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SOME OBSERVATIONS ON THE MASS-SPECTROMETRY OF BISBENZYL-ISOQUINOLINE ALKALOIDS.

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In a recent communication Tomita and coworkers described an investigation of the mass-spectrometry of bisbenzylisoquinoline alkaloids (1). In this communication we report the results of an independent study of this topic[x], and draw some conclusions which supplement the data presented by Tomita and coworkers. The mass-spectra are most conveniently discussed in terms of groups of alkaloids of similar skeletal types.

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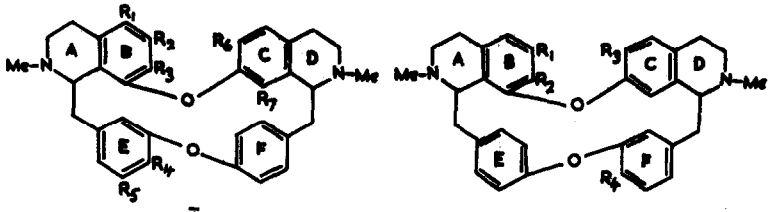
x The mass spectra were measured on an AEI MS9 mass spectrometer using the direct insertion technique.

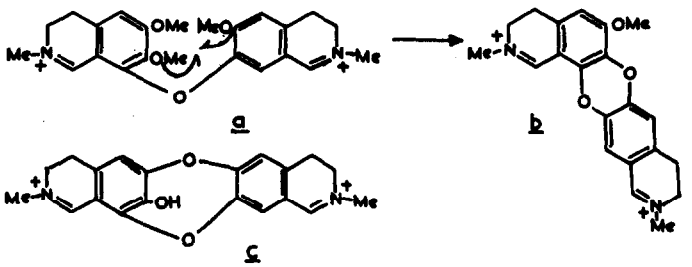
Alkaloids of types I and II



I II

A Ions resulting from the loss of rings E and F.

Alkaloids of these types have as base peak a doubly-charged ion resulting from double benzylic fission of the doubly-charged molecular ion. Thus for tetrandrine (I, $R_2=R_3=R_4=R_6=OMe$, $R_1=R_5=R_7=H$) this ion has structure a, and its concerted formation from the doubly-charged molecular ion is confirmed by the presence of a metastable peak corresponding to the transition $311^{++} \rightarrow 198^{++}$. It is unusual for doubly-charged ions to have



a b

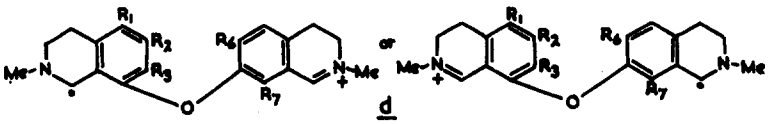
c

such great intensity, but here the two portions of the ion carrying the positive charges are well separated, and in each isoquinoline moiety the positive charges are well delocalised by interaction with the methoxylated aromatic rings.

Tomita and coworkers have described the elimination of the elements of dimethyl ether from ions of this type to give ions having dibenzo-1, 4-dioxin structures. We have also observed this transition (to b, arrows) and have shown that the elimination is concerted by the observation of the appropriate metastable peak.

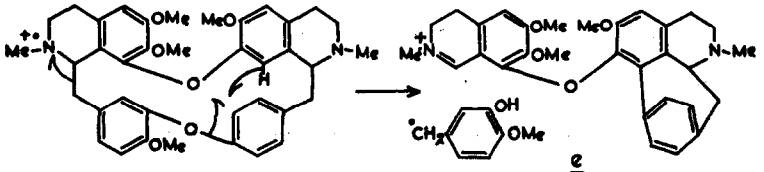
It is interesting that the corresponding ion from nortenuipine (I, R_2=R_6=OMe, R_3=OH, R_4, R_5= $-O-CH_2-O-$, R_1=R_7=H) shows a similar concerted loss of dimethyl ether to give an ion of presumed structure c with a central seven-membered ring. Cepharanthine (II, R_1=R_2= $-O-CH_2-O-$, R_3=R_4=OMe) does not show this loss of 46 mass units from the appropriate doubly-charged ion, which is to be expected since it has a methylene-dioxy group in place of the vicinal dimethoxy grouping of tetrandrine discussed previously.

Singly-charged ions are also produced by a double benzylic fission of the singly-charged molecular ion, and Tomita and coworkers have described the formation of ions of type d in this way. Our work confirms this formulation, and we agree with Tomita's rationalization of the further decomposition of this species.



