transformed by the usual sequence (tosylation, lithium aluminum hydride reduction, acid cleavage of tetra-hydropyranyl ether, and reoxidation with chromium trioxide) into 2,2,4,4-d_4-cholestan-6-one (XIX) of 50% isotopic purity (see Table I).

When cholestane-3,6-dione 6-ethylene ketal (VIIb) was exchanged three times in the same manner as the tetrahydropyranyl ether XVc, the isotopic composition of the resulting cholestan-6-one was 12% d_0, 20% d_1, 23% d_2, 33% d_3, and 12% d_4.

Mass Spectrometry in Structural and Stereochemical Problems. LXXXII.[1] A Study of the Fragmentation of Some Amaryllidaceae Alkaloids[2]

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Contribution from the Departments of Chemistry, Stanford University, Stanford, California, and Iowa State University, Ames, Iowa. Received July 6, 1965
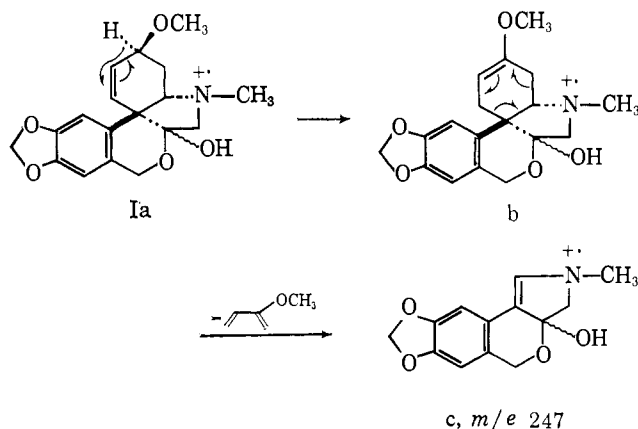
The mass spectra of 16 Amaryllidaceae alkaloids are reported. High-resolution mass spectrometry and deuterium labeling were used in the interpretation of many of the spectra. Of particular significance is the observation that minor changes in stereochemistry are frequently sufficient to cause appreciable differences in the mass spectra of many of the stereoisomers.

The Amaryllidaceae alkaloids constitute a large and chemically extensively investigated group of naturally occurring bases.[4] Although many classes of alkaloids have been subjected to mass spectral scrutiny[5] no detailed investigation of the Amaryllidaceae group has as yet been reported. It was felt that such a mass spectral survey was especially appropriate since extensive isolation and structure studies on novel Amaryllidaceae alkaloids are under way in various laboratories and mass spectrometry would be expected to play an important role in such investigations.[6]

Tazettine and Criwelline. Tazettine (I) and criwelline (II) differ only in the configuration of the methoxyl group at C-3, but this is sufficient to cause marked

I, R = OCH₃; R' = H
II, R = H; R' = OCH₃
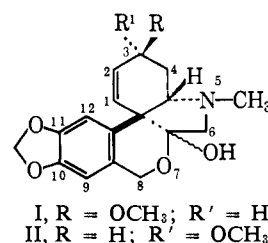
variations in relative abundance of the ions in the spectra (Figures 1 and 2) of these alkaloids. The dominant ion in the spectrum (Figure 1) of tazettine occurs at mass 247 (M − 84), while a shift to m/e 250 is reflected in the spectrum of tazettine-N-d_3. High-resolution mass spectral measurements[7] demonstrated the homogeneity and composition of this ion as $C_{13}H_{13}NO_4^+$. The appearance of a metastable ion at mass 184.6 ($247^2/331 = 184.6$) established that at least a portion of this ion yield originated from a one-step decomposition of the molecular ion of tazettine (I). Such a scheme is depicted in Ia → b → c (m/e 247) in which, following an initial hydrogen transfer, ring C is fragmented by a retro-Diels–Alder process[8] with the formation of c.

c, m/e 247

The mass spectrum (Figure 2) of criwelline (II) contains a prominent peak at m/e 301 (M − 30) which is absent in the spectrum (Figure 1) of tazettine. This ion's origin is compatible with the elimination of formaldehyde from IIa and representation as d (m/e 301). Support for this process was obtained from the results of deuterium labeling in which quantitative transfers to m/e 304 and 303 were recorded in the spectra of criwelline-N-d_3 and criwelline-8-d_2,[9] respectively. Recognition of a metastable ion at m/e 274.0 ($301^2/331 = 273.7$) in the spectrum of criwelline is consistent with the formation of at least a portion of the ion yield at m/e 301 through the following single-stage decomposition from the molecular ion.

IIa

d, m/e 301   c, m/e 247
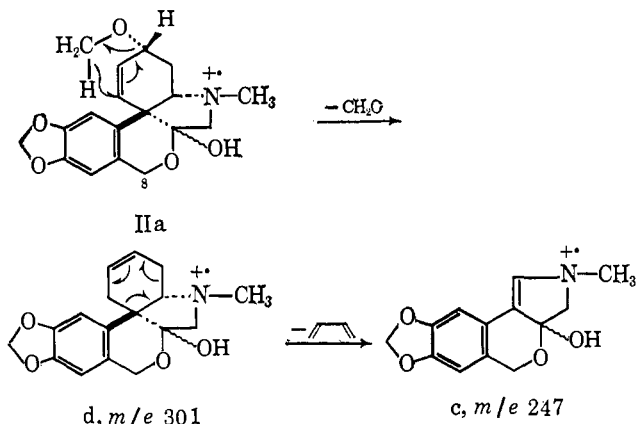
The mass spectrum (Figure 2) of criwelline, in contrast to that of tazettine (Figure 1), contains a peak of low abundance at m/e 247. High-resolution mass spectrometry[7] established the composition $C_{13}H_{13}NO_4^+$ for this ion. The mass spectra of the available deuterated analogs (criwelline-N-d_3 and -8-d_2, respectively) demonstrated that all the deuterium was incorporated into the charged species. A mechanism consistent with this evidence is illustrated by d → c (m/e 247).

Ions due to the successive loss of a methyl radical (m/e 316) and then water (m/e 298) occur in the spectra of both tazettine (Figure 1) and criwelline (Figure 2) although they are much more pronounced in the former spectrum. A possible genesis of these ions (illustrated for tazettine) is shown by Ia → e (m/e 316) → f (m/e 298) and metastable ions at mass 302.0 ($316^2/331 = 301.7$) and mass 281.0 ($298^2/316 = 281.0$) testify to the occurrence of this sequence of events. Since the key steps are visualized as proceeding around C-3 (deuterium labeling

Ia

e, m/e 316   f, m/e 298
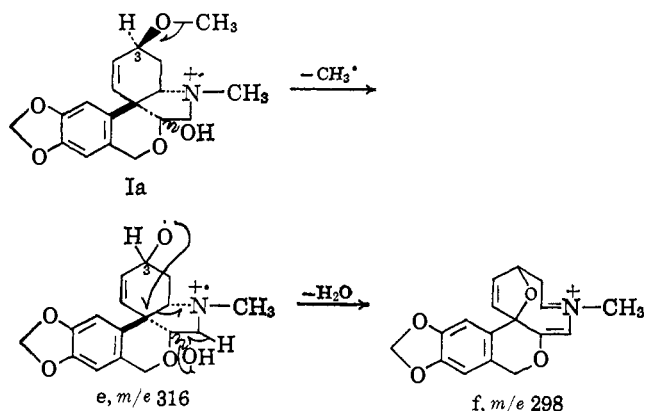
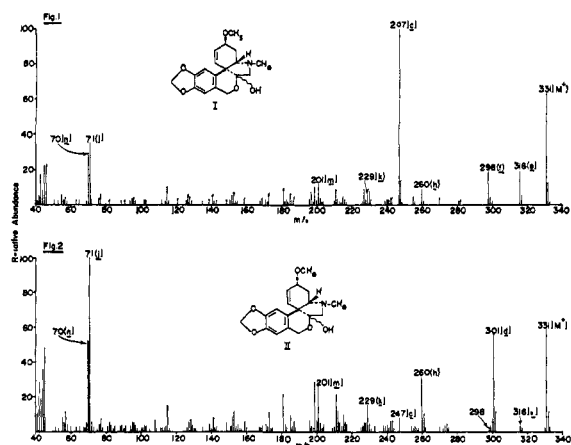(9) C. F. Murphy and W. C. Wildman, *Tetrahedron Letters*, 3863 (1964).

Figure 1. Mass spectrum of tazettine (I).
Figure 2. Mass spectrum of criwelline (II).

of the NCH$_3$ group demonstrated that only the OCH$_3$ group is implicated in the M − CH$_3$ process), which is the only center of stereochemical difference between tazettine and criwelline, it is not surprising that the intensities of the m/e 316 and 298 peaks differ in the two stereoisomers.

A peak at m/e 260 (M − 71) in the spectrum (Figure 2) of criwelline is much more pronounced than in that (Figure 1) of tazettine. This peak was unaffected in the spectra of the respective N-d_3-labeled alkaloids, but a two mass unit displacement to m/e 262 was observed in criwelline-8-d_2. A mechanism consistent with these results (drawn for criwelline) is depicted by IIb → g → h (m/e 260).

