The mass spectra of montanine- and galanthamine-type alkaloids: the structures of pancracine and habranthine

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THE MASS SPECTRA OF MONTANINE- AND GALANTHAMINE-TYPE ALKALOIDS;
THE STRUCTURES OF PANCRAINE AND HABRANTHINE

by

Costello Leon Brown

A Dissertation Submitted to the
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The Requirements for the Degree of
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Ames, Iowa
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INTRODUCTION

The utilization of mass spectrometry as an effective aid in structure elucidations has increased substantially in the last decade. Alkaloids and other large molecules are especially suitable for this technique. A new alkaloid is often isolated in minute quantities which precludes extensive chemical degradations. The gross structure and often an insight into the stereochemistry of the alkaloid may be established if the major fragmentation can be effectively correlated with documented and characteristic fragmentations of the known alkaloids of a given ring system.

Two new alkaloids, habranthine and pancracine, have been classified as galanthamine- and montanine-type alkaloids from chemical and spectroscopic data. The electron-impact induced fragmentations of alkaloids of these types had not been studied prior to this investigation. This thesis investigates the numerous fragmentation pathways for each of the ring systems and correlates these with those of the two new alkaloids providing additional support for their structures.
Alkaloids of the 5,11-Methanomorphanthridine Ring System

Montanine and coccinine

These alkaloids were first isolated in 1955, from several Haemanthus species native to South Africa. They have also been detected in H. multiflorus which is grown in the southern part of the United States as an ornamental plant. More recently, montanine was found to be the major alkaloid in Rhodophiala bifida.

Preliminary characterization of montanine and coccinine showed that these two alkaloids were isomeric and possessed the molecular formula of \( \text{C}_{17}\text{H}_{19}\text{NO}_4 \). In the catalytic hydrogenation of montanine and coccinine slightly more than one equivalent of hydrogen was absorbed. Neither alkaloid could be oxidized by manganese dioxide. Oppenauer oxidation of either montanine (1a) or coccinine (1b) afforded dehydrococcinine (2a). Dehydrococcinine was amphoteric and formed an O,N-diacetate. Infrared and ultraviolet data indicated that dehydrococcinine was an aminophenol. Methylation of dehydrococcinine gave 2b. Hoffman degradation of 2b gave an optically inactive methine (3) which showed IR and UV absorptions characteristic of a 1,1-diarylethylene. Further proof of these structures was obtained in the conversion of 2a to 4 (R = H) by Pictet-Spengler cyclization of 2a with formaldehyde and formic acid. The structure of 4 was proven by total synthesis of the corresponding methyl ether (4,R = CH\(_3\)) utilizing 5 as starting material.

The stereochemistry and absolute configuration of montanine and
coccinine were elucidated by a novel rearrangement of 11-hydroxy cринine-type derivatives to the montanine ring system. Conversion of haemanthamine (6a) to a mesylate and subsequent basic hydrolysis afforded isohaemanthamine (7a). Treatment of isohaemanthamine with manganese dioxide gave an \(\alpha,\beta\)-unsaturated ketone (7b). Sodium
Borohydride reduction of 7b gave the C2 epimer of isohaemanthamine (7e). Crinamine (6b) underwent a similar rearrangement but formed two products; 6-isocrinamine (7c) and 6-isocrinamine(7d). Attack of base on the mesylate of haemanthamine (6a) would occur mainly from the side away from the pseudo-axial methoxyl group affording a trans relationship for the functional groups at C2 and C3. In the mesylate of crinamine (6b) the pseudo-equatorial methoxy group permits attack of base from both sides of the molecule giving two products.

The proposed mechanism for the rearrangement of the haemanthamine and crinamine derivatives to the montanine-type nucleus5 is shown in Fig. 1. Attack of base at C2, migration of the double bond and
Fig. 1. The rearrangement mechanism to the montanine-type ring system nucleophilic displacement of the mesylate (as shown in 8) gives the 5,11-methanomorphanthridine ring system (9). The rearrangement does not occur with epihaemanthamine (6a, with an epimeric OH) or dihydrohaemanthamine providing further support of the proposed mechanism. The particular base and method used to hydrolyze the mesylate determines the nature of the substituent at C2 in the rearranged material. When sodium bicarbonate is used, the C2 functional group is a hydroxyl; however, with sodium methoxide in methanol the analogous methyl ether is obtained. The proposed mechanism required that the configuration of the C3 and C4a substituents in 8 be retained in 9. The configuration
of the C3 substituent in haemanthamine and crinamine were known. This established the configuration of the C3 substituent in isohaemanthamine (7a), E-isocrinamine (7c) and Z-isocrinamine (7d). The configuration of the C2 substituent in these compounds was determined by hydrogen-bonding studies. Isohaemanthamine had a hydroxyl stretching frequency of 3623 cm⁻¹ in dilute carbon tetrachloride. On this basis the C2-OH was assigned a trans quasi axial configuration relative to the C3 substituent. The C2-epimer, epiisohaemanthamine (7e) showed a completely hydrogen-bonded hydroxyl (3567 cm⁻¹). E-Isocrinamine (7c) and Z-isocrinamine (7d) had hydroxyl frequencies of 3607 and 3570 cm⁻¹ respectively. From this data, E- and Z-isocrinamine were assigned the trans and cis C2-C3 configurations, respectively.

The hydroxyl stretching frequencies for montanine and coccinine were found to be 3624 and 3566 cm⁻¹ respectively. From these observations, montanine (1a) and coccinine (1b) were assigned the trans and cis C2-C3 configurations, respectively.

Manthine

It was shown that isohaemanthamine could be converted to the corresponding dimethoxy derivative (7a→10) with potassium and methyl p-toluenesulfonate. This compound (10) was identical in all respects to manthine (mp 114-16°C, [α]D 71.3 (CHCl₃), an alkaloid which had been isolated in small quantities from the same plants that contained coccinine and montanine. The O-methylation was shown to occur with retention of configuration. Montanine (1a) could be converted to manthine by O-methylation. Manthine was also obtained from methanolation of
the mesylate of haemanthamine with sodium methoxide. These investigations along with the hydrogen-bonding studies completely interrelated the crinine- and montanine-type ring systems and established the stereochemistry of the montanine-type alkaloids.

Brunsvigine

Brunsvigine \([\text{mp 243}^\circ, [\alpha]_D -76.6^\circ \text{ (ethanol)} \text{ and } [\alpha]_D -106.5^\circ \text{ (CHCl}_3)]\) was first isolated from Brunsvigia cooperi. The investigators reported that brunsvigine contained a methylenedioxy-phenyl group, and two hydroxyl groups which probably are trans. They characterized brunsvigine by preparing picrate (mp 190\(^\circ\) or 219\(^\circ\)), hydrochloride (mp 218\(^\circ\)), and methiodide (mp 252\(^\circ\)) salts as well as an 0,0-diacetate (mp 184\(^\circ\)). The alkaloid formed a dihydro derivative (mp 203\(^\circ\)) which underwent Hoffman degradation with ease. No structure was proposed.

Later workers isolated brunsvigine from Brunsvigia radulosa. On the basis of a characteristic infrared spectrum in the 1250-1450 cm\(^{-1}\)
region, brunsvigine was postulated as the 2,3-dihydroxy analog of montanine (1a, OH instead of OCH₃). The proposed structure for brunsvigine is the same as presented in this thesis for pancracine. A comparison of the melting points of brunsvigine and pancracine and also of four derivatives indicated that these two alkaloids are not identical. 

Brunsvigine was crystallized from ethyl acetate and the specific rotation was determined in chloroform. Pancracine is completely insoluble in either hot ethyl acetate or hot chloroform.

Pancracine

A complete review of the previous isolations of pancracine was given in the historical section of the M. S. thesis of the author. Pancracine was found to be a minor alkaloid of Rhodophiala bifida. Four isolations from this plant gave pancracine in yields of 0.007%, 0.002%, 0.010% and 0.0078%. The alkaloid (mp 272-3°, [α]D 74°) was shown to have a molecular formula of C₁₆H₁₇NO₄ and formed picrate (mp 249-52°) and perchlorate (mp 163-56°) salts as well as an O,0-diacetate (mp 163-5°). In that thesis pancracine was postulated to possess the lycorine nucleus and structure 11 was assigned to the alkaloid.
Mass Spectra of Montanine-type Alkaloids

A brief report on the mass spectra of montanine and coccinine was published in 1965. Mechanisms for the formation of the m/e 270, 252, 223 and 257 ions in these compounds were proposed and are shown.

Fig. 2. Mechanism for the mass spectral ions in montanine
in Fig. 2. The m/e 270 and 252 ions were proposed as being formed in a consecutive loss of OCH₃ and H₂O from the parent ion (12→13→14). Aromatization of 14 and loss of NH=CH₂ gave the m/e 223 ion (14→15→16). Metastable ion correlations showed that the m/e 257 ion in the spectra of montanine and coccinine was formed directly from the molecular ion. A retro-Diels-Alder mechanism was proposed for this process (12→17).

Alkaloids Derived from the Dibenzo[a]furan Ring System

Galanthamine and lycoramine

Galanthamine (18) is a relatively abundant alkaloid which was first reported in 1952, as a constituent of the Caucasian Snowdrop, Galanthus woronowii. Later investigations have shown galanthamine to be present in several Galanthus, Leucojum, Narcissus, Vallota and Lycoris species. Galanthamine absorbed one equivalent of hydrogen to form a dihydro compound (19) which was identical with lycoramine (mp 120-21⁰), an alkaloid isolated from Lycoris radiata. Successive treatment of galanthamine with hydrobromic acid in glacial acetic acid at 100⁰ and zinc in alkali afforded 20a. Subsequent methylation with diazomethane gave deoxylcoramine (20b). Similar treatment of galanthamine with hydrobromic acid afforded a rearranged dibasic phenol, apogalanthamine (21a). Apogalanthamine was converted to the dimethoxyl derivative (21b) with diazomethane. Emde degradation of 21b gave 22 which was oxidized with permanganate to galanthamic acid (23). A total synthesis of 21c, 22, and 23 provided the necessary proof of these structures.
Fig. 3. Degradation of galanthamine
The relative and absolute stereochemistry were confirmed in 1964 by a three dimensional X-ray study of galanthamine methiodide. This work substantiated the earlier postulations of Barton and Kirby who found that the hydroxyl group of (+)-galanthamine showed strong intramolecular hydrogen bonding to the oxide bridge (OH—O, 3575 cm\(^{-1}\)).

**Narwedine and epigalanthamine**

Epigalanthamine (24) was isolated from *Lycoris squamigera*. Oxidation of epigalanthamine or galanthamine with manganese dioxide gave (+)-narwedine (25). Narwedine was isolated in low yield from the double narcissi "Texas and Irene Copeland". Reduction of narwedine with lithium aluminum hydride afforded both epigalanthamine and galanthamine (25→24 + 18). Based on these observations along with the
hydroxyl stretching frequency (3625 cm\(^{-1}\)) epigalanthamine (24) was shown to be the C\(_3\) epimer of galanthamine. Epimerization of galanthamine to epigalanthamine occurred in dilute hydrochloric acid (18\(\rightarrow\)24).\(^{19}\)

Narwedine exhibited rather novel crystallographic behavior. Crystallization of narwedine (obtained from the MnO\(_2\) oxidation of (-) - galanthamine) from acetone and ethanol gave (-) - narwedine [\(\alpha\)]\(_D\) -88° and (+) - narwedine [\(\alpha\)]\(_D\) +35° respectively. This spontaneous formation of (+) - narwedine in the crystallization from ethanol was found to be due to a trace of unreacted (-) - galanthamine. The infrared spectra of both enantiomers were identical with (+) - narwedine. Both compounds were racemized to (+) - narwedine at the same rate in warm ethanol. (+) - Narwedine [\(\alpha\)]\(_D\) +306° was obtained from recrystallization of a 2:1 mixture of (+) - narwedine and (-) - galanthamine using 10\% triethylamine in ethanol as a solvent. Recrystallization from benzene raised the rotation to a constant value of +405°. Similarly, a mixture of (+) - narwedine and (+) - galanthamine or (+) - epigalanthamine gave (-) - narwedine. This data showed that both enantiomers of galanthamine and epigalanthamine could be used as an effective resolving agent to obtain the desired enantiomer of narwedine. Standard resolving agents were not effective. This phenomenon was attributed to adsorption of traces of the particular resolving agent on the surface of the developing narwedine crystals. For example, an adsorbed (-) - galanthamine layer on (+) - narwedine crystals might either favor deposition of (+) - narwedine (like a biological membrane) or inhibit
deposition of (-) - narwedine. Alternative explanations such as gross seeding effects and resolution dependent on a particular functional group were discarded on the basis of further studies by the investigators.

