MASS SPECTRA OF ALKYL QUINOLINES AND TETRAHYDROQUINOLINES

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by

PATRICK MAXWELL DRAPER, B.SC.

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AUTHOR: Patrick Maxwell Draper, B.Sc. (Bishop's University)

SUPERVISOR: Professor D. B. MacLean

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SCOPE AND CONTENTS:

The mass spectra of some monomethylquinolines, dimethylquinolines, monoethylquinolines and monopropylquinolines have been determined. In addition, the spectra of 1,2,3,4-tetrahydroquinoline, 5,6,7,8-tetrahydroquinoline and some monomethyl-1,2,3,4-tetrahydroquinolines have also been studied. Fragmentation mechanisms are proposed to account for the most important peaks in the spectra of these compounds. Deuterium labelled analogues of many of the compounds have been prepared and their spectra support the proposed fragmentation mechanisms.

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GENERAL INTRODUCTION

The mass spectra of many of the important classes of organic compounds have been studied within the last decade but no systematic investigation of the spectra of alkylquinolines or tetrahydroquinolines had been reported when the work for this thesis was initiated. However, in 1967 Sample et al. (1) published the results of a study of the mass spectral behaviour of some alkylquinolines and isoquinolines.

The work reported in this thesis involves an investigation of the mass spectral fragmentation of some monomethylquinolines, dimethylquinolines, monoethylquinolines and monopropylquinolines. The mass spectra of 1,2,3,4-tetrahydroquinoline, 5,6,7,8-tetrahydroquinoline and some monomethyl-1,2,3,4-tetrahydroquinolines have also been examined. The results on the alkylquinolines parallel those of Sample et al., and in many cases the same conclusions were drawn. However, the deuterium labelling experiments in this investigation were more extensive, and thus additional insight into the fragmentation has been obtained.

The original object of this work was to determine the applicability of mass spectrometry in the identification

of alkylquinolines and tetrahydroquinolines of unknown structure which were isolated as dehydrogenation products in alkaloid studies. However, the project has been extended to a more detailed study of the fragmentation mechanisms of these compounds. Particular attention has been directed to the question of ring expansion on cleavage of a bond β to the heteroaromatic nucleus. Although tropylium ion formation in the spectra of the alkylbenzenes is well documented, there was no labelling evidence available to support formation of the analogous azatropylium ion in the fragmentation of aromatic nitrogen compounds until early 1968 when Marx and Djerassi (2) published the results of some C^{13} labelling experiments on the methylindoles and on 1-methylisoquinoline.

Deuterium labelled analogues of many of the alkylquinolines and tetrahydroquinolines have been prepared in this investigation, and their spectra have provided supporting evidence for the proposed fragmentation mechanisms. The monomethylquinolines fragment mainly by loss of H, and then HCN, and the deuterium labelling results are compatible with rearrangement of the molecular ion to a ring expanded species before loss of H. Fragmentation of the dimethylquinolines proceeds through loss of H or CH_3 and the results also suggest that ring expansion may occur prior to loss of these elements. The fragmentation of 2- and 8-

ethyl and n-propylquinolines is strongly influenced by the proximity of their alkyl side chains to the nitrogen atom, while β-cleavage (probably with ring expansion) results in the most intense fragment ion in the spectra of the other isomers. It has been possible to interpret the spectra of most of the 1,2,3,4-tetrahydroquinolines by assuming that the initial bond cleavage occurs α to the nitrogen atom.

HISTORICAL INTRODUCTION

Theory and Instrumentation of Mass Spectrometry

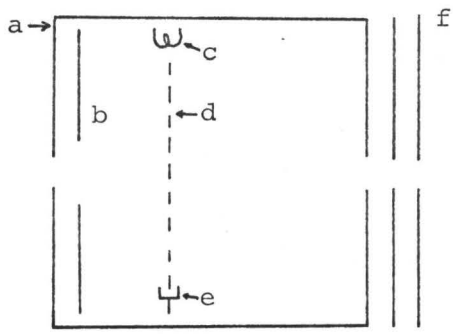
The potential use of mass spectrometry in chemical analysis was first suggested by Sir J. J. Thomson in 1913 (3) after he had constructed an apparatus in which positive ions could be separated according to their mass to charge ratios (4). The first prototypes of modern instruments were constructed by Dempster in 1918 (5) and Aston in 1919 (6). A large number of improvements on the original designs have since been made, and today a number of specialized mass spectrometers are available for applications in chemistry, physics and other fields.