IIb   g

CH$_2$=CH−N−(CH$_3$)$_2$
j, m/e 71

h, m/e 260
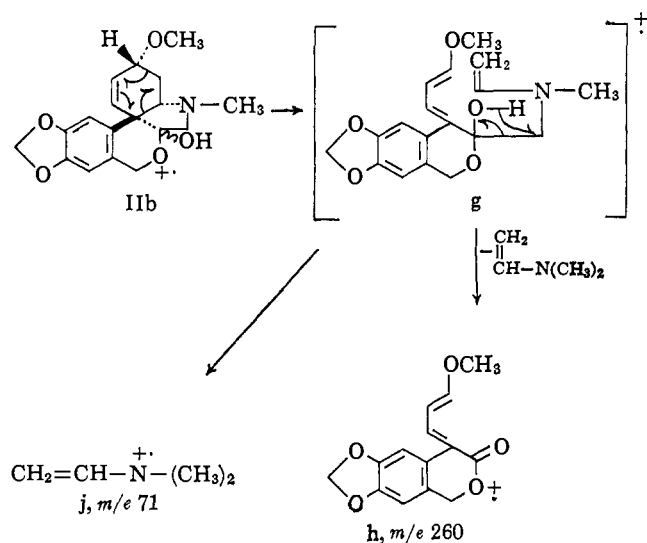
The most abundant peak in the spectrum (Figure 2) of criwelline occurs at m/e 71 (M − 260) while in the case of tazettine (Figure 1) a moderately intense peak is visible at this mass number. High-resolution mass spectrometry[7] established the composition of this ion in the spectrum of tazettine as $C_4H_9N^+$ (96%) and $C_4H_7O^+$ (4%). A probable origin for the major component (illustrated for criwelline) is hydrogen transfer in g with concomitant α-cleavage to nitrogen and formation of j (m/e 71) and a neutral lactone. The spectra of both N-d_3 analogs of criwelline and tazettine recorded quantitative displacements to m/e 74.
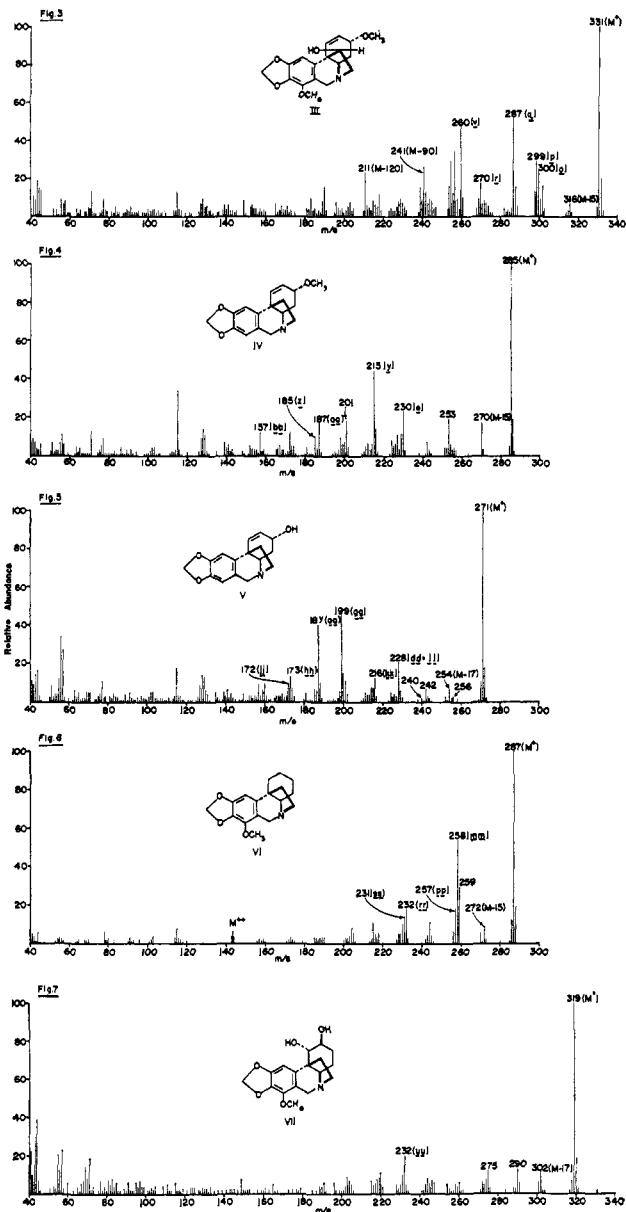
Figure 3. Mass spectrum of ambelline (III).
Figure 4. Mass spectrum of buphanisine (IV).
Figure 5. Mass spectrum of crinine (V).
Figure 6. Mass spectrum of powellane (VI).
Figure 7. Mass spectrum of deacetylbowdensine (VII).

This process (g → j) is thus analogous to IIb → g → h (m/e 260) with the exception of the localization of the positive charge.

An explanation for the origin of a peak at m/e 229 (M − 102) in the spectra (Figures 1 and 2) of tazettine and criwelline involves loss of the methoxyl group from the species h (metastable ion at mass 201.6; $229^2/260 = 201.6$) with the generation of k (m/e 229). This mechanism received additional support from the spectra of the N-d_3 analogs of both alkaloids which showed that this peak was undisturbed while that of criwelline-8-d_2 suffered a quantitative shift to m/e 231. Elimination of carbon monoxide from k would generate m (m/e 201),[10] and this process is sug-

gested for the origin of the ion at mass 201 (M − 130) in the spectra of tazettine and criwelline. The appropriate displacement (to m/e 203) was observed in the spectrum of criwelline-8-d_2.

k, m/e 229

m, m/e 201   n, m/e 70
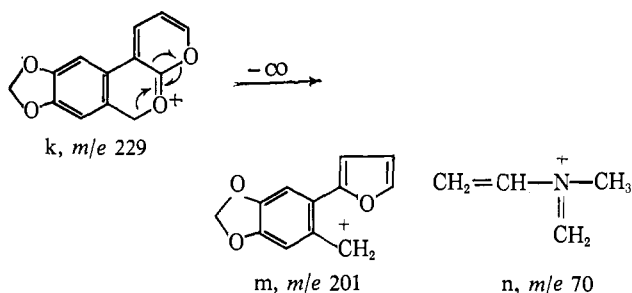
The rather abundant fragment present in the spectra of criwelline and tazettine at mass 70 (M − 261) can arise from the species g via α-cleavage to nitrogen and hence corresponds to n (m/e 70). Loss of a hydrogen atom from j (m/e 71) is not considered to be a favored process since quantitative shifts to m/e 73 were recorded in the spectra of tazettine-N-d_3 and criwelline-N-d_3. Furthermore, loss of hydrogen from the N-methyl group of N-methylated amines was not observed in studies of the electron impact induced fragmentation of such compounds.[11]

Ambelline, Buphanisine,[6b] *Crinine, Powellane, and Deacetylbowdensine.* Four Amaryllidaceae alkaloids, ambelline (III), buphanisine (IV), crinine (V), deacetylbowdensine (VII), and the alkaloid derivative powellane (VI), which are derived from 5,10b-ethanophenanthridine[4] and in which the two-carbon bridge has the β-configuration, have been included in this investigation and their spectra are reproduced in Figures 3–7, respectively. The spectra of several analogs of buphanisine (IV) differing only in the substituents of the benzene ring have been measured.[6a] Functional variations of this type do not affect the over-all fragmentation patterns but still cause appreciable changes in the

III   IV

V   VI

VII
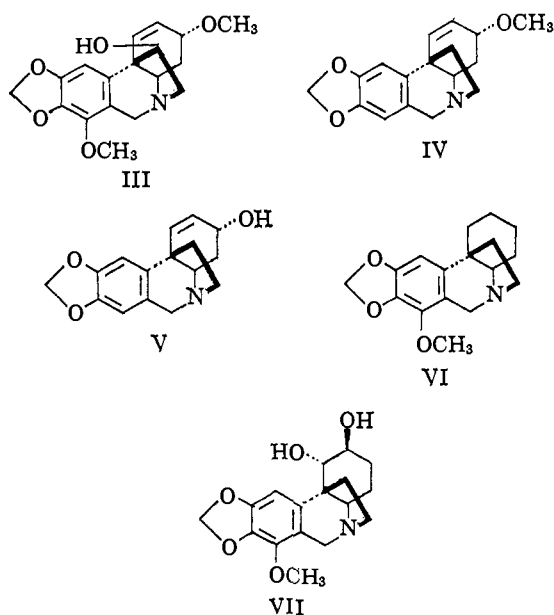
(10) The ion m may expand in part to a tropylium cation but in this, and subsequent analogous ions in this paper, we write this species for the sake of simplicity in the form of the benzylic cation.

(11) A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, 87, 810 (1965); see also A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *ibid.*, 87, 2926 (1965).

relative abundances of the fragment ions. No interpretations of the fragmentation patterns were given in ref. 6a (see however ref. 6b).

The base peak in the spectra of these five substances corresponds in each case to the molecular ion. Loss of a methyl group occurs in the spectra of all five alkaloids and is most pronounced in the spectrum (Figure 4) of buphanisine (IV). This loss can be attributed to the expulsion of a methyl radical from a methoxyl group in each alkaloid, with the exception of crinine (V) which lacks this functionality and where such a peak is very small. The spectrum of crinine (V) contains a peak at M − 17 which can be assigned to the elimination of a hydroxyl group.