The nmr of narwedine (25) exhibited an interesting long-range coupling effect. In each of the C1-H components of the AB quartet representing the two olefinic protons, an additional coupling of 2 Hz. was observed. This splitting was shown to be due to long-range coupling between the C4a and C1 protons. This was further substantiated by the nmr spectrum of deuterium labeled narwedine in which the C2 and the two C4 protons were exchanged by recrystallizing narwedine from CH3OD.

**Synthesis of galanthamine**

The resolution of (+) - narwedine was used in the total synthesis of (-) - galanthamine by Barton and Kirby. Utilizing the phenyl-phenyl oxidative coupling hypothesis advanced by Barton, 26, (R,R1,R2, R3 = H) was converted to (+) - narwedine. The resolution and reduction of (+) - narwedine gave (-) - galanthamine. Several oxidizing agents, including manganese dioxide, lead dioxide, silver oxide and potassium ferricyanide were shown to be effective in the oxidation of 26 to narwedine (20). A large quantity of polymerization products were present in all cases and a maximum yield of 1.4% was obtained. The starting material for the synthesis of 26 were p-hydroxybenzaldehyde cyanohydrin (27) and O-benzylisovanillin (28). Reduction and hydrolysis with hydroiodic acid of 27 gave 29(R=OH, R1=H) which was converted to a benzoate derivative. The acid chloride of the benzoate (29, R=Cl,
$R_1 = \text{C}_6\text{H}_5\text{CH}_2-$ was then coupled to 30 to give the amide (26, $R,R_2 = \text{C}_6\text{H}_5\text{CH}_2-$, $R_1 = 0$). The desired phenol (26, $R,R_1,R_2,R_3 = 0$) was obtained by reduction of the amide with lithium aluminum hydride and palladium-on-charcoal.

**Chemical Structures:**

- **26**
- **27**
- **28**
- **29**
- **30**
Narcissamine

The structure of narcissamine (mp 195-96°C) was originally postulated as the N-demethyl derivative of (-)-galanthamine (31). However, subsequent investigations have shown that narcissamine is a quasi-racemic mixture containing equimolar amounts of (-)-N-demethylgalanthamine (31) and (+)-N-demethylidihydrogalanthamine (32). These two compounds were separated by thin-layer-chromatography. The so called O,N-diacetylnarcissamine (mp 209-10°C) and (+)-N-acetylnarcissamine were also found to be quasi-racemates.

\[ \text{31} \]

\[ \text{32} \]

Isolation of Habranthus brachyandrus

The isolation of alkaloids from Habranthus brachyandrus (syn. Hippeastrum brachyandrum) was reported in 1959. The investigators described H. brachyandrus as having a bright red funnel shaped bloom on a single, straight, slender stem. The bulbs, of Dutch origin, were harvested in November, stored 3 months and then extracted. It was found
that the dry bulbs contained 0.14% basic material. Separation of this basic residue by column chromatography on alumina gave lycorine (22%), ambelline (9%), undulatine (7%), narcissidine (4%), lycorenine and crinamidine (2%). The percentages were based on the weight of the basic residue. These investigators also isolated one new alkaloid which they named "hippandrine". Hippandrine was eluted from alumina in 50% benzene in ethyl acetate and crystallized from acetone as prisms (mp 194°, [α]_D-110° (CHCl₃). Analytical data gave a molecular formula of C_{17}H_{19}NO₄ containing one methoxyl and no N-methyl group. The alkaloid gave a positive test for a methylenedioxy group.

The isolation of urceoline (C_{19}H_{25}O₂N, mp 189-90°) had been previously reported. At this time urceoline was postulated to be a stereoisomer of nerinine (33).
RESULTS AND DISCUSSION

The Structure of Pancracine

Although structure 11 had been postulated for pancracine there were several observations which placed a certain degree of doubt on this structure. There were no known lycorine-type alkaloids which did not have a substituent at C1. The chemical shifts of the protons in the nmr spectrum of pancracine correlated exceptionally well with the lycorine-type alkaloids; the absorptions in the uv and the extinction coefficients were also very similar. However, no common derivative could be made. Three of the four possible lycoranes \(^3\) \((\text{a, b, c})\) were prepared and an authentic sample of the fourth isomer \((\text{d})\) was also obtained. These lycoranes were all different from the corresponding basic saturated nucleus obtained from pancracine.

In an attempt to identify the basic ring system of pancracine it was found that montanine (1a) could be converted to pancracine with...
hydrobromic acid. This suggested that pancracine contained the montanine-type nucleus and might be represented by structure 34. The hydrolysis of montanine to pancracine (1a→34) did not establish the stereochemistry of the substituents since the formation of an allylic carbonium ion (35) is very probable in this reaction. Furthermore, a number of alkaloids undergo rearrangements in the presence of acid.

In order to establish the stereochemistry, other chemical conversions, as well as detailed ir, nmr and mass spectrometric studies were undertaken using pancracine and suitable montanine derivatives.
Partial hydrolysis of 0,0-diacylpancracine with 0.01 M sodium methoxide in methanol provided a mixture of the possible monoacetates (36 and 37). Compound 37 was not oxidized by manganese dioxide but afforded pancracyne upon acid hydrolysis. 3-O-Acetylpancracine (36) was oxidized by this reagent to an \( \delta, \beta \) - unsaturated ketone (38) which was identical in all respects with the ketone obtained by the oxidation of 39. Since 36 and 39 were not identical, it may be assumed that these isomers differ only in the configuration of the C2 hydroxyl group. Possible epimerization of the acetoxyl group at C2 in either 36 or 39 seems unlikely since the crude oxidation products had identical ir spectra and formed identical hydrochlorides. The products were not subjected to any alkaline conditions.

The configuration of the C2-hydroxyl groups in 36 and 39 was determined by infrared hydrogen bonding studies. Because of the conformational mobility of both ring C and the C2-acetoxyl groups, both 36 and 39 showed OH–carbonyl bonding (3603 and 3592 cm\(^{-1}\), respectively). These data are far less definitive than that found in the analogous methyl ether series. Pancracyne and the diol (39, OH instead of OAc) provided a better basis for stereochemical assignments. The latter was strongly intramolecularly bonded (3586 cm\(^{-1}\)). The lack of hydrogen bonding in 34 was suggested by its insolubility in chloroform. Comparable chloroform insolubility has been noted for lycorine, which also has vicinal \( \text{trans} \) axial-pseudoaxial hydroxyl groups.

0,0-Diacetylpancracine (40) gives a mixture of three products when hydrogenated with palladium charcoal in glacial acetic acid. Acid
The hydrolysis of this mixture and separation by preparative thick-layer-chromatography (TLC) gave dihydropancracine (41, mp 271-72°C), desoxy-dihydropancracine (42, mp 222-24°C) and a small amount of 43 (as oil).

The two hydrogenolysis products were assigned structures 42 and 43 mainly on the basis of their mass spectra which are consistent with the mode of fragmentation of the dihydro derivatives in this ring system which are discussed later. The stereochemistry of the B:C ring in dihydropancracine (41) and the two hydrogenolysis products (42 and 43)
is not known. The particular catalyst used has an effect on the relative amount of each isomer obtained. In the hydrogenation of pancracine (34), palladium-on-charcoal in acetic acid gives mainly one dihydropancracine, whereas platinum in ethanol gives two isomers in equal amounts. The hydrogenolysis products are observed only with the 0,0-diacetate.

The insolubility of pancracine in deuterochloroform prevented its use for a detailed nmr examination, even with the aid of spectral accumulation. The nmr spectrum of pancracine could be obtained in D6-DMSO; however, the nmr spectrum of 0,0-diacetyl pancracine (40) is much more amenable to interpretation (Fig. 4). The two singlets at 6.53 and 6.47 ppm correspond to the two aromatic protons. The two protons of the methylenedioxy group appear as a singlet at 5.88 ppm. The one proton multiplet at 5.47 ppm represents the olefinic proton. The two multiplets at 5.02 and 5.12 ppm correspond to the C2 and C3 protons respectively. The C2 and C3 protons were differentiated by double resonance studies which showed that the olefinic proton was coupled to the multiplet at 5.12 ppm (C2-proton), but was not coupled to the multiplet at 5.02 ppm (C3-proton). A well-defined AB pattern centered at 4.05 ppm (J = 17 Hz.) was found for the benzylic proton at C6. These two protons give this pattern due to the rigid nature of the skeleton which holds them in different environments. Decoupling studies showed that the aromatic proton having the lower chemical shift (C10) exhibited a small long-range coupling to the peak at 3.28 ppm which is assigned to the C11 proton. There is also a single proton multiplet at 3.28 ppm
Fig. 4. Nuclear magnetic resonance spectra of 0,0-diacetylpencraceine (40)
which is assigned to the C4α proton. It appears as a multiplet due to splitting by the two C4 protons and the lesser allylic splitting of the olefinic proton. The singlet at 3.02 ppm corresponds to the two protons at C12. The two methyl groups of the O,0-diacetate occur at 2.0 and 2.05 ppm. The highest field protons in the spectrum are the C4 protons which comprise a very broad multiplet of peaks between 1.4 and 2.4 ppm. Double resonance experiments show that the C4 protons are coupled to the C3 proton, but not to the C2 proton, an observation consistent with their assignment. Double resonance experiments have been carried out with montanine and findings are in complete accord with the information cited above.

The Mass Spectra of Montanine-type Alkaloids

The mass spectra of montanine and coccinine have been reported. The mass spectrum of pancracine (Fig. 5a) contained several ions of considerable abundance (m/e 185, 199, 214) which were not observed for montanine and coccinine. Montanine (1a), coccinine (1b), manthine (10), and pancracine differ in the stereochemistry of the two substituents (OH or OCH3) at C2 and C3. The nature of the substituents and their particular configuration have a very significant effect on the electron-fragmentation of these molecules. A number of compounds containing the montanine nucleus (39, 7a, 7c, 7d, 44) were available which differed only in the stereochemistry and nature of substituents at C2 and C3. The differences in fragmentation of these molecules would then necessarily be attributable to stereochemical differences in the substituents.
(7a) R=OH, R₁,R₂=H, R₃=OCH₃
(7c) R,R₂=H, R₁=OH, R₃=OCH₃
(7d) R=OH, R₁,R₂=H, R₃=OCH₃

(1a) R₁=OH, R=H
(1b) R=OH, R₁=H

at C₂ and C₃ and a correlation of fragmentation patterns with these structural variables is possible.
Direct elimination of the $C_2$ and $C_3$ substituents

As reported in the spectra of montanine and coccinine, the mass spectra of isohaemanthamine (7a, Fig. 5b), $\delta$-isocrinamine (7c, Fig. 6a) and $\alpha$-isocrinamine (7d, Fig. 6b) show an M-15 peak at m/e 286 due to the loss of the O-methyl group. In addition, 7a, 7c, and 7d exhibit weak M-OH peaks at m/e 284 which correspond to the cleavage of the $C_2$-hydroxyl group. The spectrum of manthine (10, Fig. 7a) exhibits an analogous M-15 peak at m/e 300. Pancraine (34) and 39 exhibit the loss of an hydroxyl group to give peaks at m/e 270 in their spectra.

All the compounds which possess a methoxyl group give rise to an M-31 ion. A comparison of the relative abundance of the m/e 270 peak in the spectra of 1a, 1b, 7a, 7c, and 7d showed that the intensity of this ion is independent of the stereochemistry of the methoxyl group. However, a comparison of the spectra of 1a and 1b with 7a, 7c, and 7d shows that the $C_2$ methoxyl (whether $\alpha$ or $\delta$) is cleaved in an abundance 3 to 4 times greater than the $C_3$ methoxyl group. This enhanced cleavage is probably due to the allylic $C_2$ methoxyl group. The m/e 269 ion corresponds to the loss of methanol in the spectra of 7a, 7c, and 7d. In manthine (10, Fig. 7a) and deoxyisocrinamine (44, Fig. 7b) peaks at m/e 283 and 253, respectively, represent the loss of methanol from the parent ion. The loss of methanol (M-32) is greater than the loss of the methoxyl group (M-31) only in the spectra of $\alpha$-isocrinamine (Fig. 6a) and deoxyisocrinamine (Fig. 7b). At lower electron voltages the ratio of the relative abundance of the M-32/M-31 increased in the compounds 7a, 7c, and 7d, and also in manthine (10). At 15 ev.
Fig. 5. Mass spectra

a. pancracine (34)

b. isohaemanthamine (7a)
Fig. 6. Mass spectra

a. α-isocrinamine (7c)

b. β-isocrinamine (7d)
Fig. 7. Mass spectra

a. manthine (10)

b. desoxyisocrinamine (44)
the M-32 ion observed with isocrinamine is 4 times greater than the M-31 ion.

