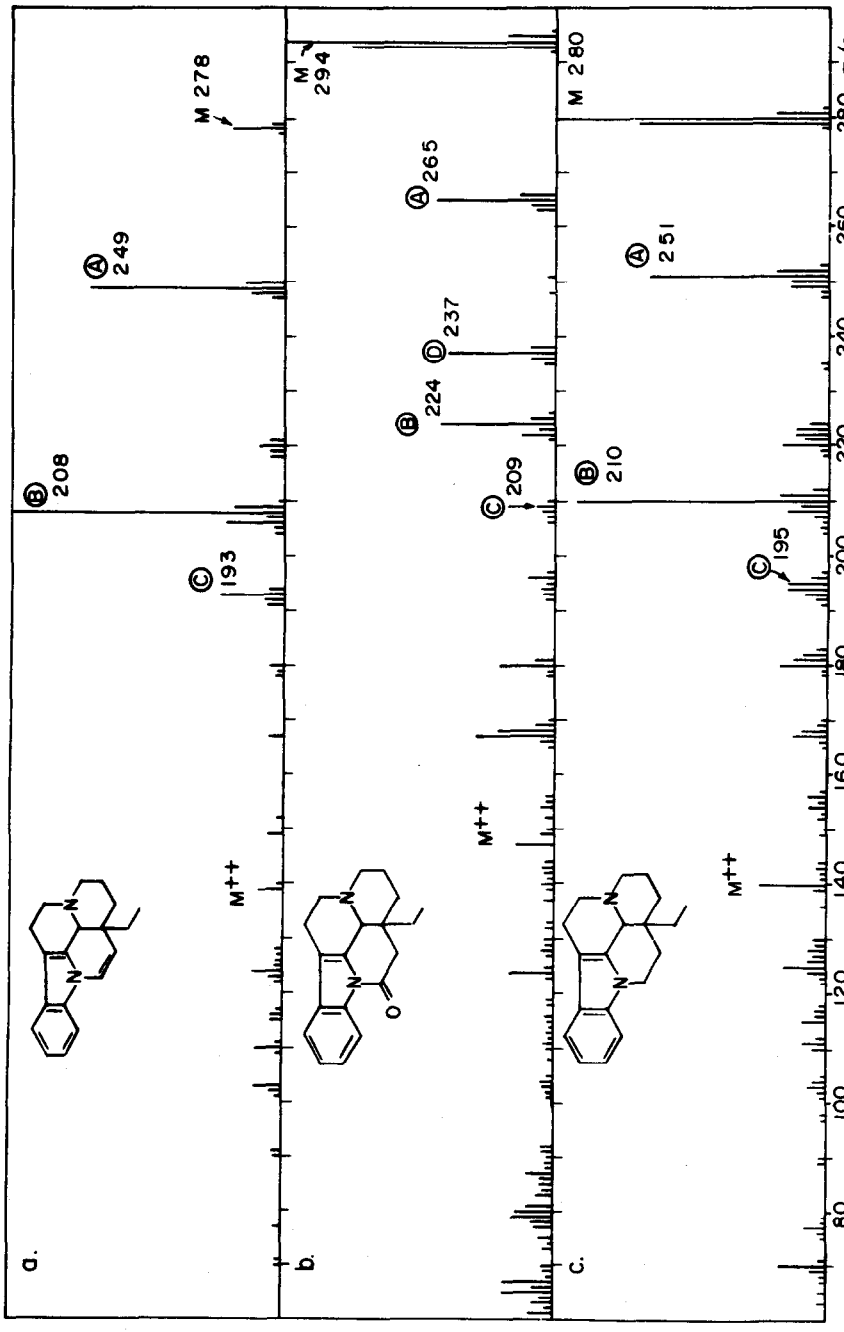

Fig. 1 Mass Spectra of (a) eburnamenine (b) eburnamonine and (c) dihydroeburnamenine

Eburnamonine (VI) exhibits in addition another peak (D) at M-57 which arises by further loss of CO (28 mass units) from the ion A (see formula page). This mechanism is corroborated by the mass spectrum of O^{18}-labeled VI (prepared by heating 2 mg. of VI with 0.5 ml. of water containing 11% O^{18} and a drop of conc. HCl for 1 hr. to 100°, addition of one drop ammonia and extraction with ether) which showed peaks of the expected intensity at m/e 226, 267 and 296 but not at m/e 239, indicating that only in the latter the oxygen atom is lost.

The detection of eburnamenine in the alkaloids of A. quebracho blanco brings to five the different alkaloid types present in that plant: Yohimbine (X), quebrachamine (II), aspidospermine (N-acetyl-17-methoxy-IV), aspidospermatine (V), and now eburnamenine (VIIa), a fact of considerable significance for the biogenetic relationships among these alkaloids. The co-occurrence of the aspidospermine and eburnamine types would support a common precursor indicated by the heavy lines in XI[7,9] which may condense either to the aspidospermine skeleton (broken arrows) or to the eburnamine skeleton (solid arrows). The recent discovery of the polyacetate unit as a direct precursor of the non-tryptamine portion of indole alkaloids[10] lends support to such a genesis, which would eliminate the need for postulating more or less elaborate rearrangements in the course of the formation of the aspidospermine skeleton.[11,12] The occurrence of four different alkaloid types, namely I, II, IV and VII in Rhazya stricta are of similar significance.

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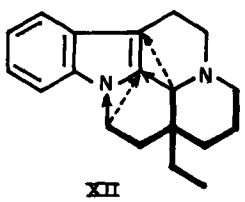
[9] E. Schlittler and W. I. Taylor, Experientia 16, 244 (1960).

[10] E. Leete, S. Ghosal and P. N. Edwards, J. Amer. Chem. Soc. 84, 1068 (1962).

[11] G. F. Smith and J. T. Wrobel, J. Chem. Soc. 1960, 1463.

[12] E. Wenkert, J. Amer. Chem. Soc. 84, 98 (1962).



XII

Because only small amounts of material were available to us it was not possible to determine the optical activity of these fractions which would be necessary to distinguish eburnamonine from its racemate, vincanorine,[13] and to differentiate between eburnamine and its epimer, isoeburnamnine.[7]

Acknowledgement: We are grateful to Dr. W. I. Taylor for a sample of dry leaves of Rhazya stricta and to the Petroleum Research Fund of the American Chemical Society and Ciba, Inc., for financial support of this investigation.

[13] J. Mokry, P. Sefcovic and I. Kompis, Symposium on the Chemistry of Natural Products, Brussels, June, 1962.