Two peaks at m/e 300 (M − 31) and m/e 299 (M − 32) in the spectrum (Figure 3) of ambelline (III) correspond to the elimination of a methoxyl radical and methanol, respectively. These losses can be formulated from the molecular ion IIIa as shown by the formation of o $(m/e\ 300)^{12}$ and p $(m/e\ 299)$.


p, m/e 299

IIIa   o, m/e 300
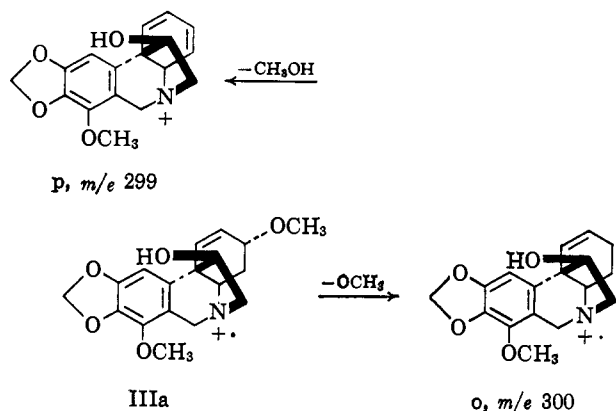
The abundant ion at mass 287 (M − 44) in the spectrum (Figure 3) of ambelline (III) corresponds to the loss of the hydroxylated ethylene bridge. This elimination may proceed from the molecular ion IIIa to yield the species q $(m/e\ 287)$.

Loss of 30 mass units from the ion o′ of mass 300 yields the peak at m/e 270 (M − 61) in the spectrum (Figure 3) of ambelline as is evidenced by the recognition of a metastable peak at m/e 243.3 $(270^2/300 =$

(12) The structure of the ion resulting from loss of a methoxyl group from IIIa may be visualized in various ways. Simple dissociation of ·OCH₃ would result in the diradical o. Formal stabilization of this diradical could be attained by cleavage of the C-4, C-4a bond yielding o′. This species, however, violates Bredt's rule and, although it is a moot point whether this rule holds under mass spectrometric conditions,¹³ the decoupled form o″, or a further rearrangement product o‴, may be considered. Similar ions will be encountered on several occasions in the following discussion and for the sake of brevity only one expression (equivalent to o′) will be considered.


o′   o″

o‴
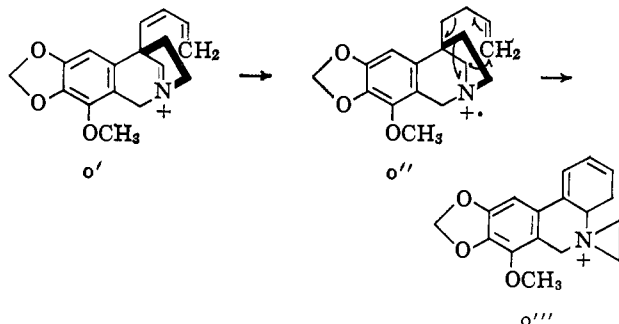
(13) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 246, 247.

IIIa

q, m/e 287
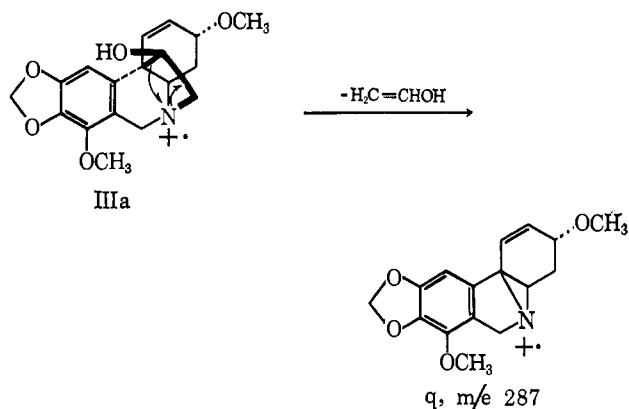
243.0). This process can be envisaged as the loss of formaldehyde from the species o′ $(m/e\ 300)$ with the production of r $(m/e\ 270)$.¹²

r, m/e 270
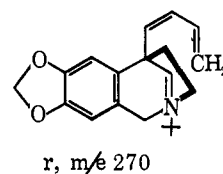
A prominent peak at m/e 260 (M − 71) in the spectrum (Figure 3) of ambelline could arise from the molecular ion IIIa via α-cleavage to s which by elimination of a methyl radical would yield t. Heterolysis of the benzylic carbon–nitrogen bond in u would furnish v $(m/e\ 260)$ as the charged species plus an amine radical. The composition $C_{15}H_{16}O_4^+$ for this ion (determined by high-resolution mass spectrometry) is compatible with its representation as v $(m/e\ 260)$.

s   t, m/e 316

v, m/e 260   u
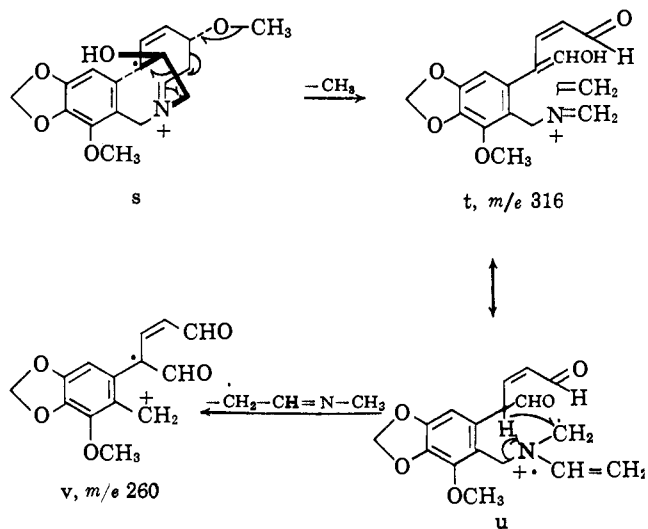
The mass spectrum (Figure 3) of ambelline (III) displays prominent ions at M − 90 $(m/e\ 241)$ and M − 120 $(m/e\ 211)$ and the origin of these ions is discussed below in conjunction with the interpretation of the mass spectra of haemanthidine (VIII), haemanthamine (IX), and 11-oxohaemanthamine (X).

The mechanistic interpretation of the mass spectrum (Figure 4) of buphanisine (IV) was assisted by the results of high-resolution mass spectral measurements[6b,7] which are collected in Table I.

Table I. High-Resolution Mass Spectral Measurements[7] of Some Ions of Buphanisine (IV)

m/e	Compn.	Calcd.	Obsd.
242	$C_{15}H_{14}O_3$ (50%)	242.0945	242.0941
242	$C_{14}H_{12}NO_3$ (50%)	242.0820	242.0817
230	$C_{14}H_{14}O_3$	230.0948	230.0943
227	$C_{14}H_{13}NO_2$	227.0944	227.0946
224	$C_{14}H_{10}NO_2$	224.0711	224.0711
215	$C_{13}H_{11}O_3$	215.0706	215.0708
201	$C_{12}H_{11}NO_2$	201.0789	201.0786
198	$C_{13}H_{10}O_2$	198.0679	198.0681
187	$C_{12}H_{11}O_2$	187.0762	187.0759
185	$C_{12}H_9O_2$	185.0605	185.0603
172	$C_{11}H_8O_2$	172.0526	172.0524
157	$C_{11}H_9O$	157.0658	157.0653

A peak at m/e 253 (M — 32) in the spectrum (Figure 4) of buphanisine (IV) arises from the expulsion of methanol and this process can be considered similar to that depicted for the loss of this entity from ambelline (IIIa → p).

The loss of 55 mass units from buphanisine (IV) furnishes an ion of mass 230 whose origin can be depicted in terms of the process IVa → w → x (m/e 230). High-resolution mass spectrometry[7] showed (Table I) the composition of this peak to be $C_{14}H_{14}O_3^+$, which is consistent with this fragment's designation as x.[10]

IVa

w   x, m/e 230
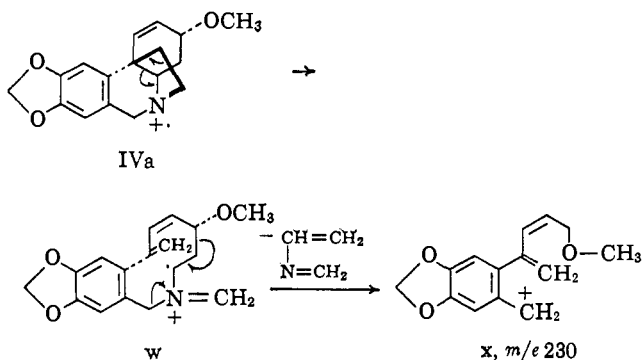
Elimination of a methyl radical from the species x would yield y (m/e 215). The process depicted by x → y is verified, at least in part, by the recognition of a metastable peak at m/e 201.0 ($215^2/230 = 200.9$). The results obtained from high-resolution mass spectral measurements[7] (Table I) are in agreement with representation y for the ion of mass 215. Loss of 30 mass units from the species y would generate the fragment z (m/e 185), and high-resolution mass spectrometry[7] (Table I) is in harmony with this assignment. A metastable ion at mass 159.5 ($185^2/215 = 159.2$) lends further support for the process y → z.