**Elimination of the C₃-C₄ atoms of ring C**

An ion corresponding to the direct loss of the C₃ and C₄ carbon atoms including any substituent at C₃ was present in the spectra of every compound investigated in the montanine series. This particular type of fragmentation gives the most abundant fragment ion (m/e 243) in the spectra of both isohaemanthamine (Fig. 5b) and ß-isocrinamine (Fig. 6b). Its origin is analogous to the retro-Diels-Alder formation of the m/e 257 ion in the spectra of montanine and coccinine as shown in the fragmentation of 45 to 46 and 47.

In the spectra of pancracine (Fig. 5a) the retro-Diels-Alder cleavage affords an ion at m/e 243. In manthine (10) and 44 the analogous ion occurs at m/e 257 and 227, respectively. The configuration of the C₂ substituent has a considerable effect on the extent to which the retro-Diels-Alder fragmentation ion is observed. There is a definite enhancement of this fragmentation when the C₂ substituent has an ß configuration (see Table 1). This is shown by a comparison of the relative
abundance of the m/e 243 ion in α-isocrinamine (Fig. 6a) and α-isocrinamine (Fig. 6b). This is further substantiated by the relative intensity of the analogous ion in isohaemanthine and manthine. In both cases the C₂-hydroxyl group has the α configuration. Another factor affecting this fragmentation is the composition of the cleaved fragment. In the compounds 1a, 1b, 34, and 39, where the cleaved fragment is CH₂=CHOH, the relative abundance of this ion is less than in fragmentations where CH₂=CHOCH₃ is lost. In the latter case, there is a distinct preference for this cleavage to occur when the C₂ substituent is α, as shown in Table 1. Attempts to explain these results on the basis of steric arguments were ambiguous. It should be noted that the low energy

Table 1. The relative abundance of the retro-Diels-Alder ion

<table>
<thead>
<tr>
<th>Substituted</th>
<th>% of Base Peak</th>
<th>m_{C}</th>
<th>m_{f}</th>
<th>Substituted</th>
<th>% of Base Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>25%</td>
<td>196.5</td>
<td>197.0</td>
<td>1b</td>
<td>8%</td>
</tr>
<tr>
<td>34</td>
<td>25%</td>
<td>205.9</td>
<td>206.0</td>
<td>39</td>
<td>25%</td>
</tr>
<tr>
<td>7d</td>
<td>63%</td>
<td>196.5</td>
<td>196.5</td>
<td>7c</td>
<td>15%</td>
</tr>
<tr>
<td>7a</td>
<td>62%</td>
<td>196.5</td>
<td>196.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>66%</td>
<td>209.7</td>
<td>210.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

spectra (20 and 15 ev.) of the compounds that undergo the retro-Diels-Alder fragmentation show a very large increase in the relative abundance
of this ion when compared to the other fragment ions.

**Fragmentations involving the loss of the nitrogen atom**

The results of high resolution measurements on several ions of considerable abundance in the mass spectrum of pancracine are shown in Table 2. These ions (m/e 223, 214, 199, and 185) are also present in the spectra of isohaemanthamine, $\mathcal{E}$- and $\mathcal{E}$-isocrinamine, and in varying relative abundance, in most of the other compounds investigated in this series. The most obvious observation concerning these ions is that, except for half of the doublet at m/e 214, none of the ions contain a nitrogen atom. A comparison of these data and the correlation

<table>
<thead>
<tr>
<th>m/e</th>
<th>Compn.</th>
<th>Calcd.</th>
<th>Obsd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>223</td>
<td>$\text{C}<em>{15}\text{H}</em>{11}\text{O}_2$</td>
<td>223.0758</td>
<td>223.0762</td>
</tr>
<tr>
<td>214a (60%)</td>
<td>$\text{C}<em>{13}\text{H}</em>{10}\text{NO}_2$</td>
<td>214.0867</td>
<td>214.0825</td>
</tr>
<tr>
<td>214b (40%)</td>
<td>$\text{C}<em>{13}\text{H}</em>{10}\text{O}_3$</td>
<td>214.0629</td>
<td>214.0620</td>
</tr>
<tr>
<td>199</td>
<td>$\text{C}<em>{13}\text{H}</em>{11}\text{O}_2$</td>
<td>199.0759</td>
<td>199.0766</td>
</tr>
<tr>
<td>185</td>
<td>$\text{C}_{12}\text{H}_9\text{O}_2$</td>
<td>185.0602</td>
<td>185.0620</td>
</tr>
</tbody>
</table>

of several metastable ions can be used to postulate possible mechanisms of formation for the nitrogen-free ions. In the spectrum of pancracine a metastable ion at m/e 188.5 ($m_c = 188.5$) showed that there is a one-step loss of 29 mass units (NH=CH$_2$) from the m/e 243 ion to give an ion,
Fig. 8. Formation of the m/e 243, 214 and 185 ions

m/e 214 (C₁₃H₁₀O₃). The other ion of the doublet at m/e 214 (C₁₂H₂NO₂) shows a direct loss of 29 mass units (m_c = 160.1, m_f = 160.8) to give an ion at m/e 185 (C₁₂H₂O₂) as shown above in Fig. 8. A proposed mechanism for this sequence is shown in Fig. 9. The retro-Diels-Alder ion (49) may rearrange to form ion 50, which loses NH=CH₂ to give 51. From the same intermediate ion (52), the formyl radical can be lost to form 53 and subsequently lose NH=CH₂ to give the m/e 185 ion (54). A loss of the formyl radical from 51 could give the same m/e 185 ion (54). Alternatively, the retro-Diels-Alder ion (49) could reclose to form 55.
which would give 56 and 57 for the two m/e 214 ions. A loss of the
formyl radical and NH=CH₂ from 57 and 56 respectively could give 58.
Isohaemanthamine (7a), β-isocrinamine (7d) and δ-isocrinamine (7c)
give the same m/e 243 peak as pancracine. There are metastable peaks
in the spectra of each of these compounds at m/e 188.5 (m_c = 188.5)
and 160.0 (m_c = 160.1) which provide evidence that these three compounds
undergo the same fragmentations as depicted for pancracine in Fig. 9.

In the mass spectra of montanine, coccinine and manthine the ana­
logous fragmentations from the initially formed retro-Diels-Alder ion
(m/e 257) as shown in Fig. 9 are not observed. A metastable peak at
m/e 204.4 (m_c = 204.0) in montanine and manthine indicates that a one­
step loss of 28 mass units from the retro-Diels-Alder ion (m/e 257) in
montanine and manthine also gives rise to a one-step loss of 33 mass
units (257→226, m_f = 199.0, m_c = 198.8) providing a peak at m/e 226.
These two fragmentations from the retro-Diels-Alder ion in the C₂-0CH₃
compounds may successfully compete with, or inhibit, the cleavages shown
in Fig. 9 for the C₂-hydroxy compounds. There is no evidence for the
loss of NH=CH₂ from the retro-Diels-Alder ion in the C₂-methoxy com­
ounds. The loss of NH=CH₂ was postulated as a process for the format­
ion of the m/e 223 ion from an ion at m/e 252 in the fragmentation of
montanine and coccinine ⁹. The m/e 252 ion was shown to originate from
an ion at m/e 270 (m_f = 235.5)⁸. There is some evidence for the occur­
rence of analogous fragmentations in pancracine which contains a rel­
atively abundant ion at m/e 223 (C₁₅H₁₁O₂). The m/e 252 peak in the
spectrum of pancracine is less than 3% of the base peak (not shown in
Fig. 9. Proposed fragmentations of pancracine (34)
Fig. 9. (Continued)
Fig. 5a), however, there is a metastable peak at m/e 235.0 which substantiates that the m/e 252 ion is formed directly from the m/e 270 ion (270 → 252, m_c = 235.3). The only other common ion of considerable abundance in the spectra of these compounds is at m/e 199 (C_{13}H_{11}O_2). This ion is unusually large (50%) in the spectrum of 44 (Fig. 7b). There are also peaks in the spectrum of 44 corresponding to M-CH_3, M-CH_3OH, M-OCH_3, at m/e 270, 253 and 254 respectively. The consecutive eliminations in 44 of CH_3OH and NH=CH_2 from the m/e 284 ion (M-1) in a process analogous to the 270 → 252 → 223 pathway discussed for pancracine would give the same ions at m/e 252 and 223. The formation of the m/e 185 ion (54 in Fig. 9) in the spectrum of 44 is probably due mainly to the stability of this ion which allows its formation by a somewhat different route than proposed in Fig. 9. The m/e 227 ion which is present in the spectrum of 44 represents the retro-Diels-Alder loss of the C_3-C_4 carbon atoms.

The dihydromontanine-type derivatives

The removal of the double bond in the alkaloids and derivatives of the montanine ring system changes the fragmentation pattern drastically (see Fig. 10). The major ions in the spectra of dihydrococcinine, dihydropancracine (41) and two hydrogenolysis products from pancracine (42 and 43) are shown in Table 3. The retro-Diels-Alder loss of the C_3-C_4 atoms does not occur in the dihydro derivatives. The ubiquitous ions in the unsaturated compounds at m/e 214, 223 and 199 are absent in the spectra of the dihydro compounds. There is no evidence for the loss of NH=CH_2 from any ion in the spectra of the dihydro derivatives.
Fig. 10. Mass spectrum of dihydromontanine (62)
Relative Abundance

[Chemical Structure]

148 175
229
272
303
Table 3. The major ions from dihydromontanine-type derivatives

<p>| Dihydro- | Dihydro- | Deoxydihydro- | 43  |</p>
<table>
<thead>
<tr>
<th>coccinine</th>
<th>pancraine (41)</th>
<th>pancraine (42)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>303 (100)</td>
<td>289 (90)</td>
<td>273 (44)</td>
<td>257 (80)</td>
</tr>
<tr>
<td>288 (10)</td>
<td>272 (17)</td>
<td>256 (13)</td>
<td>214 (12)</td>
</tr>
<tr>
<td>272 (26)</td>
<td>230 (7)</td>
<td>230 (12)</td>
<td>229 (6)</td>
</tr>
<tr>
<td>230 (9)</td>
<td>229 (6)</td>
<td>229 (4)</td>
<td>228 (9)</td>
</tr>
<tr>
<td>229 (21)</td>
<td>228 (3)</td>
<td>228 (5)</td>
<td>188 (8)</td>
</tr>
<tr>
<td>228 (9)</td>
<td>214 (4)</td>
<td>177 (9)</td>
<td>176 (17)</td>
</tr>
<tr>
<td>214 (5)</td>
<td>175 (100)</td>
<td>175 (100)</td>
<td>175 (100)</td>
</tr>
<tr>
<td>200 (7)</td>
<td>174 (38)</td>
<td>174 (39)</td>
<td>174 (27)</td>
</tr>
<tr>
<td>185 (10)</td>
<td>149 (20)</td>
<td>173 (20)</td>
<td>173 (18)</td>
</tr>
<tr>
<td>175 (53)</td>
<td>149 (25)</td>
<td>149 (13)</td>
<td>149 (36)</td>
</tr>
<tr>
<td>174 (38)</td>
<td>115 (20)</td>
<td>148 (36)</td>
<td>148 (27)</td>
</tr>
<tr>
<td>149 (23)</td>
<td></td>
<td></td>
<td>115 (17)</td>
</tr>
<tr>
<td>148 (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The number in parenthesis represents the abundance in percent of the ion relative to the base peak (100%).

Disappearance of the major ions of the montanine-type alkaloids in the dihydro derivatives demonstrates that the double bond plays a major role in the formation of these ions as the previous mechanistic proposals illustrate.

