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THE HIGH-RESOLUTION MASS SPECTRA OF AJMALIDINE AND RELATED SUBSTANCES[1]

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In connection with the determination of the structure of quebrachidine (I)[2] we had studied the mass spectra of a number of indole alkaloids possessing the carbon skeleton of ajmaline but differing in substitution and/or stereochemistry at the alicyclic ring system. In a recent paper[3] the spectrum of ajmaline (II)[4] had been published and interpreted in terms of "key fragments" which might create the impression that all compounds of that carbon skeleton should exhibit the same fragmentation process regardless of substitution in the alicyclic moiety.[5] Such an assumption is not justified, particularly if based on the spectrum of a single compound and without indicating a plausible fragmentation process leading to these "key fragments" as otherwise it is impossible to judge the variations to be expected in a compound of modified structure. As indicated in our earlier communication, epimerization at C-2, for example, leads to radically different fragmentation as illustrated by the spectrum of I.[2]

Even more surprising is the difference between the mass spectrum (Fig. 1) of ajmalidine (III)[6] and the one of ajmaline (II), the former

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[1] Application of Mass Spectrometry to Structure Problems. XVII. Part XVI: D. DeJongh and K. Biemann, J. Am. Chem. Soc., in press.

[2] M. Gorman, A.L. Burlingame and K. Biemann, Tetrahedron Letters, No. 1, 39 (1963).

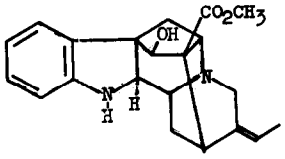
[3] G. Spiteller and M. Spiteller-Friedmann, Tetrahedron Letters, No. 3, 147 (1963).

[4] For structure see R.B. Woodward, Angew. Chem., 68, 13 (1956).

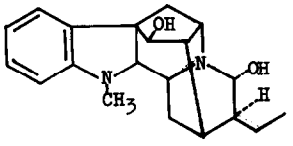
[5] For a discussion of the reliability of mass spectrometric correlation of indole alkaloids differing in the substitution at the aromatic part and and the influence of substitution at the alicyclic part see K. Biemann "Mass Spectrometry", McGraw-Hill Book Co., New York, Ch. 8, 1962.

[6] For structure see C. Djerassi, M. Gorman, S.C. Pakrashi and R.B. Woodward, J. Am. Chem. Soc., 78, 1259 (1956).

exhibiting an intense peak at m/e 198 while the peaks at m/e 182 and 183, said to be characteristic for the ajmaline skeleton, are of rather low intensity.



I



II

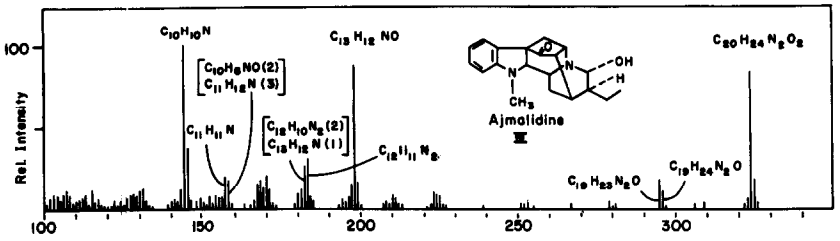
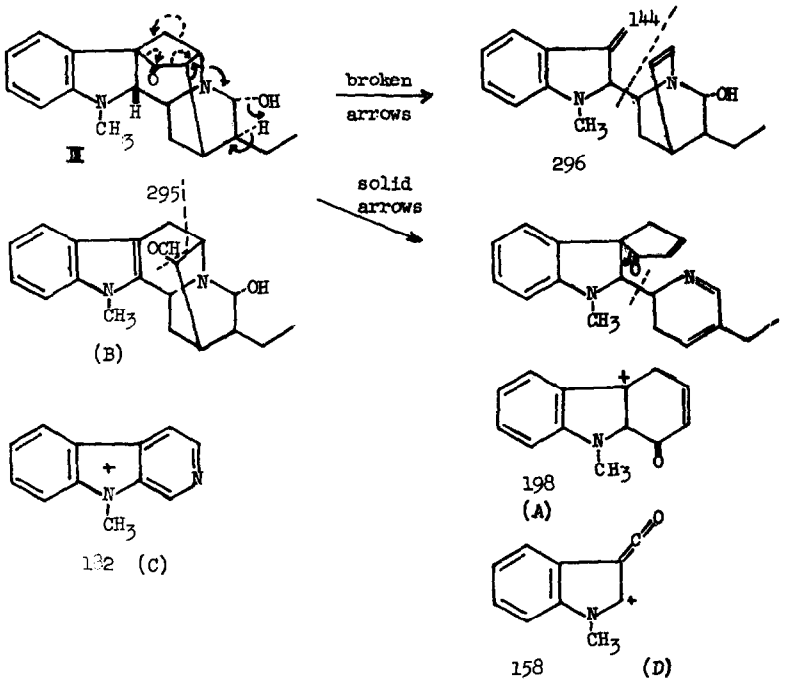