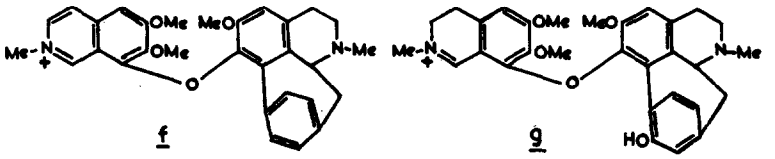
B. Ions resulting from the loss of ring E. Weak but reproducible ions are observed with alkaloids of types I and

II from a fragmentation resulting in the expulsion of ring E as a neutral fragment. This loss is confirmed by high resolution mass spectrometry in a typical case, and is of potential value as a source of information about the nature of ring E. The fragmentation may be rationalised as follows using tetrandine as an example :



e

The stoichiometry of the process requires a hydrogen transfer to the neutral fragment. There is no direct proof that the hydrogen atom shown is in fact concerned, or that the cyclisation implied in structure e has occurred (it seems likely that e may rearrange to a less strained aporphine-type structure); however in view of the fact that only ring E, never ring F is lost in this process it seems highly probable that the reaction is controlled by the availability of a hydrogen atom for transfer, and that the conveniently placed one in position 8 of ring C is involved. The point could be proved by suitable deuterium labelling, but the synthesis of the required compound would be difficult. The correctness of the formulation of e does not affect the diagnostic value of this elimination. In each case an ion at 2 mass units lower than the ion corresponding to e is presumed to be the aromatised ion (f from tetrandrine) :

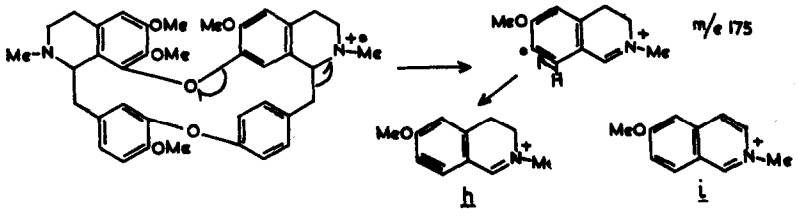


f g

Alkaloids of type II in this process will be expected to give meta-bridged ions (e.g. g from oxyacanthine, II (R_1=R_2=R_3=OMe R_4=OH)) although again isomerisation to a less strained structure may occur.

The loss of 137 mass units in the case of hernandezine to form an ion of this type is in accord with its recently revised structure (I, R_1=R_2=R_3=R_4=R_6=OMe, R_5=R_7=H) (2), but not with the original one (I, R_1=R_5=H, R_2=R_3=R_4=R_6=R_7=OMe, which had a methoxyl group in place of the hydrogen postulated as being transferred in the other examples.

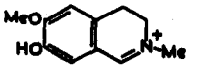
C. Ions resulting from loss of rings A,B,E and F. Tomita and coworkers noted a singly-charged ion at m/e 174 in the spectra of some alkaloids of types I and II. We have also observed this ion, and by high resolution mass-spectrometry have shown its composition to be $C_{11}H_{12}NO$. We suggest that it has the dehydrobenzene structure h, and that it is produced as shown (tetrandrine as example) :



h i

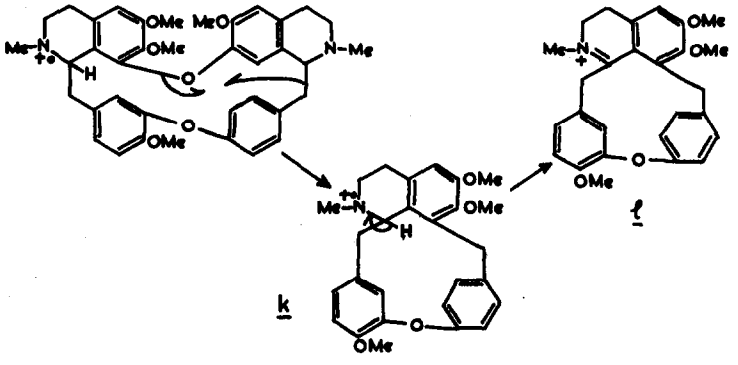
The alternative formulation i seems less likely as its formation would require considerable hydrogen rearrangement. The proposed precursor to h at m/e 175 has not been observed but this position is usually obscured by the strong doubly-charged ion discussed in section A.

A singly-charged ion of variable intensity at m/e 192 has also been observed in all alkaloids of types I and II studied. This may have structure j, but the origin of the hydroxyl hydrogen, which must be the result of a migration, is not clear.



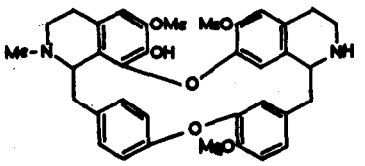
j

D. Ions resulting from the loss of rings C and D. In all the alkaloids of types I and II except cepharanthine there are reasonably strong ions at M-191 and M-192. A metastable peak at approximately M-193 shows that M-192 is formed from M-191 by loss of a hydrogen atom, rather than both from the molecular ion by separate paths. The stoichiometry can only be accommodated by loss of rings C and D, and for tetrandrine the process can be rationalised as leading to ions k and l as follows :

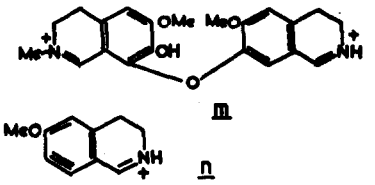


k l

Daphnandrine. This alkaloid (III) is closely related to the type II alkaloids already studied, but has one -NH-group. This leads to useful mass shifts which substantiate the conclusions already drawn. The base peak, as expected, corresponds



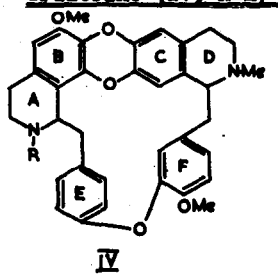
III



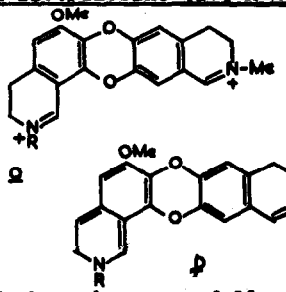
m n

to the doubly charged ion m, and the other general features of type II alkaloids already discussed appear in the spectrum. As expected there is no ion at m/e 174 and the homologous ion n appears at m/e 160.