Heretofore, there has been no simple spectral method to assign a
given Amaryllidaceae alkaloid to the montanine ring system. However, as shown in the mass spectra of dihydromontanine (Fig. 10) and in Table 3, there is a substantial ion at m/e 175. This ion has an empirical formula of C\textsubscript{10}H\textsubscript{9}NO\textsubscript{2}. A proposed mechanism for the formation of this ion is given in Fig. 11. In this fragmentation (59\rightarrow60) ring C

Fig. 11. Proposed mechanism for the formation of the m/e 175 ion
is cleaved in its entirety. The presence of this m/e 175 ion in the spectra of dihydro compounds serves as a good diagnostic test for the presence of the montanine ring system. It is present in the spectra of all dihydro derivatives of the montanine ring system, and usually is the base peak. The nature of the substituents and their stereochemistry have no effect on the presence of this ion. This ion (m/e 175) is not present in any significant abundance in the mass spectra of the dihydro derivatives of the other ring systems of the Amaryllidaceae.

A somewhat less abundant ion (m/e 148) is present in all the dihydro derivatives which could be formed from the m/e 175 ion. It has an empirical formula of C₉H₈O₂. A possible structure is 61. Two other ions that are characteristic of the dihydromontanine nucleus are observed at m/e 229 (C₁₄H₁₅NO₂) and m/e 230 (C₁₃H₁₂NO₃). The m/e 229 ion observed in the spectrum of dihydromontanine (62, Fig. 10) is formed in a one-step process from the molecular ion. A proposed mechanism is shown below (62→63):
High resolution mass spectrometric examination of the m/e 230 ions in dihydromontanine and deoxydihydropancracine (42) showed that both had the composition of $C_{13}H_{12}NO_3$. This m/e 230 ion represents the loss of $C_2H_5O$ and $C_3H_5$ from dihydromontanine and 42, respectively. The composition of the m/e 230 ion showed that the $C_3$ carbon including the hydroxyl group in 42 is retained. This suggests that the loss of $C_3H_5O$ from 42 may occur as shown below. Cleavage of dihydromontanine (62) in a similar manner would give the same m/e 230 ion.

![Diagram](image_url)
The Structure of Habranthine

Habranthine was isolated from *Habranthus brachyandrus* (syn. *Hippeastrum brachyandrum*) in 0.006% yield. An earlier isolation study of *H. brachyandrus* produced no new alkaloid having the same physical constants or composition as habranthine. Habranthine (C_{17}H_{21}NO_{4}) formed dihydro and O,O-diacetyl derivatives. The basic ring system of habranthine was established to be that of galanthamine (18) when the successive treatment of dihydrohabranthine with thionyl chloride and lithium aluminum hydride afforded deoxylycoramine (20b). The identity of this degradation product with authentic 20b was proven by TLC, gpc and mass spectral criteria. Other chemical degradations, e.g., HBr rearrangement and MnO_{2} oxidation, which were successful in the galanthamine-type alkaloids, led to no useful characterizable products when applied to habranthine. The major evidence for the assignment of structure 64
for habranthine rests on spectroscopic data.

The nmr spectrum of OD<sub>2</sub>-habranthine (Fig. 12a) in deuterochloroform showed two hydroxyl protons between 2.4 and 3.0 ppm. The spectrum shows the presence of two adjacent aromatic protone (6.63 ppm, <i>J</i><sub>AB</sub> = 8 Hz.). The olefinic protons appear as a rather complex multiplet between 6.24 and 5.60 ppm. The presence of the aromatic methoxyl and N-methyl groups are indicated by the 3 proton singlets at 3.83 and 2.56 ppm respectively. The two benzylic protons at C<sub>9</sub> in the spectrum appear as a doublet (partially collapsed AB) at 3.67 ppm. In the nmr spectrum of 0,0-diacetylhabranthine the two benzylic protons appear as a well defined AB quartet (<i>J</i><sub>AB</sub> = 16 Hz.). The doublet at 3.05 ppm was assigned to the two C<sub>11</sub> protons. The protons at C<sub>3</sub> and C<sub>12</sub> appear as triplets at 4.10 and 3.43 ppm, respectively. In the spectrum of the 0,0-diacetylhabranthine these two triplets shift to 5.30 ppm (C<sub>3</sub>) and 4.88 ppm (C<sub>12</sub>). The C<sub>3</sub> and C<sub>12</sub> protons in habranthine were distinguished by decoupling experiments. The triplet representing the C<sub>12</sub>-hydrogen collapsed to a singlet on irradiation at the frequency of the C<sub>11</sub> proton at 3.05 ppm. The two C<sub>4</sub> protons are quite different in chemical shift and show a geminal coupling of 16 Hz. One of these protons is centered at 2.0 ppm and the other at ~2.7 ppm. Half of the latter proton is hidden beneath the N-methyl peak. The C<sub>4a</sub> proton appears as a triplet at 5.33 ppm. In the spectrum of 0,0-diacetylhabranthine this triplet shifts upfield to 4.70 ppm which approximates the chemical shift observed for this proton in galanthamine (4.58 ppm). This suggests that the unusually low chemical shift of the C<sub>4a</sub> proton of habranthine is due to an anisotropic
Fig. 12a. Nuclear magnetic resonance spectrum of OD$_2$-habranthine

Fig. 12b. ORD and CD spectra of galanthamine (18), epigalanthamine (24) and habranthine (64) (A, B, and C, respectively)
deshielding effect of the C\textsubscript{12} hydroxyl group which is absent in the 0,0-diacetate.

The mass spectrum of habranthine is quite characteristic of alkaloids having the galanthamine-type ring system and will be discussed in a later section.

The alkaloid is recovered unchanged when treated with lithium aluminum hydride and shows no reactions characteristic of an alpha hydroxy amine. The chemical shift of the two C\textsubscript{11} protons in the nmr spectrum (3.05 ppm) provides additional support for assignment of a hydroxyl group to the C\textsubscript{12} position in the alkaloid.

In very dilute carbon tetrachloride solution, habranthine shows two intramolecularly hydrogen-bonded hydroxyl groups (3570 and 3457 cm\textsuperscript{-1}). The former absorption is comparable to that observed for the OH-O bonding in galanthamine (18, 3575 cm\textsuperscript{-1})\textsuperscript{15}. Based on this correlation, the C\textsubscript{3}-OH in habranthine was assigned the same configuration as galanthamine. ORD and CD data further substantiated the stereochemical assignment for the C\textsubscript{3}-hydroxyl group as well as the basic ring system of 64. The curves of habranthine (Fig. 12b) closely parallel those of galanthamine and differ from the C\textsubscript{3}-epimer of 18, epigalanthamine.

The C\textsubscript{3}-OH could be distinguished from the C\textsubscript{12}-OH by evidence that the C\textsubscript{12}-OH (3457 cm\textsuperscript{-1}) was very strongly hydrogen-bonded to the lone pair of the nitrogen atom. The addition of a trace of mineral acid to the solution removed the 3457 cm\textsuperscript{-1} absorption and a free hydroxyl group absorption was observed at 3623 cm\textsuperscript{-1}. The 3570 cm\textsuperscript{-1} absorption of the C\textsubscript{3} hydroxyl remained. The OH-N hydrogen bonding of the C\textsubscript{12}-OH does not
enable the configurational assignment of the $C_{12}$ hydroxyl group. Because of the mobility of the seven-membered ring containing the nitrogen atom, hydrogen bonding may exist with either possible configuration of the $C_{12}$-OH group. However, these data and the previously mentioned anisotropic effect of the $C_{12}$-OH group on the $C_{4a}$ proton in the nmr suggest that the $C_{12}$-OH may have the configuration shown in the structure below. Molecular models indicate that the configuration of the $C_{12}$-OH group in this structure is in a much more favorable position to cause the above observations than the corresponding $C_{12}$ epimer.

Galanthamine and epigalanthamine

The mass spectra of galanthamine (18, Fig. 13) and epigalanthamine (24, Fig. 14) contain the same major peaks and will be discussed together. These peaks differ only in relative intensities. The major
fragmentations are represented in both spectra by relatively intense peaks at m/e 286, 270, 244, 230, 216, and 174. All of these ions have been found to be characteristic of the galanthamine-type derivatives. Mechanistic pathways for the formation of these ions in the spectra of galanthamine and epigalanthamine will be discussed in detail and correlated with the mass spectra of the remaining galanthamine-type alkaloids and derivatives that were investigated. The major fragmentations common to the alkaloids of this ring system have been divided into types (A,B,...) and will be discussed in this manner.

\[
\begin{align*}
18. & \quad (R=OH, R_1=H) \\
24. & \quad (R_1=OH, R=H)
\end{align*}
\]

The molecular ion at m/e 287 in the spectra of galanthamine and epigalanthamine is the base peak. The M-1 peak at m/e 286 is almost as intense as the molecular ion. A mechanism for the formation of this ion (m/e 286) is shown above (18 → 65). The facile cleavage of a benzylic hydrogen atom which is alpha to a tertiary nitrogen atom has been documented by deuterium labeling studies in the lycorine ring system.
Fig. 13. Mass spectrum of galanthamine (18)
Fig. 14. Mass spectrum of epigalanthamine (14)
The formation of the M-1 ion in dihydrolycorine is shown above \( (66 \rightarrow 67) \). The m/e 270 peak in the spectra of galanthamine and epigalanthamine represents the elimination of the allylic hydroxyl group \( (68 \rightarrow 69) \). Configuration of the hydroxyl group has no effect on the relative abundance of this ion since the intensity is approximately the same for both epimers. This fragmentation is further substantiated by the loss of -OD in the spectrum of OD-epigalanthamine to give the same m/e 270 peak.

High resolution showed that the rather abundant m/e 244 peak in the spectrum of galanthamine is a doublet composed of a major ion \( (C_{15}H_{18}NO_2) \), and a minor ion \( (C_{15}H_{16}O_3) \). Metastable peaks in both galanthamine and epigalanthamine at m/e 207.6 \( (m_c = 207.4) \) indicate that one or both of
these m/e 244 ions are formed directly from the molecular ion. The origin of the minor ion may be explained by consecutive cleavages of the bonds $\sigma$- and $\pi$- to the nitrogen atom. A proposed mechanism for this process, which is designated as a type A₁ fragmentation, is shown below in Fig. 15.

Fig. 15. Proposed mechanism for the type A₁ fragmentation
The major ion at m/e 244 \((C_{15}H_{18}NO_2)\) may be explained by a retro-Diels-Alder cleavage of the C\(_4\)-C\(_{4a}\) atoms with the subsequent elimination of ketene. A mechanism for this overall process (type A\(_2\) fragmentation) is proposed in Fig. 16. Further evidence for the mechanisms and structures proposed for both m/e 244 ions was obtained from the spectra of deuterium labelled derivatives \((73a,73b,74)\). The m/e 244 peak in epigalanthamine shifts to m/e 245 in the spectrum of
2-\text{D}_1\text{-epigalanthamine (73a). The minor and major ions at m/e 245 from the}
fragmentation of 73a would be consistent with 71b and 72b respectively.
The mass spectrum of 2,3,4,4\text{-D}_4\text{-epigalanthamine (74) contained a}
major peak at m/e 246 and minor ions at m/e 247 and 248. A type A_2
fragmentation (Fig. 16) with the elimination of CD_2\text{CO} from 74 would
leave two deuterium atoms in the molecule which is consistent with
structure 72c for the major m/e 246 ion in this spectrum. The
structure proposed for the minor ion at m/e 244 in epigalanthamine
(71a) requires that the analogous ion from the fragmentation of 74
contain four deuterium atoms as in 71c. This would account for the
minor m/e 248 peak observed in the spectrum of 74. The origin of the
m/e 247 peak in the spectrum of 74 is explained by the following
shifts of the m/e 243 and 245 peaks in epigalanthamine; 243\text{→}247
and 245\text{→}247. This suggests that the m/e 243 and 245 ions in
epigalanthamine may be represented by 71c-H and 71c+H respectively.
The m/e 244 peak shifts to m/e 245 in the spectrum of
OD-epigalanthamine. This is consistent with the mechanisms proposed in Fig. 15 and Fig. 16.