The first important application of mass spectrometry to organic chemistry was found in the petroleum industry (7), where it was found to be ideally suited for rapid and accurate analysis of complex mixtures of hydrocarbons. Although hydrocarbons give very reproducible mass spectra, their fragmentation patterns are often unpredictable. For this reason, it was thought that mass spectrometry would be of limited use in structural studies, and its applications to organic chemistry were at first limited to analytical work. However, it was later found

that the spectra of organic compounds containing heteroatoms were more readily interpretable, and thus the applicability of mass spectrometry for structural studies became apparent. The development of instruments with heatable glass inlet systems (8) and direct insertion probes (9) has allowed the spectra of even relatively involatile and thermally sensitive organic compounds to be readily determined. Detailed reviews of the development, instrumentation, and applications of mass spectrometry are available in books by Duckworth (10) and Kiser (11).

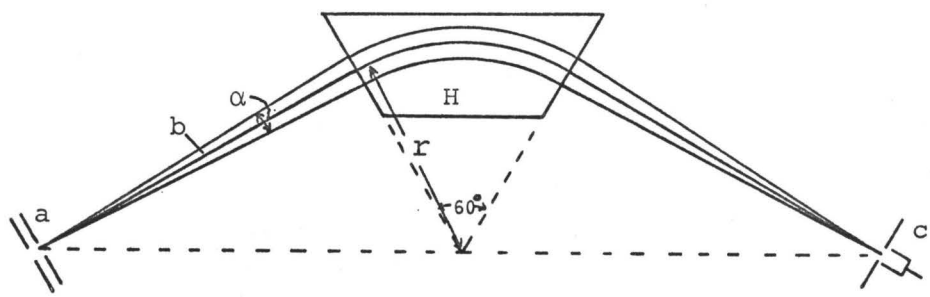
A commonly-used instrumental design for organic chemical applications is shown in Fig. 1. The molecules of mass M are admitted into the ion source through a slit in the back of the chamber, and they are ionized by an electron beam whose energy can be adjusted between about 8-100 electron volts. Energy in excess of that required for ionization may be imparted to the molecule in the ionization process, and the excess energy may be sufficient to cause decomposition of the molecular ion into a number of smaller fragment ions. The positive ions are pushed towards the accelerating region by the repeller plates held at a small positive value with respect to the source. The source is maintained at a positive potential, V, giving the ions a potential energy eV, where e is the ionic charge. After acceleration through the potential drop, V, the kinetic energy of the ion will be equal to its potential energy before acceleration:

a)



a chamber
b repeller electrodes
c electron source
d electron beam
e electron target
f accelerating electrodes

b)



a source slit
b ion beam
c collector slit
H magnetic field

Fig. 1a) Ion source and b) 60° sector magnetic analyzer.

$$eV = \tfrac{1}{2} Mv^2 \qquad 1)$$

In the magnetic field of strength H, the ions will experience a centripetal force, HeV, which is just counterbalanced by a centrifugal force $\frac{Mv^2}{r}$

$$HeV = \frac{Mv^2}{r} \qquad 2)$$

Elimination of v from equations 1) and 2) results in the mass spectrometer equation 3).

$$\frac{M}{e} = \frac{H^2 r^2}{2V} \qquad 3)$$

Either magnetic scanning (change of H) or electric scanning (change of V) may be used to focus ions of different M/e on the collector and thus obtain a spectrum. From equation 3) it is seen that the mass to charge ratio of the ions collected varies as the square of the magnetic field, and inversely with the accelerating voltage. Therefore, a larger mass range can be covered in a single sweep by magnetic scanning. In addition, resolution is affected at high mass with electric scanning since contributions of initial thermal or kinetic energy become significant at low accelerating potential. In spite of the advantages of magnetic scanning, electronic scanning is sometimes used because it is easier to achieve electronically, and because the magnetic field in the source can be kept constant (in 180° instruments).

The focusing properties of a magnetic field are not necessarily restricted to a 180^{o} field, and many modern instruments employ a 90^{o} or 60^{o} deflection as shown in Fig. 1. A much smaller magnet is required for a 60^{o} sector instrument, and in addition, both the ion source and collector are outside the magnetic field which allows greater accessibility to these regions.