y, m/e 215

z, m/e 185
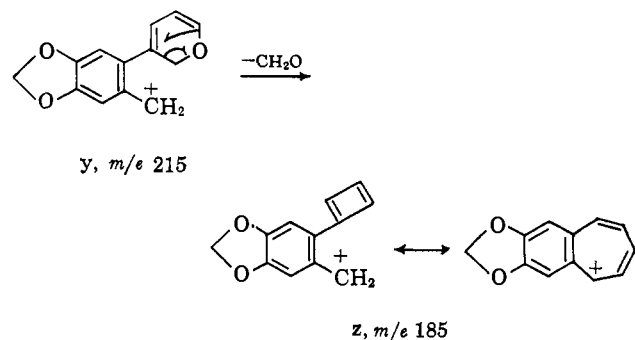
High-resolution mass spectrometry[7] (Table I) established the composition of the peak at m/e 187 (M — 98) in the buphanisine spectrum as $C_{12}H_{11}O_2^+$. The origin of this fragment can be considered as involving the loss of carbon monoxide from the species y' and to be represented by aa (m/e 187).

y', m/e 215   aa, m/e 187
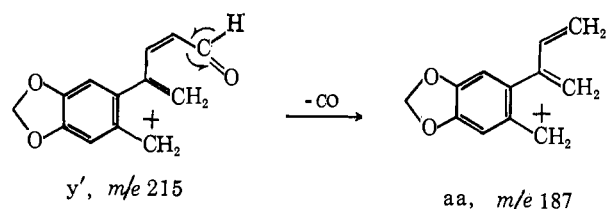
The elimination of formaldehyde (M — 30) from the methylenedioxy group of the species aa (m/e 187) would furnish the ion of mass 157 (M — 128) in the spectrum (Figure 4) of buphanisine. This fragment can thus be assigned structure bb (m/e 157), and this representation is in agreement with the results (Table I) from high-resolution mass spectrometry.[7]

bb, m/e 157
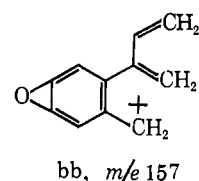
The peak at m/e 201 (M — 84) in the spectrum (Figure 4) of buphanisine corresponds[7] to $C_{12}H_{11}NO_2^+$ (Table I). This result is consistent with the formal elimination of ring C in buphanisine.

The mass spectrum (Figure 5) of crinine (V) displays a strong molecular ion while peaks of low abundance corresponding to fragments at M — 15, M — 17, M — 29, and M — 31 are visible. The first ion of appreciable abundance occurs at mass 228, and high-resolution mass spectrometry[7] showed this peak to be a doublet of the composition $C_{14}H_{12}O_3^+$ (65%) and $C_{14}H_{14}NO_2^+$ (35%; Table II). Fragmentation of the

Table II. High-Resolution Mass Spectral Measurements[a] of Some Ions of Crinine (V)

| m/e	Compn.	Calcd.	Obsd.
228	$C_{14}H_{12}O_3$ (65%)	228.0790	228.0786
	$C_{14}H_{14}NO_2$(35%)	228.1029	228.1025
216	$C_{13}H_{12}O_3$	216.0786	216.0786
199	$C_{13}H_{11}O_2$	199.0759	199.0759
187	$C_{12}H_{11}O_2$	187.0762	187.0759
173	$C_{11}H_9O_2$	173.0601	173.0602
172	$C_{11}H_8O_2$	172.0526	172.0524

[a] See ref. 7.

molecular ion (Va) of crinine to yield cc and elimination therefrom of a neutral amine fragment would generate the species dd (m/e 228) and would thus explain the origin of the major component of mass 228 in the spectrum (Figure 5) of crinine.

A mechanism for the formation of the minor fragment of mass 228 ($C_{14}H_{14}NO_2^+$) in the spectrum (Figure 5) of crinine would involve the formation of the species ee, from the molecular ion Va followed by the elimination of $\cdot CH_2CHO$ and production of ff (m/e 228).[12]

Va → cc

$-\overset{\triangle}{\underset{H}{N}}\longrightarrow$

dd, m/e 228

Va →

CH₂ ... CHO
ee

$-\dot{C}H_2-CHO \longrightarrow$

CH₂
ff, m/e 228
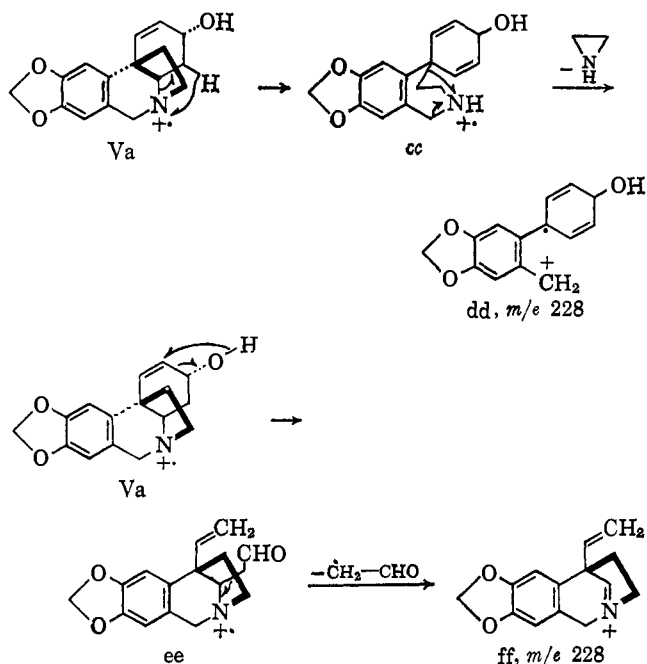
A prominent ion of mass 199 (M − 72) in the spectrum (Figure 5) of crinine corresponds[7] to $C_{13}H_{11}O_2^+$ (Table II), and the origin of this ion can be considered to be the expulsion of a formyl radical from the species dd to yield gg (m/e 199). Loss of acetylene from gg would furnish hh (m/e 173), while the elimination of a hydrogen atom from hh would yield the oxygenated naphthalene ion jj (m/e 172). Both suggestions are in harmony with the results (Table II) of high-resolution mass spectrometry.[7]

gg, m/e 199 $- HC≡CH \longrightarrow$ hh, m/e 173 $- H· \longrightarrow$

jj, m/e 172
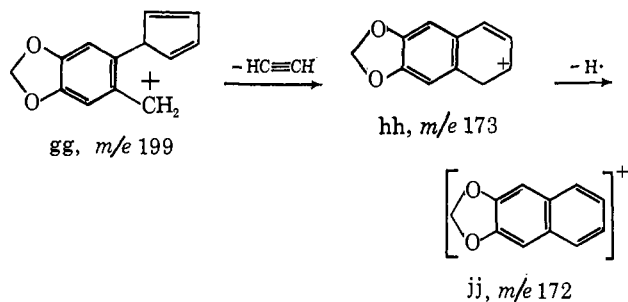
High-resolution mass spectrometry[7] also established the composition of the peak at m/e 216 (M − 55) in the spectrum (Figure 5) of crinine to be $C_{13}H_{12}O_3^+$ (Table II). The origin of this ion can be depicted by a sequence similar to that invoked (IVa → w → x, m/e 230) for the formation of the ion of mass 230 in the spectrum (Figure 4) of buphanisine such that the charged entity can be represented by kk (m/e 216).[10] Loss of the elements of ·CHO from kk would yield aa (m/e 187),[10] and this process is in harmony with the results obtained from high-resolution mass spectrometry[7] (Table II).

kk, m/e 216 $-CHO \longrightarrow$ aa, m/e 187
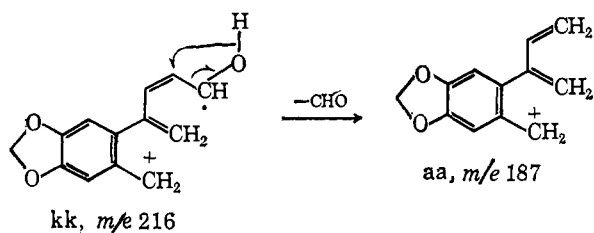
The mass spectrum of powellane (Figure 6) is dominated by the molecular ion while the fairly abundant peak at m/e 259 (M − 28) probably corresponds to the elimination of the two-carbon bridge. High-resolution mass spectral measurements showed the peak at m/e 258 (M − 29) in the spectrum (Figure 6) of powellane to be a doublet ($C_{15}H_{16}NO_3^+$ (30%) and $C_{16}H_{18}O_3^+$ (70%)). The minor component of this peak could arise from the elimination of the two-carbon bridge plus one hydrogen atom and correspond to mm (m/e 258) while the major constituent could be produced via the sequence VIa → nn → oo (m/e 258). High-resolution mass spectrometry established the composition of the peak at m/e 257 (M − 30) in the spectrum (Figure 6) of powellane to be $C_{16}H_{17}O_3^+$, and this species may be represented by pp (m/e 257).