There is little evidence to indicate extensive fragmentation of either of the m/e 244 ions once they are formed. Loss of water from the minor m/e 244 ion (71a → 75) would give the m/e 226 peak observed in the spectra of both galanthamine (Fig. 13) and epigalanthamine (Fig. 14). The retention of a m/e 226 peak in OD-epigalanthamine (73b) indicated that the hydroxyl group was not present in this ion.
The m/e 226 peak shifts to m/e 227 and 229 in the spectra of 73a and 74 respectively, providing further evidence for this fragmentation.

There is a very large metastable peak in the spectra of galanthamine and epigalanthamine at m/e 197.0 which corresponds to the
loss of 15 a.m.u. from the m/e 226 ion to give the ion observed at m/e 211 (m_C = 197.0) in both spectra. Cleavage of the methyl group in 75 would give the m/e 211 ion (76).

**Type B₁ fragmentation** The m/e 230 peak is relatively abundant in the spectra of both galanthamine and epigalanthamine. High resolution mass spectrometry (HRMS) showed that this ion is also a doublet, composed of a major and minor ion (C_{14}H_{14}O_{3} and C_{14}H_{16}NO_{2} respectively). A metastable peak at m/e 184.5 in galanthamine and epigalanthamine confirmed that one or both of these ions is formed directly from the molecular ion at m/e 287 (m_C = 184.3). The m/e 230 ion represents the loss of 57 a.m.u. (C_{3}H_{7}N) from the molecular ion. The proposed mechanism for this process (type B₁ fragmentation) is shown in Fig. 17. Ample precedent for this type of fragmentation exist in the mass spectra of morphine alkaloids 28, 29. A metastable peak at m/e 194.5 which was present in the spectra of galanthamine and epigalanthamine provided evidence that the major m/e 230 ion (78) is also formed directly from an m/e 272 ion (272 → 230, m_C = 104.5). The m/e 272 ion is formed in a direct loss of a methyl group (M-15) from the molecular ion (m_f = 258.2 m_C = 257.7). The aromatic methoxyl and N-methyl groups are the two places from which one could expect the loss of a methyl group, since the m/e 272 peak must be formed by the initial cleavage of the N-methyl group from the molecular ion (68) or from 77.

There are peaks in the spectra of both epigalanthamine and
galanthamine at m/e 229, 228, 227. HRMS indicate that these peaks represent a consecutive loss of 3 hydrogen atoms from the m/e 230 ion. The driving force for this process is probably the formation of the more stable m/e 227 ion (79) in which the C ring is aromatic.

There is a relatively abundant peak at m/e 231 in galanthamine and epigalanthamine which has the composition C_{14}H_{15}O_{3}. The composition of this ion suggests that the elimination of the C_{12}-C_{11}-N-CH_{3} fragment (type B_{1}) also occurs in an alternate manner with a hydrogen atom transfer. A mechanism for this process showing the formation of the m/e 231 ion (80) is given in Fig. 18.

Fig. 18. Proposed mechanism for the formation of the m/e 231 ion
A proposed mechanism for the formation of the minor m/e 230 ion (C_{14}H_{16}NO_{2}) is shown in Fig. 19. The intensity of this ion indicates that this particular mode of fragmentation (68 → 81) probably occurs only to a limited extent.

The two deuterated epigalanthamine derivatives (73a and 74) are consistent with the mechanisms and structures proposed in Fig. 17 and Fig. 19 for both m/e 230 ions. The most abundant peak in the m/e 230 region of 73a is at m/e 231 which is consistent with structure 78.
In this spectrum the m/e 230 peak is about half the intensity of the m/e 231 peak. The m/e 230 peak represents contributions from the minor m/e 230 ion (81) and also the m/e 229+D ion from Fig. 17. The spectrum of D_4-epigalanthamine (74) shows a definitive shift of the m/e 230 peak to m/e 234 providing further evidence for 78. In OD-epigalanthamine the m/e 230 peak shifts to m/e 231.

A metastable peak in the spectra of galanthamine and epigalanthamine at m/e 201.0 showed that either one or both ions at m/e 230 loses a methyl group (230 → 215), m_c = 201.0) to give the observed peak at m/e 215. No further evidence for the fragmentation of either m/e 230 ions was found.

Fig. 20. Proposed mechanism for the type C fragmentation
Type C fragmentation

The most dramatic difference between the spectra of epigalanthamine and galanthamine is seen in the relative abundance of the m/e 216 peak. The ratio of the relative intensity of the m/e 216 peak in epigalanthamine to galanthamine is 2:1. There is a metastable peak in both spectra at 162.8 which shows that this ion is formed directly from the molecular ion (287 → 216, m<sub>e</sub> = 162.6). There was no shift of the m/e 216 peak in the spectra of 73a, 73b, or 74. This suggested that the fragmentation was occurring mainly in ring C with the elimination of at least the C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> atoms. A proposed mechanism for this particular fragmentation (type C) is shown in Fig. 20. Because of the observed metastable peak, the mechanism depicts a concerted pathway with the simultaneous loss of H<sub>2</sub>C=CHOH, acetylene,
and a hydrogen atom. It is convenient in this mechanism to place the initial charge on the oxygen atom. This is justified because the spectra of both galanthamine and epigalanthamine contain a large number of doubly charged ions. This indicates that under electron bombardment, ionization occurs and can be stabilized in more than one part of the molecule. Low energy spectra at 20 and 15 ev. of galanthamine and epigalanthamine indicate that the formation of this m/e 216 ion is a relatively low energy process. These observations, when considered with the intense M-1 ion in both spectra, suggest that the m/e 216 peak may have some contribution from an ion such as 83. The formation of 83 from 18 is similar to the type C fragmentation except for the initial loss of the benzylic hydrogen atom. A metastable peak, found in the spectrum of epigalanthamine at m/e 173.0, indicated that the m/e 216 ion is also formed directly from the m/e 270 ion (69, 270→216, m_c= 172.3).

The reason for the difference in relative intensity of the m/e 216 peak in the spectra of epigalanthamine and galanthamine is not known. As shown previously in the montanine-type alkaloids, a change in configuration at only one asymmetric center can have a remarkable effect on the extent to which a particular fragmentation is observed. The C_3-OH hydrogen bonding in galanthamine (18) causes the C ring to have a conformation which is different from that of epigalanthamine (24). This particular conformation of the C ring in galanthamine may decrease the extent to which type C fragmentation occurs.

The only other peak of relatively large abundance in the spectra of galanthamine and epigalanthamine is at m/e 174. HRMS showed that
Fig. 21. Proposed mechanism for the formation of the m/e 174 and 159 ions.
this ion has the composition of $C_{11}H_{10}O_2$. The spectra of $D_1$-epigalan-
thamine (73a) and $OD_1$-epigalanthamine showed no shift of the m/e 174
peak; however, this peak shifted to m/e 176 in the spectrum of $D_4$-epi-
galanthamine (74). No metastable peaks were observed which would in-
dicate a direct precursor to the m/e 174 ion. A mechanism is proposed
in Fig. 21 for the formation of the m/e 174 ion from the type B ion (84).
This mechanism also shows how two deuterium atoms could be retained as
is observed in the spectrum of $D_4$-epigalanthamine (74). In some of
the proposed structures (85,86) the charge has not been localized be-
cause it is difficult to justify in highly conjugated systems. There
are minor peaks at m/e 173, 172, and 171 in the spectra of galanthamine
and epigalanthamine whose composition indicate a possible loss of three
successive hydrogen atoms from the m/e 174 ion ($C_{11}H_{10}O_2$) to the m/e
171 ion ($C_{11}H_7O_2$). It is difficult for this type of fragmentation to
occur in 85. However, the high degree of conjugation and stability of
85 makes this a particularly desirable structure. A minor isomeric ion
at m/e 174 may possibly give rise to the m/e 173, 172, and 171 ions.
Cleavage of the O-methyl group in 85 would give an ion at m/e 159
(86, $C_{10}H_7O_2$) observed in the spectra of both galanthamine and epigal-
anthamine.

N-demethylgalanthamine

The base peak in the spectrum of N-demethylgalanthamine
(87, Fig. 22) is the molecular ion at m/e 273. As in the spectra of
galanthamine and epigalanthamine, the M-1 peak (m/e 272) is almost of
equal intensity. The most subtle difference between the spectra of
Fig. 22. Mass spectrum of N-demethylgalanthamine (87)
galanthamine and 87 is the composition of the m/e 230 ion. In galanthamine this ion was a doublet with a major (C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}) and minor ion (C\textsubscript{14}H\textsubscript{16}NO\textsubscript{2}). These ions were postulated as forming via type B\textsubscript{1} (Fig. 17) and B\textsubscript{2} (Fig. 19) fragmentations, respectively. The analogous type B\textsubscript{1} and type B\textsubscript{2} fragmentations in 87 would give ions at m/e 230 (78, C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}) and m/e 216 (88, C\textsubscript{13}H\textsubscript{12}NO\textsubscript{2}), respectively (Fig. 23). The m/e 216 peak is present in the spectrum of 87. Differing from galanthamine, the major m/e 230 peak in the spectrum of 87 represents an ion (89) having the composition of C\textsubscript{14}H\textsubscript{16}NO\textsubscript{2} instead of C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}. The type A\textsubscript{2} fragmentation (Fig. 16) postulated for the formation of the m/e 244 ion in galanthamine and epigalanthamine would generate this major ion (89, C\textsubscript{14}H\textsubscript{16}NO\textsubscript{2}) which was observed at m/e 230 (244-14) in the spectrum of 87. A metastable peak at m/e 194.0 in the spectrum of 87 confirmed that there is a direct loss of 43 a.m.u. (C\textsubscript{2}H\textsubscript{5}O) from the molecular ion peak to give the m/e 230 ion (273 $\rightarrow$ 230, m\textsubscript{c} = 193.8). There is some evidence to indicate that the nitrogen free ion (88, C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}) at m/e 230 may be present in the spectrum of 87. The HRMS showed a very broad shoulder on the side of the major m/e 230 peak, but the intensity of this peak was so small that it could not be measured.

The absence of the N-methyl group does not extensively alter the remaining fragmentations that were discussed for galanthamine and epigalanthamine. The formation of a peak at m/e 202 having a composition of C\textsubscript{12}H\textsubscript{12}NO\textsubscript{2} provides additional evidence for the proposed type C fragmentation (see Fig. 20). The m/e 202 ion (90) in the spectrum of 87 corresponds to the m/e 216 ion (82) in galanthamine and epigalanthamine.
Fig. 23. Proposed fragmentations of N-demethylgalanthamine (87)
A metastable peak at m/e 149.5 substantiated that this ion is formed directly from the molecular ion (273 → 202, m_c = 149.5). The peak at m/e 242 in the spectrum of 87 has a composition of C_{15}H_{16}NO_2 (91) and represents the loss of -OCH_3 (31 a.m.u.) from the molecular ion. Elimination of the allylic hydroxyl group from 87 would give rise to the m/e 256 ion (92). The m/e 174 ion in the spectrum of 87 has the same composition (C_{11}H_{10}O_2) as in the spectra of galanthamine and epigalanthamine and probably would be formed in a similar manner (Fig. 21). The fragmentations and ions from N-demethylgalanthamine are summarized in Fig. 23.

HRMS showed that the m/e 187 ion in the spectrum of 87 has a composition of C_{12}H_{11}O_2. It is also present in the spectra of both galanthamine and epigalanthamine. Due to the relatively low intensity of this peak no definitive shifts were observed in the spectra of the deuterium labeled derivatives. A mechanism showing the formation of the m/e 187 ion from the previously discussed m/e 230 ion has been proposed (78 → 93 → 94). In the mechanism, two new rings are formed with the elimination of the C_2-C_3-OH fragment. High resolution data indicate that there are peaks at m/e 186, 185, and 184 having compositions of C_{12}H_{10}O_2, C_{12}H_{9}O_2, and C_{12}H_{8}O_2, respectively. This stepwise loss of hydrogen atoms suggests the formation of a highly conjugated and more stable ion as in 95.

The m/e 181 peak in the spectrum of 87 (Fig. 22) has essentially the same relative intensity as the m/e 187 peak. This ion (m/e 181, C_{13}H_{9}O) is interesting because it is one of the few ions present that
contain only one oxygen atom. It is difficult to decide which of the three possible oxygen atoms remains in this ion. It can be seen from the spectrum of 87 at 20 ev. that the elimination of the methoxyl group is a relatively low energy process and it is reasonable to postulate that the methoxyl oxygen is not the oxygen atom retained in the m/e 191 ion. Structure 96 is proposed for the m/e 181 ion. This ion could originate from the m/e 230 ion or any of the previously discussed ions where the C ring is still intact. The only other peak of considerable abundance is at m/e 115. This peak was present in the spectra of most of the compounds investigated and probably is the ubiquitous indenyl ion (97).