A collector slit of variable width is placed at the focal point of the ion beam, and the collector is placed behind the slit. On arrival at the collector, the ion current may be amplified by an electron multiplier and fed to the recorder. An oscillograph recorder consisting of a mirror galvanometer which shines on photographic paper will cover a wide range of peak intensities, and allows the spectrum of a complex molecule to be recorded in a convenient length of time. Such an arrangement has been discussed in greater detail by Biemann (12).

The above instrument is known as a single or direction focusing mass spectrometer. Thus, in a direction focusing instrument an ion beam having ions of the same M/e, and homogeneous in energy, which leaves the source slit at a small divergent angle α is refocused at a point after deflection by the magnetic field (at C in Fig. 1_b). Before acceleration, however, the ions will have a spread in kinetic or thermal energies, and this will contribute to

the total kinetic energy after acceleration. From equation (3) it is seen that a spread in the magnitude of V will result in a spread of r for a given value of M/e. This broadening or "velocity dispersion" results in a loss of resolving power. However, the double focusing principle, described briefly below, compensates for the velocity dispersion, and thus greatly increased resolution may be obtained.

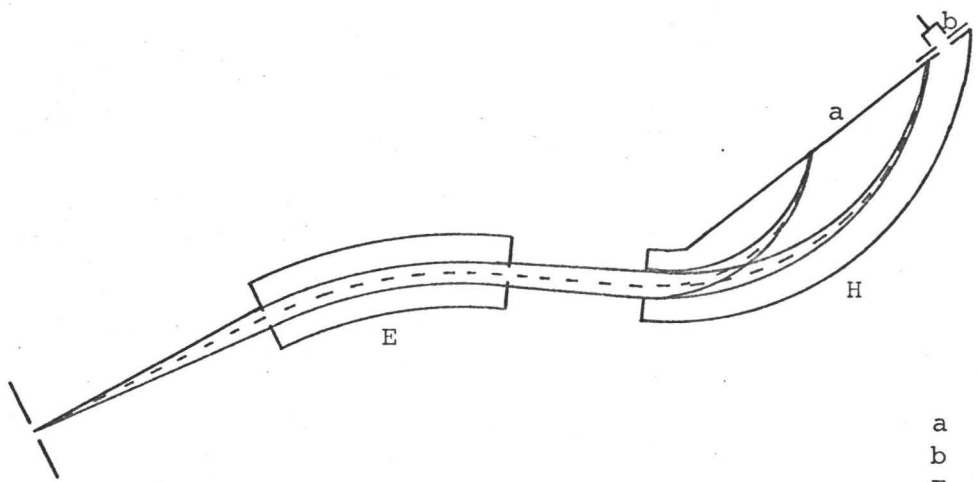
If the ion beam is made to pass through a radial electrostatic field before magnetic deflection, then the ions will suffer a velocity dispersion as in the magnetic field. If the electrostatic and magnetic fields are constructed such that the velocity dispersion suffered in the electrostatic field is exactly compensated by the magnetic field, then ions of the same M/e but with different velocities are focused at a single point (the velocity focusing point) after emerging from the magnetic field. The condition for double focusing of ions of a given M/e, therefore, is that the point of velocity focusing must coincide with that of direction focusing. The theory of ion optics and instrumental parameters required for double focusing are described in publications by Duckworth (10,13).

Application of double focusing or high resolution mass spectrometry to organic chemistry was pioneered by Beynon, and is discussed in his book (14). High resolution

instruments are useful in organic structural studies since the mass of a given ion can be measured sufficiently accurately to determine its elemental composition. The double focusing design of Mattauch and Herzog (15,16) shown in Fig. 2 is particularly useful in organic chemistry since double focusing for all masses may be obtained simultaneously. An electrical detector may also be provided for determination of a single mass.

The exact mass of an unknown fragment may be determined electronically by the "peak matching" technique originally described by Nier (17). In this method, the difference in accelerating potential required to bring two ions into focus is measured by coinciding the peaks on an oscilloscope. The potential difference which can be measured with high accuracy may be expressed in terms of difference in mass, and the mass of the unknown ion may then be calculated. Standard mass peaks may be provided by introducing a sample of perfluorokerosene with the compound to be measured.