Fig. 1 Mass Spectrum of Ajmalidine (III). The values in parentheses refer to the intensity ratios of the components of the multiplet which were determined from the high resolution spectrum along with the elemental composition of the ions.

With the aid of high resolution mass spectrometry,[7] a technique which shows great promise in the investigation of natural products, we have been able to resolve the apparent inconsistency in the mass spectra of these two closely related compounds by determining the accurate mass and hence the elemental composition of all the ions formed in the spectrometer.

The composition of the ion of m/e 198 from III was found to be $C_{13}H_{12}NO$ and thus eliminated the possibility of an oxygen containing analog of the β-carboline ion suggested for m/e 182 in II.[3] Because of its low hydrogen content, the ion of m/e 198 must contain the indole moiety and the nitrogen and oxygen atoms lost are most plausibly those of the quinuclidine ring. Elimination of water, retro-Diels-Alder cleavage and rupture of the C-2, C-3 bond leads to an ion in which the positive charge may be stabilized

[7] A double focusing mass spectrometer (CEC 21-110)was used with a photographic plate for the recording of the ions and measuring their accurate mass. The samples were introduced directly into the ion source. A detailed discussion of the operating and measuring techniques will be presented elsewhere.



either by the neighboring nitrogen atom or by expansion of the spiro-ring to a carbazole-type skeleton (*A*). In the case of ajmaline (II) the same fragmentation process leads to a peak at m/e 200. Its intensity is relatively low (in comparison with m/e 198 from III) because further elimination of water leads to yet another ion of nominal mass 182. This process was revealed by the occurrence of a triplet at m/e 182 in the high resolution spectrum of II instead of the single species assumed previously[3] on the basis of a conventional mass spectrum. The two major components turned out to be $C_{12}H_{10}N$ and $C_{12}H_{10}N_2$.

The elimination of CO from the cyclopentanone ring is another process observed with III but impossible for II. The resulting fragment, $C_{19}H_{24}N_2O$, contains an acyclic N-C-C-N system the cleavage of which leads to the most intense peak in the spectrum of III (m/e 144, $C_{10}H_{10}N$).

It is of interest to note that the peak at m/e 295 in Fig. 1 is a singlet resulting entirely from the loss of CHO (rather than C_2H_5) which may be due to loss of hydrogen after loss of CO, or to loss of CHO from a rearranged molecular ion formed by transfer of hydrogen from C-2 to C-17. Such a transfer leads to the formation of a sarpagine skeleton (B), the fragmentation of which had previously been shown[8] to give rise to intense peaks at m/e 182 (C) and 183. Their absence in the spectra of the 2-epi series (e.g. I) supports this proposal because the hydrogen at C-2 is, in those molecules, trans to C-17.

Another doublet revealed by the high resolution spectrum of III is at m/e 158 due to $C_{10}H_8NO$ and $C_{11}H_{12}N$. Both components are of about equal intensity and while the latter represents merely the indole moiety plus two additional carbon atoms (presumably C-5 and C-6) the oxygen-containing species must contain C-17 and its oxygen atom in addition to the elements of the indole system and is represented by D. It indicates the presence of oxygen within one carbon atom from that system. The diagnostic value of this fragment, easily overlooked in a low-resolution spectrum, is supported by the fact that we have found it in the spectra of all ajmaline derivatives oxygenated at C-17 and possessing a 7,17-bond.