**Acetylgalanthamine**

The general appearance of the spectrum of acetylgalanthamine (98, Fig. 24) is quite different from galanthamine. However, the presence of the acetate group does not alter extensively, the basic fragmentations discussed for galanthamine. The base peak in the spectrum of 98 is at m/e 270 and represents the loss of the allylic acetyl group from the molecular ion at m/e 329. A metastable peak in the spectrum at m/e 222.0 substantiated that this ion (99) is formed directly from the molecular ion (329 → 270, m_c = 221.6). A type B_1 fragmentation in 99 would give the ion (100) observed at m/e 213 in the spectrum. Aromatization of 100 with the loss of two hydrogen atoms would give the m/e 211 ion (101). The type B_1 fragmentation from the molecular ion (98) is not a major fragmentation of this molecule. The relatively small m/e 272 ion (102) which would be formed in the process (98 → 102)
Fig. 24. Mass spectrum of acetylgalectamine (98)
Fig. 25. Proposed fragmentations for acetylgalanthamine (98)
may lose the acetyl group to give the m/e 213 ion (100).

The type C fragmentation of 98 would give the m/e 216 peak in the spectrum. As in the previously discussed type C fragmentations, this ion (82) is formed directly from the molecular ion \((329 \rightarrow 216, m_c = 141.9, m_f = 142.0)\). Loss of \(\text{CH}_3\text{CO}\) from 98 would give the m/e 286 peak \((M-43)\).

The major fragmentations of acetylgalanthamine are summarized in Fig. 25. The mechanisms for the formation and structures of the m/e 115, 174, and 181 peaks observed in the spectrum of acetylgalanthamine (Fig. 24) should be the same as those discussed previously for galanthamine and epigalanthamine.

**Habranthine**

The mass spectrum of habranthine (Fig. 26) is characteristic of alkaloids having the galanthamine-type ring system. The base peak in its spectrum is at m/e 230 \((C_{14}H_{14}O_3)\). A metastable peak in the spectrum at m/e 174.4 \((303 \rightarrow 230, m_c = 174.6)\) showed that this ion is formed directly from the molecular ion at m/e 303. This ion \((m/e 230)\) represents a loss of \(C_3H_7NO\) from the parent ion and has the same composition as the major m/e 230 ion in the spectra of galanthamine and epigalanthamine.

The origin of this ion may be explained by the previously discussed type B1 fragmentation \((64 \rightarrow 103 \rightarrow 78)\). The m/e 230 peak in the spectra of galanthamine and epigalanthamine is 15% of the base peak. In the spectrum of habranthine (Fig. 26) the m/e 230 ion is the base peak. This large enhancement of the m/e 230 ion in habranthine provides further evidence for the previous assignment of the \(C_{12}\) hydroxyl group. It is
Fig. 26. Mass spectrum of habranthine (64)
well known that the probability of cleaving a bond in the mass spectrometer is greatly enhanced when the bond is beta to a hetero atom. An initial ionization of the C_{12} oxygen atom with a subsequent cleavage beta to the C_{12}-O and ring closure (64 \rightarrow 104 \rightarrow 103) is an interesting variation of the type B_1 fragmentation. It would be very difficult to explain how the OH group could cause such a tremendous enhancement of this fragmentation at any position in the molecule other than C_{12}.

The previously discussed type A_2 and C fragmentations both give
ions which retain the $C_{12}-C_{11}-N$- bridge. The analogous ions in habrantithine should possess an additional hydroxyl group. The peaks for type $A_2$ and $C$ fragmentations in habrantithine would be expected to appear in the spectrum at $m/e$ 260 ($244 + 16$) and $m/e$ 232 ($216 + 16$) respectively. These ions are present in the spectrum of habrantithine and are represented by structures 105 (type $A_2$ ion) and 106 (type $C$ ion). The previously discussed $m/e$ 115, 174, 181, 187, and 231 peaks are all present in the spectrum of habrantithine. These peaks were postulated as being formed from ions (mainly the 230 ion) which had already lost the ethanyleamine bridge. The structures and mechanistic pathways to these ions in habrantithine should therefore be the same as in the previous cases. The $m/e$ 181, 187, and especially the $m/e$ 174 ions may be considered as diagnostic ions for compounds having the galanthamine-type nucleus.

The other major peaks in the spectrum of habrantithine are structurally less important. The $m/e$ 286 ion ($C_{17}H_{20}O_3N$) represents the loss of a hydroxyl group from the molecular ion. This cleavage probably represents the cleavage of the $C_7$-allylic hydroxyl group. Loss of the $C_{12}$-$OH$ from the $m/e$ 230 ion gives the relatively abundant ion (100) at $m/e$ 213 ($C_{14}H_{13}O_2$). The low mass region of the spectrum contains relatively large peaks at $m/e$ 77 ($C_6H_5$) and $m/e$ 91 ($C_7H_7$). These ions may be represented by structures 107 and 108 respectively.

\[
\begin{align*}
\text{107} & \quad \begin{array}{c}
\text{108}
\end{array} \\
\end{align*}
\]
**0,0-Diacetylhabranthine**

The mass spectrum of 0,0-diacetylhabranthine (Fig. 27) has a base peak at m/e 328. (The m/e 83, and 85 peaks in this spectrum are derived from an impurity of chloroform which gives $[\text{CCl}_2^{35}]^+$ and $[\text{CCl}_2^{37}]^+$.) The base peak represents a loss of 59 a.m.u. (CH$_3$COO) from the molecular ion peak (109) at m/e 387. The initial elimination of the C$_3$-allylic acetate should predominate to give 110. Loss of acetic acid from 110 affords 111 which may lose the C$_{12}$-C$_{11}$-N-fragment (type B$_1$) to give the relatively abundant peak observed in the spectrum at m/e 213. Aromatization of the m/e 213 ion (100) with the loss of 2 hydrogen atoms would provide the relatively abundant peak observed in the spectrum at m/e 211. A type B$_1$ fragmentation in the molecular ion would give the m/e 272 ion. Elimination of the acetyl group (272 - 59) affords the same m/e 213 ion (100) as was derived from 111. The m/e 345 peak represents the loss of 43 a.m.u. (CH$_3$CO) from the parent ion and could originate from cleavage of either the C$_3$ or C$_{12}$ acetyl groups. Loss of 31 a.m.u. (OCH$_3$) from 109 could explain the origin of the m/e 241 peak in the spectrum. The elimination of the C$_3$-C$_4$ atoms as shown in 110→112 would provide the m/e 301 ion.

A type C fragmentation from the molecular ion would give the ion (113) observed in the spectrum at m/e 274. A metastable peak at m/e 168.5 substantiated the fact that the m/e 274 ion undergoes a direct loss of 59 a.m.u. (CH$_3$COO) to give the relatively small m/e 215 peak (274→215, m$_e$=168.7). The fragmentations of 0,0-diacetylhabranthine are summarized in Fig. 28.
Fig. 27. Mass spectrum of O,O-diacetylhabranthine
Fig. 28. Proposed fragmentations for 0,0-diacetylhabranthine (109)
The Mass Spectra of the Dihydrogalanthamine-type Derivatives

There are two known naturally occurring galanthamine-type alkaloids which possess no double bond at the C$_1$-C$_2$ position. These alkaloids are lycoramine (19) and (+) - N-demethylidihydrogalanthamine (32). The other compounds discussed in this section were prepared by hydrogenation of the corresponding unsaturated analog. The mass spectra of the saturated galanthamine-type derivatives are quite different in appearance from the corresponding unsaturated alkaloids. This is seen in a comparison of the spectra of lycoramine (Fig. 29) and epilycoramine (Fig. 30) with the previous discussed galanthamine and epigalanthamine spectra. Some of the major types of fragmentations are the same and will be discussed first.

Type B$_1$ fragmentation

The m/e 232 peak is present in the spectra of both lycoramine (19) and epilycoramine (113). This ion has a composition of C$_{14}$H$_{16}$O$_3$ and is formed directly from the molecular ion with a loss of C$_3$H$_7$NO ($m_f$ = 186.5, $m_c$ = 186.2). The previous discussed type B$_1$ fragmentation explains the derivation of this ion (114) from lycoramine (19). A consecutive loss of H$_2$O and a hydrogen atom would give 115, and 116, observed in the spectra at m/e 214 and 213, respectively. This type B$_1$ fragmentation was further documented by the spectra of deoxylycoramine (20b, Fig. 31) and deoxydemethyllycoramine (20a, Fig. 32). Type B$_1$ fragmentation peaks are present in the spectra of 20b and 20a at m/e 216 and 202 respectively. These ions are represented by structures 117a (m/e 216) and 117b (m/e 202). A metastable peak found in the spectrum
113. (R=H, R₁=OH)
19. (R=OH, R₁=H)

115  (m/e 214)

(117a) R₁=CH₃ (m/e 216)
(117b) R₁=H (m/e 202)
Fig. 29. Mass spectrum of lycoramine (19)
Fig. 30. Mass spectrum of epilycoramine (113)
Fig. 31. Mass spectrum of deoxylycoramine (20b)
Fig. 32. Mass spectrum of deoxydemethyllycoramine (20a)
Fig. 33. Mass spectrum of dihydrohabranthine (123)
of 20b at m/e 171.0 confirmed that the formation of the m/e 216 ion occurred directly from the molecular ion (273→216, m<sub>c</sub> = 171.2). No metastable peak for the analogous transformation in 20a (259→202) was observed.

As in the spectrum of habranthine, the spectrum of dihydrohabranthine (Fig. 33) contained a much more abundant type B ion at m/e 232. A possible explanation for this enhancement was given in the proposed alternate type B₁ mechanism for habranthine. The same type of mechanistic pathway would be applicable to dihydrohabranthine.

The lack of C₁-C₂ unsaturation in the type B₁ ion (114) in lycoramine inhibits the ready aromatization of the C ring which occurred with the stepwise loss of three hydrogen atoms in galanthamine to form 79 (see Fig. 17). HRMS of lycoramine indicated that only one hydrogen atom is lost from the m/e 232 ion (114) to give the m/e 231 ion (118). The formation of the m/e 233 ion (119) in the spectrum of lycoramine is analogous to the mechanism proposed in Fig. 18 for the formation of the m/e 231 ion in galanthamine.
Evidence for the further fragmentation of the type $B_1$ ion (114) to an ion at $m/e$ 188 was shown by a metastable peak at $m/e$ 152.5 in the spectra of lycoramine and epilycoramine ($232 \rightarrow 188, m_c = 152.6$). There are relatively abundant peaks in the spectra of lycoramine, epilycoramine.
and deoxylycoramine (Fig. 31) at \(m/e\) 189 \((\text{C}_{12}\text{H}_{13}\text{O}_{2})\), 188 \((\text{C}_{12}\text{H}_{12}\text{O}_{2})\)
and \(m/e\) 187 \((\text{C}_{12}\text{H}_{11}\text{O}_{2})\). Less intense peaks are also present at \(m/e\) 186 \((\text{C}_{12}\text{H}_{10}\text{O}_{2})\) and \(m/e\) 185 \((\text{C}_{12}\text{H}_{9}\text{O}_{2})\). The mechanistic pathway and structures of these ions would be similar to the previously discussed \(m/e\) 187 (94) and 185 ions (95) in \(N\)-demethylgalanthamine. The mechanism is shown in Fig. 34 for the formation of these ions from 114. A similar fragmentation to the \(m/e\) 189 ion from the \(m/e\) 231 ion (118) would explain the origin of this peak. In the spectrum of 20a, the peaks which correspond to these ions \((m/e\) 187, 188, 189) are found at \(m/e\) 173, 174, and 175, respectively \((14 \text{ a.m.u. lower})\).