The peak matching method becomes extremely time consuming if more than a few peaks are to be accurately measured. However, in the Mattauch type of double focusing spectrometer (Fig. 2) all masses are focused in a single focal plane, and thus a complete spectrum can be recorded by placing a photographic plate on the focal plane. The



a photographic plate
b collector
E electrostatic field
H magnetic field

Fig. 2 Double focusing design of Mattauch and Herzog.

ions of different masses are recorded as parallel lines whose distance from that of a standard mass can be measured with high precision with a comparator, and the line density (peak intensity) may be measured with a densitometer. In this way, a complete spectrum may be obtained in a much shorter time than by the peak matching technique, with the added advantage of requiring a smaller sample.

A complete spectrum of a complex organic molecule contains hundreds of lines, so the line positions and densities are usually fed automatically onto magnetic computer tape, and the computer converts position and density readings into mass and relative intensity values, respectively. The vast amount of data thus obtained may be printed out concisely by the computer in the form of an element map described by Biemann (18). In an element map, the main fragment ions are printed out according to their heteroatom content, and the approximate relative abundances of the ions are also indicated. Other methods of data presentation are discussed in the book by Budzikiewicz, Djerassi and Williams (19).

The sample size required to obtain a mass spectrum of an organic compound is often much less than a milligram. Gas chromatography is therefore ideally suited for the separation and purification of samples for mass spectrometry.

Techniques have been perfected (20,21) which allow the effluent of a gas chromatograph to enter directly into the mass spectrometer, thus alleviating the necessity of condensing each compound as it comes out of the gas chromatograph. Molecular separators, based on the principle that the carrier gas has a faster diffusion rate than the organic sample, are used to remove most of the carrier gas before the effluent enters the mass spectrometer. A recent review on the techniques of combined gas chromatography - mass spectrometry is available (22).

Interpretation of Mass Spectra

When the mass spectrum of an unknown organic compound has been obtained, one is faced with the problem of interpreting the spectrum in terms of the molecular structure. Therefore, a brief description of the methods commonly used in the interpretation of the mass spectra of organic compounds is presented in this section.

Perhaps the most obvious piece of information to be obtained from a spectrum is the molecular weight of the compound. In the mass spectra of most organic compounds the peak at highest mass (neglecting peaks due to molecules containing heavy isotopes) corresponds to the molecular ion. Therefore, the determination of the molecular

weight of an organic compound by mass spectrometry is usually a straightforward process. However, there are examples where the peak at highest mass is not the molecular ion, and it is important that such examples be recognized.

Occasionally, peaks at masses greater than that of the molecular ion are observed. These are caused by ion-molecule collisions with transfer of an atom, or group of atoms, from the molecule to the molecular ion. Such peaks may be recognized by the fact that they arise by bimolecular collisions, and thus their intensities are proportional to the square of the sample pressure. Peaks due to ion-molecule reactions are rare at the sample pressures normally used to obtain mass spectra of organic molecules.

In the mass spectra of some organic compounds (particularly secondary and tertiary alcohols) no peak corresponding to the molecular ion is observed, rather the peak at highest mass is a fragment ion. A number of methods are available whereby a molecular ion may be differentiated from a fragment ion. Firstly, the molecular weight of an organic compound containing C, H, O, and an even number of nitrogen atoms is even, whereas simple fragments of such molecules have odd mass numbers (unless the fragment arises by rearrangement and elimination of

a neutral molecule). In addition, the difference in mass between the supposed molecular weight and the next lowest fragment peak must correspond to loss of a group by a favourable fragmentation process. Biemann (23) has used similar criteria in writing a computer program which allows the molecular ion in a high resolution spectrum to be uniquely determined. Finally, chemical treatment of the molecule may give a species which shows a molecular ion or characteristic fragment ion of appreciable intensity. Thus, an alcohol may be converted to its trimethylsilyl derivative which exhibits an intense M-15 ion in its spectrum (24).

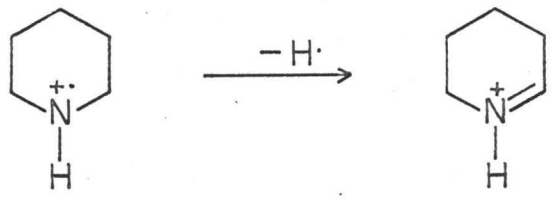
A theory of mass spectra known as the "Quasi-equilibrium theory of mass spectra" has been developed (25) in an attempt to describe the fragmentation undergone by a molecule in the mass spectrometer. The theory assumes that the initial effect of bombardment of a complex molecule by electrons of relatively high energy (50-70 eV) is to cause ionization by a vertical, Franck Condon type of ionization. The molecule ion is formed with excess energy which can distribute itself over the molecule in a random fashion. When energy equal to the dissociation energy of a particular bond has accumulated, then fragmentation may be expected. The decomposition of the molecular ion may then be regarded as a unimolecular reaction of an isolated

system. By applying the absolute rate theory, the mass spectra of hydrocarbons such as propane have been calculated and found to agree well with experimental values. A somewhat simplified discussion of the theory is presented in the book by Field and Franklin (26).