Table I lists the masses determined for a number of characteristic peaks in the spectra of ajmalidine (III) and its 12-methoxy derivative, vomalidine,[9] indicating the accuracy which we presently obtain in routine measurements. The possibility of the determination of the elemental composition of indole alkaloids is clear from these data. Furthermore, the validity of the "mass spectrometric shift technique" for the correlation of alkaloids[5] is considerably enhanced: the ions from ajmalidine and vomalidine differ not only by 30 mass units but by CH_2O (H vs. CH_3O) as required by the difference in substitution.

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[8] K. Biemann, Tetrahedron Letters, No. 15,9 (1960); J. Am. Chem. Soc., 83, 4801 (1961).

[9] A. Hofmann and A.J. Frey, Helv. Chem. Acta, 40, 1866 (1957). The methoxyl group has been shown to be at C-12 by P.R. Ulschafer and W.I. Taylor. A. Hofmann has reached the same conclusion (private communications).

Table I

Ajmalidine (III)			Vomalidine (12-methoxy-III)		
324.1843[a]	(+0.5)[b]	$C_{20}H_{24}N_2O_2$	354.1955	(+1.3)	$C_{21}H_{26}N_2O_3$
296.1868	(-1.9)	$C_{19}H_{24}N_2O$	326.1973	(-2.0)	$C_{20}H_{26}N_2O_2$
295.1803	(-0.6)	$C_{19}H_{23}N_2O$	325.1893	(-2.2)	$C_{20}H_{25}N_2O_2$
198.0925	(+0.7)	$C_{13}H_{12}NO$	228.1021	(-0.3)	$C_{14}H_{14}NO_2$
183.0918	(-0.4)	$C_{12}H_{11}N_2$	213.1016	(-1.2)	$C_{13}H_{13}N_2O$
182.0973	(+0.5)	$C_{13}H_{12}N$	212.1066	(-0.9)	$C_{14}H_{14}NO$
182.0839	(-0.4)	$C_{12}H_{10}N_2$	212.0932	(-1.7)	$C_{13}H_{12}N_2O$
158.0962	(-0.3)	$C_{11}H_{12}N$	188.1073	(-0.2)	$C_{12}H_{14}NO$
158.0618	(+1.3)	$C_{10}H_8NO$	188.0715	(+0.4)	$C_{11}H_{10}NO_2$
157.0901	(+1.0)	$C_{11}H_{11}N$	187.0979	(-1.7)	$C_{12}H_{13}NO$
145.0895	(+0.4)	$C_{10}H_{11}N$	175.1003	(+0.7)	$C_{11}H_{13}NO$
144.0806	(-0.7)	$C_{10}H_{10}N$	174.0914	(-0.5)	$C_{11}H_{12}NO$

[a]Mass found for the monoisotopic species (^{12}C=12.0000). [b]Deviation (in millimass units) from value calculated for the elemental composition in the next column.

On the basis of the high resolution spectra of all the ajmaline derivatives we have examined one can conclude that those in which one or both hydroxyl groups are either absent or have the opposite stereochemistry at C-17 behave like II. However, 21-hydroxy-17-keto derivatives undergo a modified fragmentation process, namely the one discussed above for III. Epimerization at C-2 prevents the fragmentation characteristic of I but leads to spectra of which the one of quebrachidine (I) is a typical example.[4] A more detailed discussion of all these spectra shall be presented in the full paper.

The conclusions reached in this paper demonstrate that high resolution mass spectrometry--a technique pioneered by Beynon[10]--greatly facilitates the interpretation of mass spectra of natural products and, in addition, reveals an otherwise unexpected complexity of the fragmentation of organic molecules in the spectrometer.

Acknowledgments. We are indebted to Prof. R.B. Woodward, Dr. W.I. Taylor and Dr. Norbert Neuss for gifts of samples, and to the National Science Foundation and Ciba (Summit) for financial support.

[10] For a recent review of this work see R.A. Saunders and A.E. Williams in "Mass Spectrometry of Organic Ions", F. W. McLafferty, ed., Academic Press, New York, 1963.