**Type A\text{\textsubscript{2}}** fragmentation

The type A\text{\textsubscript{2}} fragmentation discussed for galanthamine (see Fig. 16) also occurs in the dihydro derivatives. The mass spectrum of lycoramine (Fig. 29) has a peak at \(m/e\) 246 \((\text{C}_{12}\text{H}_{18}\text{O}_{2})\) which represents the lost of 43 a.m.u. \((\text{C}_2\text{H}_2\text{N})\) from the molecular ion. There is a metastable peak in the spectrum at \(m/e\) 209.7 \((m_c=209.4)\) which shows that this ion (121) is formed directly from the molecular ion. The observation of another metastable peak in the spectrum at \(m/e\) 211.0 \((m_c=211.3)\) indicated that the \(m/e\) 246 ion (121) loses \(\text{H}_2\text{O}\) to give an ion (122) observed in the spectrum of lycoramine at \(m/e\) 228. Analogous M-43 peaks in the spectra of 20b and 20a are found at \(m/e\) 230 and 216, respectively. A metastable peak in the spectrum of 20b at \(m/e\) 180.5 \((259\rightarrow216, m_c=180.2)\) provided further documentation of the proposed type A\text{\textsubscript{2}} fragmentation.
The type C fragmentation (see Fig. 20) was proposed to explain the intense m/e 216 peaks in the spectra of galanthamine and epigalanthamine. The absence of the C₁-C₂ double bond in lycoramine and epilycoramine has made this mode of fragmentation insignificant in these molecules. There is a small peak at m/e 216 in the spectrum of lycoramine (Fig. 29) and a somewhat smaller m/e 216 peak in the spectrum of epilycoramine (Fig. 30). This m/e 216 ion (C₁₃H₁₄O₂N) in lycoramine has the same composition as in galanthamine and probably is formed in a similar manner. The other dihydro derivatives do not provide additional evidence for the type C fragmentation. The type C fragmentation would give peaks at m/e 232, 216, and 202 in the spectra of 123, 20b, and 20a, respectively.
The origin of each of these peaks is preferentially explained by the well-documented type B₁ fragmentation. Due to the minor intensity of the type C peak (m/e 216) in the spectra of lycoramine and epilycoramine, it is reasonable to assume that these peaks in 123, 20b, and 20a, represent very little contribution from the type C ion.

Type D fragmentation

The spectra of lycoramine (19), epilycoramine (113), and deoxylycoramine (20b) contain relatively abundant peaks at m/e 202. The analogous peak is found in the spectrum of deoxymethyllycoramine (20a) at m/e 188 (202 -14). The metastable peaks given in Table 4 show that these ions are formed in two consecutive transitions (a and b) from the molecular ion. The first transition (M - 28) affords the peaks observed at m/e 261 in the spectra of 19 and 113. The M-28 peaks are found in the spectra of 20b and 20a at m/e 245 and 231, respectively. The second transition gives the m/e 202 peak in the spectra of 19, 113, and 20b. The analogous transition in 20a gives the peak observed in the
Fig. 35. Proposed mechanism for the type D fragmentation of lycoramine
Table 4. Metastable ions for the type D fragmentation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transition</th>
<th>Metastable found</th>
<th>Metastable calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>19, 113</td>
<td>289 → 261</td>
<td>236.0</td>
<td>235.7</td>
</tr>
<tr>
<td>19, 113</td>
<td>261 b → 202</td>
<td>156.4</td>
<td>156.3</td>
</tr>
<tr>
<td>20b</td>
<td>273 a → 245</td>
<td>220.3</td>
<td>219.8</td>
</tr>
<tr>
<td>20b</td>
<td>245 b → 202</td>
<td>166.5</td>
<td>166.5</td>
</tr>
<tr>
<td>20a</td>
<td>259 a → 231</td>
<td>206.1</td>
<td>206.0</td>
</tr>
<tr>
<td>20a</td>
<td>231 b → 188</td>
<td>153.5</td>
<td>153.0</td>
</tr>
</tbody>
</table>

spectrum at m/e 183. HRMS on lycoramine showed that these two transitions (a and b, in Table 4) represent the loss of C₂H₄ and C₂H₂O₂. No evidence for this type of fragmentation was observed in the spectra of galanthamine, epigalanthamine or any of the C₁-C₂ unsaturated compounds investigated. A rather involved mechanism for this entire fragmentation process (type D) in lycoramine is proposed in Fig. 35. Elimination of the C₁-C₂ atoms would generate the M-28 ion (124, m/e 261). There are some important points to be considered in the subsequent m/e 261 → 202 transition. The metastable peaks previously mentioned require that the m/e 261 ion (124) eliminate C₂H₂O₂ directly to give the m/e 202 ion. The formation of the m/e 188 peak in 20a (202 - 14) requires that the m/e 202 ion in the spectrum of lycoramine possess the aromatic methoxyl group. The proposed mechanism is consistent with these data. Considering these requirements, the number of alternate pathways to this ion is
very limited. The simple and less involved formation of the m/e 202 ion (125) directly from the molecular ion (19→125) would seem much more probable. However, no evidence for this transformation in any of the spectra was observed. There is also no evidence to indicate that dihydrohabranthine undergoes the type D fragmentation. The enhanced elimination of the C_12-C_11-N- bridge (type B_1 fragmentation) probably would compete successfully with or inhibit the type D fragmentation in dihydrohabranthine.

**General fragmentations**

The m/e 149 peak is quite intense in the spectrum of 20b and is present also in 20a. The spectra of lycoramine and epilycoramine have only minor peaks at m/e 149. This peak (m/e 149) is often found as an impurity (126) from the oil used in the diffusion pumps of the mass spectrometer. High resolution data on the m/e 149 peak in lycoramine showed that it is composed of two ions (C_9H_9O_2 and C_9H_9O_3) in equal abundance. The latter ion (C_9H_9O_3) substantiated the presence of the impurity (126). The other ion (C_9H_9O_2) should originate from lycoramine.

A proposed structure for this ion is shown in structure 127. It is difficult to propose a mechanism for the formation of 127, since it could be formed by several pathways from many of the previously discussed ions of higher mass.

The m/e 174 peak in lycoramine is composed of two ions in a ratio of 5:3. The more abundant ion (C_11H_10O_2) has the same composition as the m/e 174 ion (85) previously discussed in the unsaturated compounds (Fig. 21) and should have been formed in a similar manner. Loss of
ethylene from the rearranged m/e 202 ion (128) gives an ion (129) having the same composition as the other part of the doublet at m/e 174 (C_{11}H_{12}ON). There is a doubly charged ion (130) at m/e 81.5 (C_{11}H_{10}ON^{++}) which could be formed by the loss of a hydrogen atom from 129. Structures postulated for peaks observed in the spectrum of lycorenine at m/e 99.5 (C_{13}H_{13}ON^{++}), 92.5 (C_{12}H_{11}ON^{++}), and m/e 74.5 (C_{10}H_{9}ON^{++}) are shown in 131, 132, and 133, respectively. The observation of these doubly charged ions shown in Fig. 36 is consistent with the high degree of conjugation in the proposed structures.

Peaks representing the loss of methyl, methoxyl, and hydroxyl groups at M-15, M-31, and M-17, respectively were found in the spectra of all the dihydro derivatives containing these groups.
Fig. 36. Proposed structures of doubly charged ions in lycoramine
SUMMARY

Degradative and spectroscopic evidence has been presented to show that paneracine, an alkaloid isolated from Pancratium maritinum, Narcissus poeticus and Rhodothalia bifida possesses the structure 34. The mass spectral fragmentation patterns observed for montanine, paneracine and other alkaloids containing the 5,11-methanomorphanthridine nucleus are discussed in detail.

A new Amaryllidaceae alkaloid, habranthine, has been isolated from Habranthus brachyandrus, and the structure (64) has been postulated. A detailed mass spectral study of habranthine and other alkaloids of the galanthamine-type ring system has been carried out. Mechanistic proposals for the formation of the major ions are given.
EXPERIMENTAL

The proton nuclear magnetic resonance spectra were obtained in deuterochloroform solution using either a Varian HR-60 or A-60 spectrometer. All low resolution mass spectra were determined with an Atlas CH-4 mass spectrometer using the TO-4 ion source. The spectra were run at 70 ev. except where stated otherwise. The high resolution data were obtained on either a CEC 110-B or a A.E.I. M.S.-9 spectrometer. Melting points were observed on a Köfler microscope hot-stage and are corrected. Optical rotations were determined with a Jasco Model ORD/UV 5 recording spectropolarimeter. Ultraviolet spectra were obtained in methanol or ethanol solutions using either a Beckman DK-2 ultraviolet-visible or Cary Model 14 spectrophotometer. Infrared spectra were obtained with a Beckman Model IR-12 spectrophotometer. All gas phase analyses were done on a Chromalab Model A-110 gas phase chromatograph using a 12 ft. glass column containing 1% or 3% Silicone GE SE-30 on Gas-Chrom Q (Applied Science Laboratories). The elemental analyses were carried out by Ilse Beetz Microanalytical Laboratory, Kronach, West Germany. Thin-layer chromatography was carried out on a Silica gel PF 254 and 366 (Merck) using ultraviolet light of the appropriate wavelengths. The proof of identity of any two compounds was determined by a comparison of melting points, mixture melting points, infrared spectra, thin layer and gas phase chromatographic data.
Pancracine and Derivatives

Pancracine (34)

The alkaloid, mp 272-73°, crystallized from methanol as elongated prisms, $[\alpha]_D = -74^\circ$ (c 0.02, methanol); the ultraviolet spectrum showed maxima at 292 and 241 μ (log ε = 3.72 and 3.64, respectively).

Anal. Calcd. for C₁₆H₁₇NO₄: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.71; H, 6.12; N, 4.73.

Pancracine formed crystalline picrate (mp 249-52°) and perchlorate (mp 163-6°) salts.

0,0-Diacetylpancracine (40)

A solution of 200 mg of pancracine in 25 ml of dry pyridine was treated with 1.5 ml of acetic anhydride for 2 minutes at 100° and then allowed to stand at room temperature for 28 hours. The reaction mixture was treated with aqueous potassium carbonate and extracted with chloroform to give 220 mg of product, (mp 163-5°) after recrystallization from benzene-petroleum-ether.

Anal. Calcd. for C₂₀H₂₁NO₆: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.48; H, 5.98; N, 3.67.

2-O-Acetylpancracine (37) and 3-O-acetylpancracine (39)

0,0-Diacetylpancracine (190 mg) was dissolved in 25 ml of methanol. Sodium methoxide (0.3 ml/0.01 M) was added. The solution was stirred 40 minutes, then an additional 0.3 ml of sodium methoxide solution was added.

The experimental details for the isolation of pancracine and other alkaloids from R. bifida have been reported³,⁴. No new isolations have been carried out.
added. The solution was stirred for 35 minutes. The reaction mixture was acidified with a few drops of acetic acid and evaporated to dryness on a rotary evaporator. The residue was dissolved in 2 ml of chloroform. The chloroform solution was spread on 2 silica gel plates (20 cm x 20 cm, 1 mm thick) and eluted with chloroform, ethanol, and ammonia (15:2:0.1). The plates showed 3 bands. Elution of the band at $R_f = 0.9$ gave 0,0-diacylpancracine (84 mg). The middle band ($R_f = 0.6$) contained a mixture of both 2- and 3-0-acetylpancracine (35 mg). The recovered 0,0-diacylpancracine was subjected to the same separation. The mixture of the two monoacetates ($R_f = 0.6$) was combined and triturated with methanol. 3-0-Acetylpancracine, mp 213-6° (30 mg) crystallized from the mixture. The ultraviolet spectrum showed absorption maxima at 293 μm (log ε = 4.71) and 241 μm (log ε = 4.64). The nmr (CDCl₃) showed peaks at ($\delta$ values) 6.60 (1H, singlet), 6.52 (1H, singlet), 5.90 (2H, singlet), 5.57 (1H, multiplet), 5.0 (1H, multiplet), 4.0 (AB, J = 17 Hz.), 4.03 (1H singlet, OH), 3.33 (2H, multiplet), 3.08 (2H, singlet), 2.03 (3H, singlet 1.4-2.1 (2H, multiplet).

Anal. Calcd. for C₁₈H₁₉NO₆: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.70; H, 5.94; N, 4.37.

2-0-Acetylpancracine (17 mg) was obtained from the filtrates of 3-0-acetylpancracine. All attempts to crystallize 2-0-acetylpancracine were unsuccessful. 2-0-Acetylpancracine was left unchanged after stirring with 30 ml of chloroform and manganese dioxide (100 mg) for 2.5 hr. A sample of 2-0-acetylpancracine for an elemental analysis was obtained by evaporative distillation under reduced pressure (150°). The uv
spectrum of 2-0-acetylpancracine showed absorption maxima at 293 μm
(log ε = 4.71) and 241 μm (log ε = 4.66). The nmr spectrum is
essentially the same as reported for 3-0-acetylpancracine.