OCH₃
mm, m/e 258   ←   OCH₃
VIa

mm', m/e 258   nn (OCH₃)

pp, m/e 257 $\xleftarrow{-H·}$ oo, m/e 258
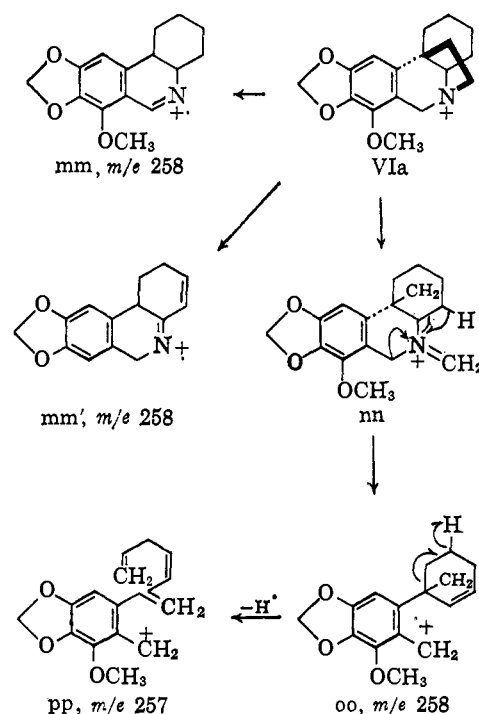
The origin of a fragment of mass 232 (M − 55) in the spectrum (Figure 6) of powellane can be rationalized by the mechanism VIa → qq → rr (m/e 232)[10] which is similar to that (IVa → w → x, m/e 230) depicted for the loss of 55 mass units from buphanisine.

OCH₃
VIa   →

qq (OCH₃) $\xrightarrow{-CH_2=N-CH=CH_2}$ rr, m/e 232 (OCH₃)
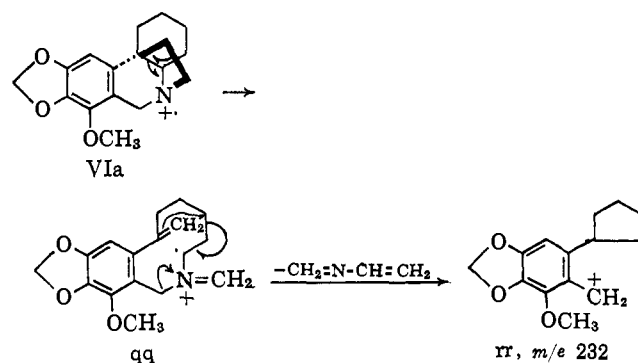
The presence of a peak at m/e 231 (M − 56) in the spectrum (Figure 6) of powellane can be interpreted mechanistically in terms of the scheme VIa → ss (m/e 231).

Figure 8. Mass spectrum of haemanthidine (VIII).
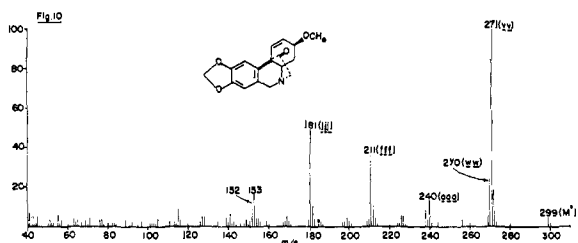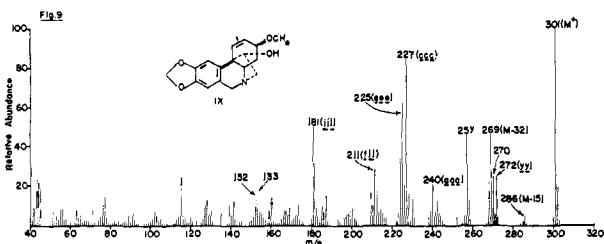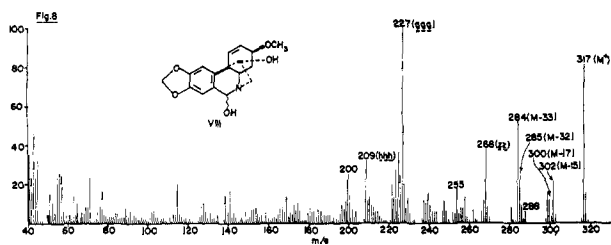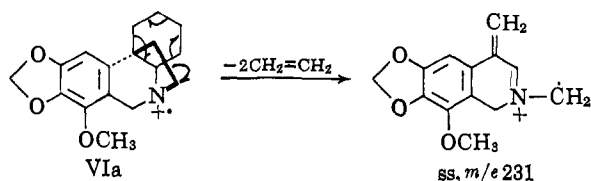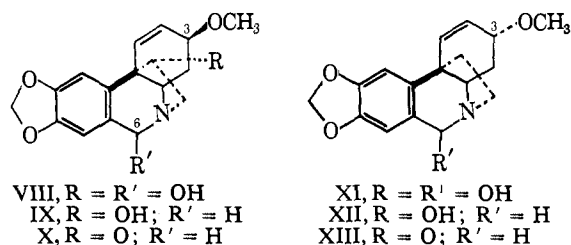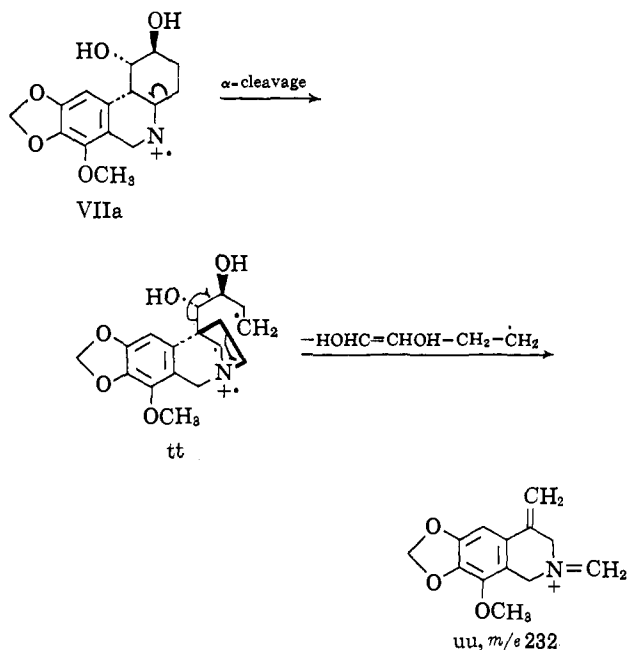Figure 9. Mass spectrum of haemanthamine (IX).
Figure 10. Mass spectrum of 11-oxohaemanthamine (X).


VIa → $-2CH_2=CH_2$ → ss, m/e 231

The most prominent ion in the spectrum (Figure 7) of deacetylbowdensine (VII) is again the molecular ion. Few other peaks attain prominence, one exception being that at m/e 232 (M − 87). A probable genesis of this ion is illustrated in VIIa → tt → uu (m/e 232).

VIIa → α-cleavage

tt → $-HOHC=CHOH-CH_2-\dot{C}H_2$ →

uu, m/e 232

Haemanthidine, Haemanthamine, 11-Oxohaemanthamine, 6-Hydroxycrinamine, Crinamine, and 11-Oxocrinamine. The mass spectra of four Amaryllidaceae alkaloids derived from 5,10b-ethanophenanthridine[4] having the two-carbon bridge in the α-configuration with a hydroxyl group at C-11 have been determined. Two C-11 ketones, prepared by the oxidation of the corresponding alkaloids, were studied also. Of these six, the mass spectra of three, haemanthidine (VIII), haemanthamine (IX), and 11-oxohaemanthamine (X) (Figures 8, 9, and 10), are conveniently interpreted together since the presence of an additional functional group[14a] (haemanthidine, VIII) or a change in one of the functionalities (11-oxohaemanthamine, X) may permit use of the mass spectral shift technique.[14] The remaining three bases, 6-hydroxycrinamine (XI), crinamine (XII), and 11-oxocrinamine (XIII) have the C-3 methoxyl group in the α-configuration and are thus the respective stereoisomers of VIII, IX, and X, and their mass spectra will be discussed later in this paper.

VIII, R = R′ = OH
IX, R = OH; R′ = H
X, R = O; R′ = H

XI, R = R′ = OH
XII, R = OH; R′ = H
XIII, R = O; R′ = H

Both the spectra (Figures 8 and 9) of haemanthidine (VIII) and haemanthamine (IX) display peaks at M − 15 (probably due to the loss of a methyl radical from the methoxyl group) and at M − 17 (expulsion of a hydroxyl radical) while these fragmentations are absent in the spectrum (Figure 10) of 11-oxohaemanthamine (X).

The most abundant ion in the spectrum (Figure 10) of 11-oxohaemanthamine occurs at m/e 271 (M − 28) and its origin can best be ascribed to the loss of carbon monoxide as depicted by Xa → vv (m/e 271). Elimination of a hydrogen atom from the species vv (metastable ion at m/e 269.0 ($270^2/271 = 269.0$)) can then generate ww (m/e 270).