2. Trilobine (IV, R=H) and isotrilobine (IV, R=Me).



IV



o

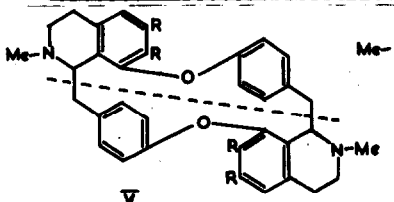
p

The spectra of these alkaloids have been carefully analysed by Tomita and coworkers, and we agree with their rationalisation of the cracking pattern, to give as the most abundant ions the doubly charged structures o and singly charged ones p.

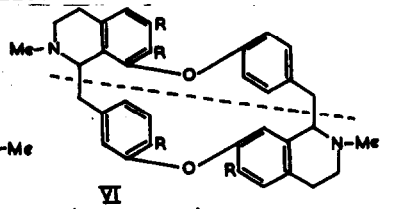
Of diagnostic value is the absence of ions resulting from loss of rings C and D (analogues of k and l) since their

formation would involve the rupture of two C-O bonds. There is also no evidence for the loss of ring E (107 mass units). The reason for this is less clear, and may be connected with the greater rigidity of alkaloids of type IV, making the geometrical requirement for the loss of this ring unattainable.

3. Alkaloids of types V and VI.

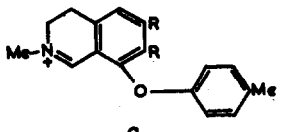


V
(R=OH or OMe)

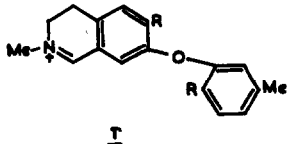


VI
(R=OH or OMe)

Tomita and coworkers examined a number of alkaloids of type V, and showed that fission occurred at the dotted line with hydrogen transfer. We have also observed this fission and transfer, and a similar one with type VI alkaloids. The resultant ions are presumably of structures q and r, but the sources of the transferred hydrogen are not clear, and could only be established by labelling techniques which are not easily applicable to these compounds.



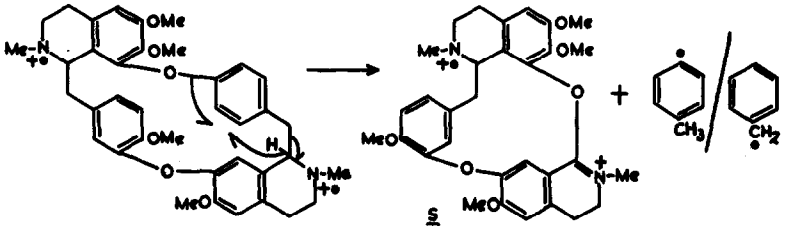
q



r

Tomita also pointed out that all alkaloids of type V showed an ion at $(\frac{M-91}{2})^{++}$. We have observed this ion in type VI alkaloids also, and it seems most reasonable to suggest that it

involves the loss of C_7H_7 - the unsubstituted benzyl group - from the doubly charged parent ion. This ion may be formulated as s using dimethyl curine as an example :



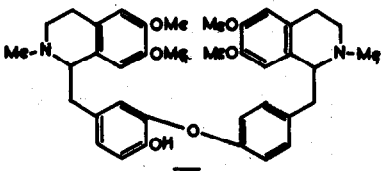
s

The nature of the neutral product will depend upon the terminus of the hydrogen transfer. The complementary ion to the neutral fragment occurs at m/e 91 in all type V and VI alkaloids examined and is presumably the stable tropylium cation. It is interesting to note that those alkaloids of types II, III and IV (in which ring E is unsubstituted) show a significant ion of somewhat variable intensity at m/e 90, with little accompanying m/e 91. This ion may well have structure t, and an accompanying ion at m/e 89 and metastable peak at approximately m/e 88 suggest that further decomposition to ion u occurs.

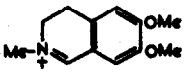
t u

It is suggested that an ion of reasonable intensity at m/e 90 may be used diagnostically to infer an unsubstituted ring E.

Alkaloids of type VII.



VII



V

Like the structurally similar tetramethylmagnolamine examined by Tomita and coworkers, dauricine (VII) gives as base peak the ion y at m/e 206. We have also observed the loss of a methyl radical from y to give an ion at m/e 191. An ion of m/e 192 is difficult to rationalize, and may indicate contamination of the sample by a nordauricine, as with other samples of amorphous dauricine (3).

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