Anal. Calcd. for C₁₆H₁₉O₅: C, 65.64; H, 5.81; N, 4.25. Found;
C, 65.46; H, 5.97; N, 4.21.

The Rf = 0.1 band from the plate was pancracine (28 mg).

2-0xo-3-0-acetylpancracine (28)

A solution of 41 mg of 3-0-acetylpancracine in 7 ml of chloroform
was mixed with 200 mg of manganese dioxide. The mixture was stirred
four hours, filtered and the chloroform evaporated to yield a residue
of 35 mg. The infrared spectrum (CHCl₃) of this residue was identical
with an authentic sample of 2-oxo-3-0-acetylisolo-11-hydroxyvittatine.

2-0xo-3-0-acetylpancracine hydrochloride

A few drops of methanol, saturated with gaseous HCl, was added to
3 mg of 2-oxo-3-0-acetylpancracine. Trituration with acetone afforded
white needles, mp 189-94⁰. A mixture melting point determination
of this material and an authentic sample of 2-oxo-3-0-acetylisolo-11-hy-
doxyvittatine hydrochloride was not depressed (mp 188-92⁰).

Pancracine (34) from montanine (1a)

Montanine (1.95 g as the acetone solvate) was refluxed with 25%
HBr (25 ml) for 1.5 hours. The solution was cooled and diluted with
150 ml of water. The aqueous acidic solution was made basic (pH 8) with
ammonium hydroxide and extracted several times with chloroform. The
aqueous basic solution was extracted further with 25% ethanol in chloro-
form. The aqueous solution was adjusted to pH 12 with 20% NaOH and
and extracted with 25% ethanol in chloroform. All chloroform and ethanol extracts were combined and evaporated. Trituration with ethanol-acetone gave 300 mg of pancracine, mp 272-3°. Evaporation of the filtrate and further trituration with ethanol-acetone gave an additional 22 mg of pancracine. Unreacted montanine (922 mg) was also recovered.

**Hydrogenation of 0,0-diacetylpancracine (40)**

0,0-Diacetylpancracine (150 mg) in glacial acetic acid (1.5 ml) was added to a pre-reduced mixture of 10% palladium-on-charcoal (200 mg) in 15 ml of acetic acid. The mixture was stirred under a hydrogen atmosphere for four hours. The material absorbed 1.2 eq. of hydrogen. The catalyst was removed by filtration. The filtrate was poured into 100 ml of water, and dilute sodium hydroxide was added to adjust the pH to 10. The basic solution was allowed to stand overnight, then extracted several times with chloroform and 20% ethanol in chloroform. This solution was evaporated to dryness under a reduced pressure to give a brown residue (126 mg). The residue was dissolved in a small volume of ethanol, and this solution was spread on a silica gel plate (20 cm x 20 cm, 1 mm thick) and eluted in chloroform, ethanol, ammonium hydroxide (70/30/5). There were three bands (approx. $R_f = 0.3, 0.4, 0.2$). The middle band ($R_f = 0.4$) was removed, and the residue obtained was crystallized twice from acetone to give 19 mg of 2-deoxydihydropancracine (42); (mp 222-4°) UV absorptions at 293 and 236 μ (log ε = 4.72 and 3.53 respectively).

Anal. Calcd. for $C_{16}H_{19}O_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.22; H, 7.10; N, 4.95.
The lower band (R_f = 0.2) was removed, and the material obtained was recrystallized from methanol to give 45 mg of dihydropancracine; mp 271°, uv absorptions at 293 and 234 με (log ε = 3.71 and 3.54 respectively).

Anal. Calcd. for C_{16}H_{19}NO_4: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.60; H, 6.45; N, 4.83.

The top band (R_f = 0.8) gave 10 mg of 43 (an oil). Attempts to crystallize this material were unsuccessful. The mass spectrum of this material is summarized in Table 3. The ir showed no hydroxyl absorption, and the uv is essentially the same as that reported for 2-deoxydihydropancracine.

Isolation of Habranthine from Habranthus brachyandrus

The H. brachyandrus bulbs (622 g) were ground in ethanol with a Waring Blender. The mixture was filtered and this process was repeated four times using a total of 2 gallons of ethanol. The ethanolic solution was evaporated to dryness under a reduced pressure. The residue obtained was dissolved in 2N HCl. The acidic solution was extracted several times with chloroform. Evaporation of the chloroform extract gave 300 mg of the chloroform soluble hydrochloride residue. The aqueous acidic solution was made basic to pH 8 with ammonium hydroxide and extracted several times with chloroform. Evaporation of the chloroform extract gave 622 mg of brown residue.
Chloroform soluble hydrochlorides

The chloroform soluble hydrochlorides (300 mg) from above were dissolved in 2N HCl and extracted twice with ether. The ether extract contained mostly neutral substances and was not investigated further. The aqueous acidic solution was made basic with a few milliliters of concentrated ammonium hydroxide. The basic solution was extracted several times with chloroform and the chloroform was evaporated to dryness under a reduced pressure. The residue crystallized when triturated with ethanol. The crystalline material (195 mg, mp 208-12°) was identical with nerinine (reported mp 208-10°). The nmr of the filtrate (30 mg) showed that the ethyl acetal of nerinine was the major component. Efforts to crystallize the acetal were unsuccessful.

pH 8 Extract

The pH 8 extract (603 mg) was dissolved in 25% benzene in chloroform and placed on a small Fluorisil column. Fractions 1-6, (50 ml each) were eluted with 25% benzene in chloroform and gave no alkaloidal material. Fractions 7-16, eluted in chloroform gave a mixture of about three compounds which were not identified. Fractions 17-25, eluted with 1% methanol in chloroform gave 50 mg of a brown residue. Trituration of this material in acetone gave 40 mg of crystalline material (mp 170-80°). Recrystallization from ethanol afforded 35 mg of pure habranthine (mp 198-99°). The remaining eluents (222 mg) from the column were not investigated further.
Habranthine (64)

The alkaloid crystallized from ethanol as elongated prisms (mp 198-99°, $\lambda_\alpha = -320°$, acetanisol). The ultraviolet spectrum showed absorption maxima at 233 μμ (log $\varepsilon = 3.94$) and 290 μμ (log $\varepsilon = 3.38$). HRMS Calcd. for $C_{17}H_{21}O_4$: 304.15620. Found: 304.15488.

ORD: (CH$_3$OH), 25°; (M)$_{350} = -1240°$, (M)$_{308} = 0°$, (M)$_{295} = +5620°$, (M)$_{288} = 0°$, (M)$_{250} = -16400°$.

CD: (CH$_3$OH), 25°; $[\Theta]_{303} = 0°$, $[\Theta]_{285} = +11000°$, $[\Theta]_{255} = 0°$, $[\Theta]_{250} = -1285°$, $[\Theta]_{245} = 0°$, $[\Theta]_{240} = +7460°$, $[\Theta]_{235} = 0°$.

O,O-Diacetylhabranthine (40)

Habranthine (20 mg) was added to a solution containing 0.5 ml of acetic anhydride in 2 ml of pyridine. The mixture was allowed to stand at room temperature for 12 hours. The reaction mixture was poured in water and made basic with potassium carbonate. The basic solution was extracted several times with chloroform. Evaporation of the chloroform afforded 24 mg of a brown residue. All efforts to crystallize this residue were unsuccessful. The residue was purified by preparative TLC (solvent, 5% ethanol in chloroform saturated with NH$_3$). Efforts to crystallize the purified residue (16 mg) were also unsuccessful. The nmr of this material showed the presence of two acetyl groups. The ultraviolet spectrum was essentially the same as for habranthine. The mass spectrum is given in Fig. 27.
Deoxylycoramine (20b) from habranthine (64)

Habranthine (20 mg) was dissolved in 3 ml of ethanol and added to 15 ml of ethanol containing 60 mg of pre-reduced 10% palladium-on-charcoal. The reaction mixture was stirred under a hydrogen atmosphere for 6 hours. The solution was filtered and evaporated to provide 17 mg of semi-crystalline material (mp 175°) which was insoluble in chloroform. Thionyl chloride (15 ml) was added to the dihydrohabranthine residue and the resulting solution was refluxed for 1.5 hours. The thionyl chloride was removed under a reduced pressure and the residue was partially dissolved in 2N HCl. A considerable amount of acid insoluble material was separated. The aqueous acid solution was made basic with ammonium hydroxide and extracted several times with chloroform. Evaporation of the chloroform solution to dryness gave 16 mg of a dark brown residue. This residue was dried at 1.0 mm for 15 minutes, then dissolved in warm tetrahydrofuran. Lithium aluminum hydride (150 mg) was added to the cooled solution and the mixture was refluxed for 9.5 hours. The mixture was cooled and the lithium aluminum hydride was destroyed with ethyl acetate and water. A few ml of 20% sodium hydroxide was added and the mixture was filtered. The residue was washed several times with chloroform. Evaporation of the filtrates gave 9 mg of the crude material which was purified by TLC using 2% ethanol in chloroform saturated with ammonia. Deoxylycoramine (20b) was isolated (3 mg). A comparison of this material with an authentic sample of deoxylycoramine by gpc, TLC, and mass spectrometry showed that the two compounds were identical.
Preparation of Deuterium Labeled Derivatives

Oxogalanthamine (Narwedine) (25)

Galanthamine (100 mg) was added to 1.0 g of MnO₂ in 10 ml of chloroform and the reaction mixture was stirred for 5 hours. The solution was filtered and the filtrates were evaporated to dryness under a reduced pressure. Trituration of the dry residue with ethanol afforded 86 mg of oxogalanthamine (mp 187-89°).

2-D₁-Epigalanthamine (73a)

Oxogalanthamine (15 mg) was added to 4 ml of dry ether containing 30 mg of lithium aluminum deuteride. The solution was refluxed for 13 hours. The reaction mixture was cooled and a few drops of ethyl acetate, water and dilute NaOH were added. The mixture was filtered and the filtrate was evaporated to dryness. Trituration of this residue with ethanol gave impure 2-D₁-epigalanthamine (mp 170-80°). (TLC of this material indicated that galanthamine was also formed in this reduction.) Three recrystallizations from ethanol gave pure 2-D₁-epigalanthamine (mp 190-91°). The mass spectrum gave a molecular ion at m/e 288 (96% D₁).

4,4-D₁-Oxogalanthamine

Oxogalanthamine (35 mg) was dissolved in 0.5 ml of CD₂OD and refluxed for 10 minutes. The solution was evaporated to dryness giving crystalline material. This material was sublimed at 170° (0.05 mm). The mass spectrum of this material showed the incorporation of 3 deuterium atoms into the molecule affording a molecular ion at m/e 288. Trace impurities in the spectrum at m/e 306 and 324 indicated the addition of a molecule of H₂O and CD₂OD to the oxogalanthamine. An earlier preparation
of 2,4,4-D$_3$-oxogalanthamine in which the positions of the three deuterium atoms were confirmed by nmr has been reported.$^{19}$

2,2,4,4-D$_4$-Epigalanthamine (74)

The 2,4,4-D$_3$-oxogalanthamine (15 mg) was added to an ether solution containing 35 mg of lithium aluminum deuteride and the mixture was refluxed for five hours. The reaction mixture was cooled and a few drops of ethyl acetate, water and dilute NaOH were added. The mixture was filtered and the filtrates were evaporated to dryness. Several recrystallizations of this residue from ethanol afforded 2,3,4,4-D$_4$-epigalanthamine. The mass spectrum of this material showed a molecular ion at m/e 291 (>96% D$_4$).

OD-Epigalanthamine (73b)

A mass spectrometer cartridge (sample holder) in a glass capillary was filled with about 1 mg of epigalanthamine (24) and a drop of CH$_3$OD and D$_2$O was added. The material was dried under a nitrogen atmosphere and the process was repeated. D$_2$O was added and the wet cartridge was placed in the mass spectrometer. The sample was left in the high vacuum system for an hour and the spectrum was run. The spectrum showed 71% D$_1$ incorporated in the molecule. The percent of D$_1$ was shown to be inversely proportional to the amount of time the material was in the instrument.


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