Xa → $-CO$ →

vv, m/e 271   →$-H\cdot$→   ww, m/e 270
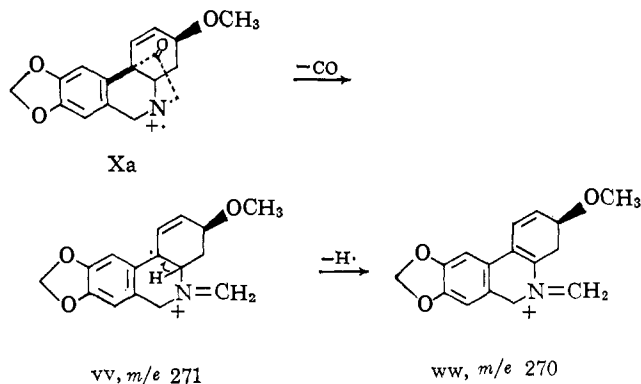
Expulsion of 29 mass units in the electron impact induced fragmentation of haemanthamine (IX) yields an ion of mass 272 (Figure 9) while the same loss in the case of haemanthidine (VIII, Figure 8) is much less pronounced and affords an ion of mass 288. These

(14) (a) Reference 13, p. 305; (b) ref. 5, pp. 11, 48, 124.

fragmentations could occur (illustrated for haemanthamine; see Figure 9) *via* the sequence IXa → xx → yy (*m/e* 272) and the elementary composition ($C_{18}H_{18}NO_3$) of yy is substantiated by high-resolution mass measurements.

IXa

xx

yy; *m/e* 272
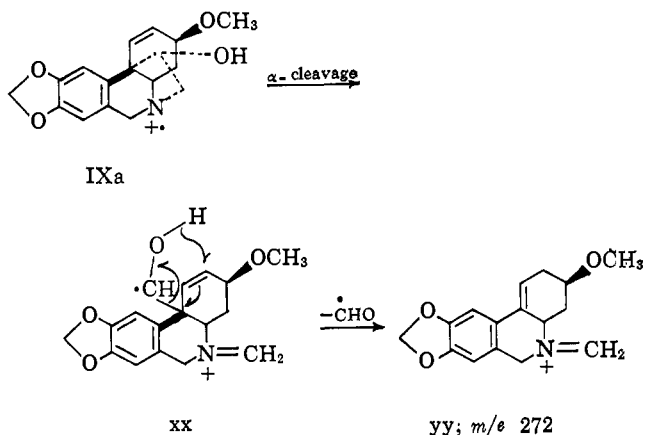
The expulsion of methanol (M − 32) from the molecular ions of haemanthamine and haemanthidine is a relatively favorable process (see peaks at *m/e* 285 and 269 in Figures 8 and 9). This step can be considered analogous to the loss of methanol from ambelline (see IIIa → p) and requires no additional representation.

Ejection of a methyl radical followed by loss of water yields the ion of mass 284 (M − 33) in the spectrum (Figure 8) of haemanthidine (VIII), as is evidenced by the appearance of a metastable ion at mass 201.4 ($284^2/302 = 201.3$). By analogy the ion of mass 268 (M − 33) in the spectrum (Figure 9) of haemanthamine (IX) is assumed to have a similar origin.

A peak at *m/e* 257 (M − 44) in the spectrum (Figure 9) of haemanthamine corresponds to the loss of the hydroxylated ethylene bridge, and this fragmentation has been depicted for ambelline (see IIIa → q). It is noteworthy that the spectra (Figures 8 and 11) of haemanthidine (VIII) and 6-hydroxycrinamine (XI), which contain a hydroxyl group at C-6, lack a peak corresponding to the elimination of the hydroxylated bridge.

The prominent peak at *m/e* 268 (M − 49) in the spectrum (Figure 8) of haemanthidine arises by the elimination of a hydroxyl radical from the M − 32 species. While this fragment can best be assigned structure zz (*m/e* 268), the evidence at hand does not exclude involvement of the bridge hydroxyl group.

zz, *m/e* 268
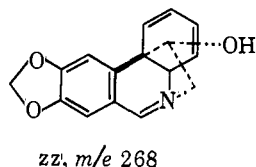
An ion of mass 240 (M − 59) in the spectrum (Figure 10) of 11-oxohaemanthamine (X) could have its origin through the loss of a methoxyl radical from the species vv (*m/e* 271) and correspond to aaa (*m/e* 240).[15] The

(15) This process could equally well be envisaged as proceeding from the molecular ion (Xa) which could lose the elements of carbon monoxide and a methoxyl radical in a concerted manner. No metastable ion corresponding to the transition *m/e* 271 → *m/e* 240 could be discerned.

peaks present at *m/e* 256 (M − 61) and *m/e* 240 (M − 61) in the spectra (Figures 8 and 9) of haemanthidine and haemanthamine may arise by a related process (CH_2O rather than CO elimination) as used to explain the origin of the ion aaa of mass 240.

vv, *m/e* 271   aaa, *m/e* 240
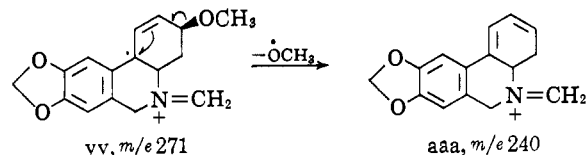
Haemanthamine (IX) upon mass spectrometric fragmentation (Figure 9) yields two intense peaks at *m/e* 227 (M − 74) and *m/e* 225 (M − 76). The first of these fragments was shown by high-resolution mass spectrometry to correspond to $C_{14}H_{11}O_3^+$, and an origin consistent with this result is shown in IXa → bbb → ccc (*m/e* 227).[10] High-resolution mass spectral measurements established the composition of the ion of mass 225 in the spectrum of haemanthamine to be $C_{14}H_9O_3^+$ (67%) and $C_{14}H_{11}NO_2^+$ (33%). The major component of this mixture could arise from the loss of two hydrogen atoms from ccc furnishing the ion ccc' (*m/e* 225).[10] The nitrogen-containing species of mass 225 could arise by the scheme depicted by IXa → ddd → eee (*m/e* 225).

IXa   bbb

ccc, *m/e* 227   ccc', *m/e* 225

ddd   eee, *m/e* 225
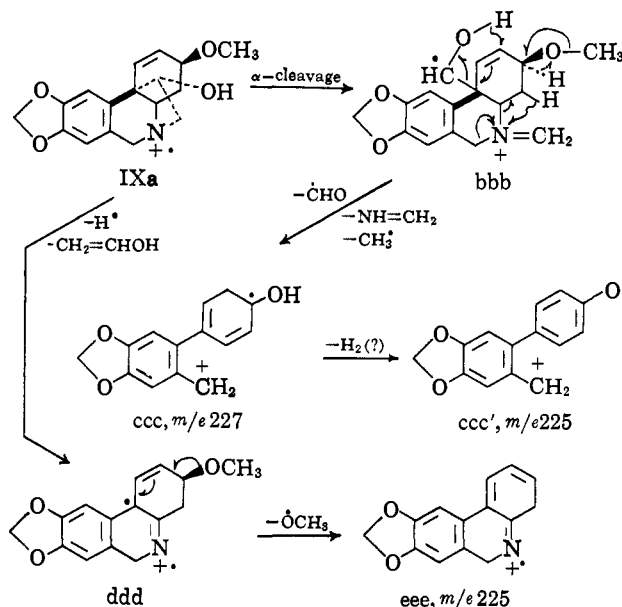
High-resolution mass spectrometry established the composition of the peak at *m/e* 211 in the spectra (Figures 9 and 10) of haemanthamine (IX) and 11-oxohaemanthamine (X) as $C_{14}H_{11}O_2^+$. The origin of this species can be depicted by the loss of the neutral fragment NH=CH₂ from the ion aaa (*m/e* 240) with the formation of fff (*m/e* 211),[10] and this pathway is supported by the presence of a metastable ion at mass 185.5 ($211^2/240 = 185.4$) in the spectrum of 11-oxohaemanthamine.

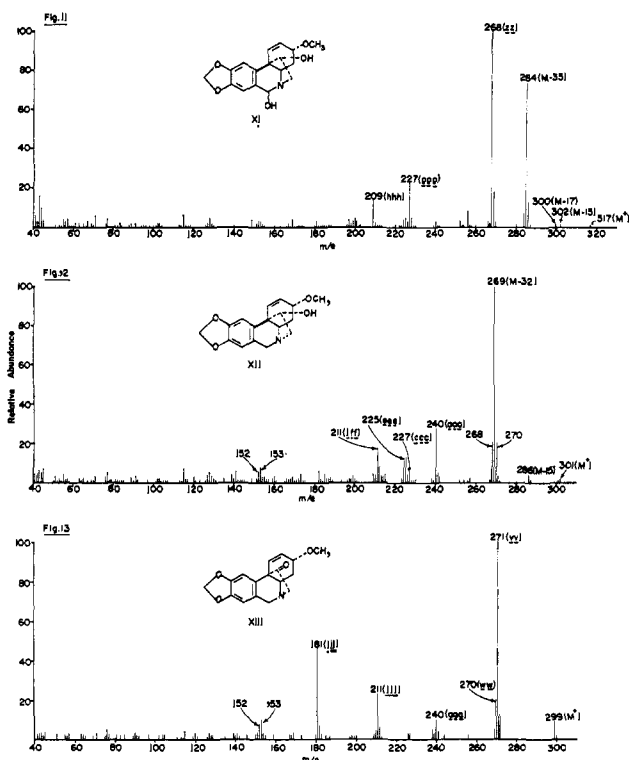aaa, *m/e* 240   fff, *m/e* 211
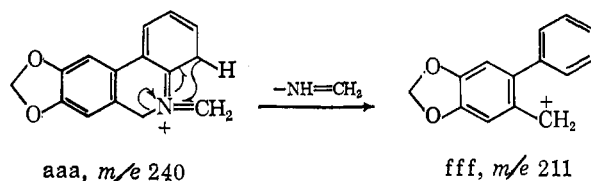
Figure 11. Mass spectrum of 6-hydroxycrinamine (XI).
Figure 12. Mass spectrum of crinamine (XII).
Figure 13. Mass spectrum of 11-oxocrinamine (XIII).

The peaks present at m/e 227 and 211 in the spectra (Figures 8 and 9) of haemanthidine (VIII) and haemanthamine (IX) correspond to the loss of 90 mass units, and their geneses can be depicted in a similar manner as that of species fff. In haemanthidine (VIII) the M — 90 fragment would be ggg (m/e 227) which by the elimination of water could yield the ion hhh (m/e 209).

ggg, m/e 227   —H₂O→   hhh, m/e 209
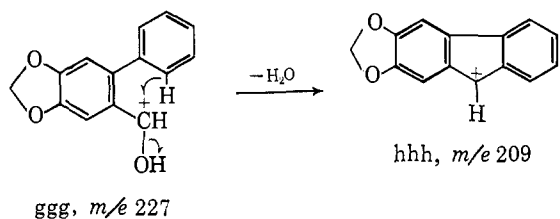
The ion of mass 211 (M — 90) in the spectra (Figures 9 and 10) of haemanthamine (IX) and 11-oxohaemanthamine (X) can lose 30 mass units by the ejection of formaldehyde from the methylenedioxy group, and the product of this decomposition may be represented by jjj (m/e 181).[10] This formulation is compatible with the results from high-resolution mass spectrometry which demonstrated this ion's composition to be $C_{13}H_9O^+$.

jjj, m/e 181
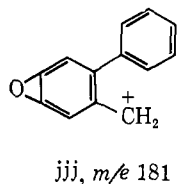
The earlier discussed mass spectrum (Figure 3) of ambelline (III) contains a prominent peak (m/e 241) corresponding to the loss of 90 mass units. The origin of this fragment can be envisaged through a process analogous to that depicted by Xa → aaa → fff, while the loss of a further 30 mass units (M — 120 peak at m/e 211) may be ascribed to a process similar to fff → jjj.

A peak at m/e 153 (M — 146) in the spectrum (Figure 10) of 11-oxohaemanthamine could arise from the elimination of carbon monoxide from the fragment jjj (m/e 181). By analogy the ion of mass 153 (M — 148) in the spectrum of haemanthamine (IX) is assumed to have a similar origin.

The Amaryllidaceae alkaloids 6-hydroxycrinamine (XI), crinamine (XII), and 11-oxocrinamine (XIII) all contain an α-methoxyl group at C-3 and are thus stereoisomeric with haemanthidine (VIII), haemanthamine (IX), and 11-oxohaemanthamine (X). In view of the previously discussed results with the stereoisomers tazettine (I) and criwelline (II) it is not surprising that the spectra of the stereoisomeric partners generally show considerable quantitative differences (compare Figures 8 with 11, 9 with 12, and 10 with 13). However, the ions present at any one mass number in the alkaloids XI, XII, and XIII may be considered to arise through analogous procedures as described above for their stereoisomeric partners (VIII, IX, and X). An important difference between the spectra of these alkaloids, stereoisomeric at C-3, is the strikingly low abundance of the molecular ion and the facile loss of methanol (M — 32) in the spectra (Figures 11 and 12) of 6-hydroxycrinamine (XI) and crinamine (XII) and of 28 mass units (carbon monoxide) in the spectra (Figure 13) of 11-oxocrinamine (XIII). The driving force for the elimination of methanol or carbon monoxide in these compounds is presumably the release of steric strain originating from the proximity of the methoxyl group and the two-carbon bridge.

XIV
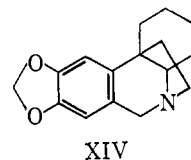
The base peak in the spectrum (Figure 14) of (±)-crinane (XIV; high-resolution mass spectral measurements compiled in Table III) corresponds to the molecular ion. A prominent peak at m/e 229 (M — 28) in the spectrum of (±)-crinane (Figure 14) represents the loss of C_2H_4 (Table III), and its origin can be visualized in terms of expulsion of the ethylene bridge analogous to the formation of the ion q (m/e 287) from ambelline (III). Further loss of one hydrogen atom accounts for one-half of the m/e 228 peak (Table III), while the other half probably arises from expulsion of CH_2=NH analogous to the formation of the ion xx from IXa.

The formation of the ion of mass 202 (M — 55) in the spectrum (Figure 14) of (±)-crinane (XIV) may be explained by loss of ring C accompanined by hydrogen transfer to give kkk while peaks at m/e 201, 200 (in part), 185, and 174 (in part) constitute fragment ions comprising the benzene ring with its methylenedioxy group and several carbon atoms of the alicyclic frame

Table III. High-Resolution Mass Spectral
Measurements of Some Ions of (±)-Crinane (XIV)

m/e	Compn.	Calcd.	Obsd.
229	$C_{14}H_{15}NO_2$	229.1103	229.1106
228	$C_{14}H_{14}NO_2$ (50%)	228.1024	228.1029
	$C_{15}H_{16}O_2$ (50%)	228.1150	228.1147
202	$C_{12}H_{12}NO_2$	202.0868	202.0874
201	$C_{13}H_{13}O_2$	201.0915	201.0958
200	$C_{12}H_{10}NO_2$ (70%)	200.0711	200.0718
	$C_{13}H_{12}O_2$ (30%)	200.0837	200.0822
185	$C_{12}H_9O_2$	185.0603	185.0619
174	$C_{10}H_8NO_2$ (25%)	174.0555	174.0556
	$C_{11}H_{10}O_2$ (75%)	174.0681	174.0687

work. However, since no labeled analogs of crinane (XIV) were available, the following structures should only be considered tentative rationalizations.

kkk, m/e 202

mmm

nnn

|—ĊH₂—N≡CH₂CH₃

ooo, m/e 201

ppp, m/e 200

qqq, m/e 185

rrr, m/e 174

sss, m/e 174
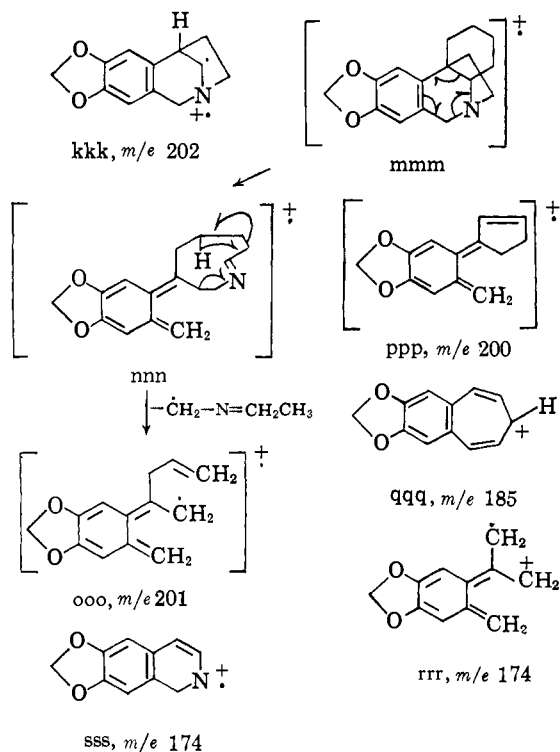
Montanine (*XV*) *and Coccinine* (*XVI*). The spectra (Figures 15 and 16) of montanine (XV) and coccinine (XVI) display intense molecular ions while less abundant ions at mass 286 (M − 15) are probably due to the loss of a methyl radical from the methoxyl group.

XV

XVI
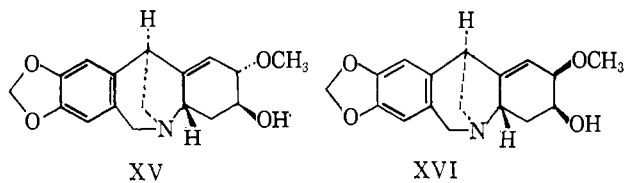
Both montanine[16] (XV) and coccinine[16] (XVI) show intense peaks in their spectra at m/e 270 (M − 31) whose genesis is best envisaged as due to the loss of the allylic methoxyl group according to (illustrated for montanine) XVa → ttt (m/e 270).

(16) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, J. Org. Chem., 25, 2153 (1960).

Figure 14. Mass spectrum of (±)-crinane (XIV).
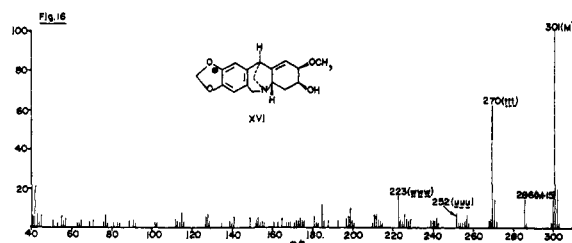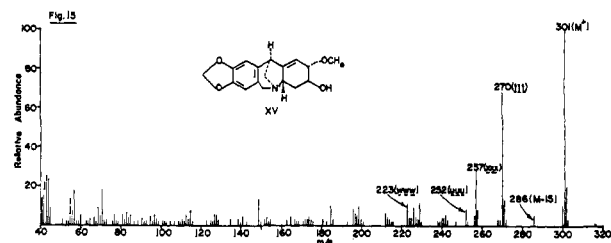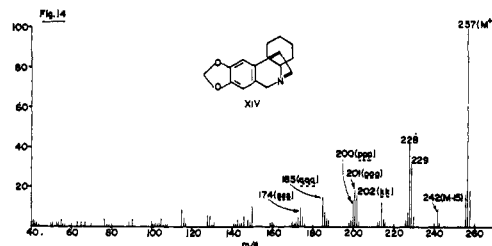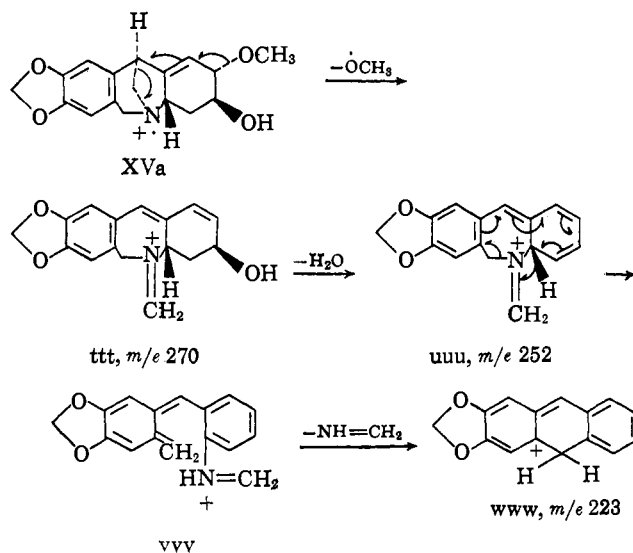Figure 15. Mass spectrum of montanine (XV).
Figure 16. Mass spectrum of coccinine (XVI).

XVa

ttt, m/e 270

uuu, m/e 252

vvv

www, m/e 223

Metastable ions at mass 235.5 ($252^2/270$ = 235.3) in the spectra (Figures 15 and 16) of montanine (XV) and coccinine (XVI) testify to the loss of water from the species ttt. This process can best be visualized as a 1,2-elimination with the formation of uuu (m/e 252). Further decomposition of the species uuu is possible by the elimination of 29 mass units (CH_2=NH) according to the scheme uuu → vvv → www (m/e 223).

A peak of substantial abundance at m/e 257 (M − 44) in the spectrum (Figure 15) of montanine has its origin in a retro-Diels–Alder fragmentation[8] of ring C according to XVa → xxx (m/e 257). Recognition of a metastable ion at mass 219.5 ($257^2/301$ = 219.4) established that at least a portion of the ion yield at

m/e 257 arose from such a single stage decomposition of the molecular ion of montanine.

XVa

xxx, *m/e* 257
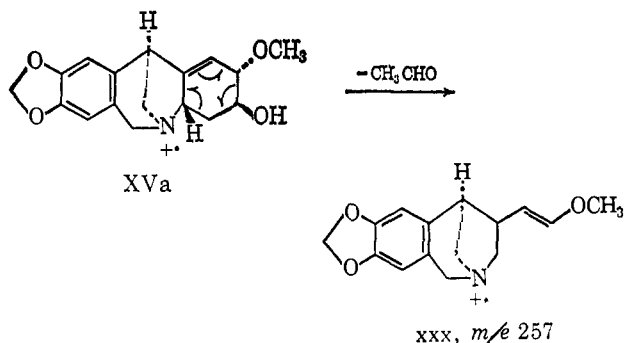
Experimental Section[17]

Criwelline-N-d₃. A solution of 200 mg. of 6-hydroxycrinamine and 1.5 ml. of methyl iodide-d_3[18] in 10 ml. of methanol–acetone (1:5) was allowed to stand

(17) All low resolution mass spectra were determined with an Atlas CH-4 mass spectrometer using the TO-4 ion source (70 e.v.). High resolution mass spectra, unless designated otherwise, were determined using an A.E.I. MS-9 double focussing mass spectrometer, with an apparent resolution of 12,000.

(18) F. A. Cotton, J. A. Fassnacht, W. D. Horrocks, and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

at room temperature for 30 min. The excess methyl iodide-d_3 and solvents were removed by distillation and collected in a liquid nitrogen trap. The residue was dried at room temperature under reduced pressure, dissolved in water, and made basic (pH 10) with 10% sodium hydroxide. The basic solution was extracted three times with chloroform and the chloroform was removed under reduced pressure to give 202 mg. of criwelline-N-d_3, m.p. 201–202° (from acetone–chloroform). The deuterium incorporation was greater than 98% as determined by mass spectrometry and by the complete absence of the N-methyl peak in the n.m.r. spectrum of criwelline-N-d_3.

Tazettine-N-d₃. The methyl iodide-d_3 solution recovered in the synthesis of criwelline-N-d_3 was added to 50 mg. of haemanthidine (VIII). The solution was allowed to stand at room temperature for 30 min. The solvents were removed by distillation and collected in a liquid nitrogen trap. The residue was dried under reduced pressure, dissolved in water, and made basic (pH 10) with 10% sodium hydroxide. The aqueous solution was extracted three times with chloroform and the chloroform was removed under reduced pressure to give 42 mg. of tazettine-N-d_3 which was recrystallized twice from acetone and sublimed at 200° (0.001 mm.), m.p. 211–213°.

6-Hydroxycrinamine and Haemanthidine

R. W. King, C. F. Murphy,[1] and W. C. Wildman

Contribution from the Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010. Received July 20, 1965

On the basis of chemical and spectroscopic studies, it is suggested that haemanthidine, 6-hydroxycrinamine, and all derivatives of these alkaloids having a 6-hydroxyl group exist in solution as a mixture of C-6 epimers.

6-Hydroxycrinamine (Ia) and haemanthidine (Ib) are unique among the numerous alkaloids of the Amaryllidaceae derived from the 5,10b-ethanophenanthridine nucleus because these two bases alone possess an hydroxyl substituent at C-6. The structures assigned to these alkaloids are based both on reductive transformations to known 6-deoxy derivatives[2] and on the facile conversion of Ia and Ib to criwelline (IIa) and tazettine (IIb), respectively, by methylation and treatment with dilute base.[3-5] The structures of IIa and IIb have been firmly established by degradative and synthetic methods.[4,6]

(1) NASA Fellow, 1964-1965.

(2) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960).

(3) H.-G. Boit and W. Stender, *Chem. Ber.*, **89**, 161 (1956).

(4) H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959).

(5) C. F. Murphy and W. C. Wildman, *Tetrahedron Letters*, 3863 (1964).

(6) S. Uyeo and co-workers have thoroughly studied the chemistry and stereochemistry of tazettine. See S. Uyeo, H. Irie, U. Kitayama, T. Hirose, and A. Yoshitake, *Chem. Pharm. Bull.* (Tokyo), **12**, 489 (1964), and references cited therein.
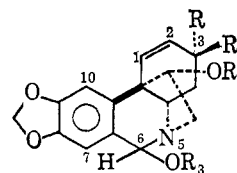
Ia, R₁, R₂, R₃ = H; R = OCH₃ (6-hydroxycrinamine)
 b, R, R₂, R₃ = H; R₁ = OCH₃ (haemanthidine)
 c, R₁, R₂, R₃ = H; R = OCH₃; no double bond at C-1-C-2 (dihydro-6-hydroxycrinamine)
 d, R₁, R₃ = H; R = OCH₃; R₂ = CH₃CO (11-acetyl-6-hydroxycrinamine)
 e, R₁, R₃ = H; R = OCH₃; R₂ = CH₃CO; no double bond at C-1-C-2 (11-acetyldihydro-6-hydroxycrinamine)
 f, R₁ = H; R = OCH₃; R₂, R₃ = CH₃CO; no double bond at C-1-C-2 (diacetyldihydro-6-hydroxycrinamine)
 g, R = H; R₁ = OCH₃; R₂, R₃ = CH₃CO (diacetylhaemanthidine)
 h, R = H; R₁ = OCH₃; R₂, R₃ = CH₃CO; no double bond at C-1-C-2 (diacetyldihydrohaemanthidine)
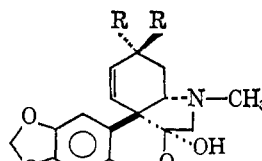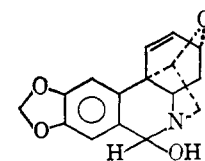
IIa, R = OCH₃; R₁ = H   III
 b, R = H; R₁ = OCH₃   apohaemanthidine

In a recent communication[5] on the mechanism of the conversion of Ia to IIa, we reported that the n.m.r.