The Quasi-equilibrium theory, however, is very complicated mathematically and does not give good agreement with experimental values for more complex molecules. Therefore, a somewhat empirical approach to the interpretation of the mass spectral fragmentation of organic compounds is more often used by the organic chemist. In this approach, an attempt is made to localize the positive charge in the molecular ion, and subsequent bond fissions are rationalized in terms of such an ion (27). Thus, Biemann (28) has attempted to interpret the fragmentation in terms of carbonium ion chemistry, and has classified favourable fragmentation processes into eight types of simple cleavage and five rearrangement types.

The concept of charge localization, and the use of carbonium ion chemistry has proved to be a very useful guide in the interpretation of the mass spectral fragmentation of organic molecules. Thus, it has been observed that the stability of the bond to be broken, the stability of the positive ion formed, and the stability of the neutral fragment all influence the intensity of a given

fragment ion. For example, cleavage of a bond α to a nitrogen atom as in the piperidine molecular ion, 1, results in a stable ion represented by 2.



1 2

This energetically favourable transformation results in an intense fragment ion corresponding to loss of H in the mass spectrum of piperidine. Similarly, it has been observed that pairing of the electron at the electron deficient site in the molecular ion is a low energy process, and is thus an important factor in determining the fragmentation pathway. These examples illustrate the analogy that can be made between mass spectral fragmentations and conventional carbonium ion chemistry.

Although predictions based on carbonium ion chemistry are useful in the interpretation of mass spectra, they are often inadequate, and sometimes give an erroneous picture of the actual situation. It must also be emphasized that the ions formed in a mass spectrometer are not isolated and their structures cannot be

determined by classical methods. Thus, there is little assurance that an ion in question has the structure assigned to it. However, a number of methods have been used whereby further insight into mass spectral processes may be gained, and at least indirect evidence obtained for assuming that the structures proposed for fragment ions are indeed correct. A summary of these techniques, with examples, is presented in the following discussion.

The use of isotopic labelling techniques has perhaps found the widest application in the interpretation of mass spectral fragmentation processes. In this method, a stable isotope is specifically introduced by a reaction of known mechanism, and the degree of retention of label in the fragment ions gives an indication of how the molecule decomposes. A number of deuterium labelled organic compounds as well as a few C^{13} and N^{15} enriched compounds are commercially available. The chemical methods for introducing heavy isotopes into organic compounds have been discussed in detail in books by Biemann (29) and Budzikiewicz, Djerassi and Williams (30).

An isotope effect favouring loss of hydrogen preferentially over deuterium has been observed where chemically equivalent hydrogen and deuterium atoms are both present. A discussion of this isotope effect has been presented in the book by Field and Franklin (31).

In addition, hydrogen is also transferred more readily than deuterium in reactions where a hydrogen is transferred from one site to another (e.g., McLafferty rearrangement)(32). The magnitude of such isotope effects appears to vary considerably (31,32). A possible isotope effect should, therefore, be considered when interpreting labelling results.

In a very recent communication, the use of radioactive C^{14} labelling in the study of mass spectral mechanisms has been suggested (33). In this method, the mass spectrum of the labelled compound obtained on a photographic plate is compared with a second spectrum, obtained on a plate which is sensitive to C^{14} ions only. It is suggested that this method may be useful since C^{14} labelled compounds are more widely available commercially, and are less expensive than C^{13} labelled analogues.

The results of a considerable amount of study have recently been reported on the use of metastable ion characteristics in the determination of the structure of fragment ions. Metastable peaks are usually broad peaks of relatively low intensity occurring at non-integral mass numbers. They are caused by ions which form when the parent ion decomposes to a daughter ion and neutral fragment after acceleration across the voltage drop V, but before deflection in the magnetic field H (34). (In

double focusing instruments they are caused when ions decompose in the field free regions between the electrostatic and magnetic analyzers.) The species has, therefore, been accelerated as one ion and deflected as another ion of lower mass, and will be observed at a mass different from that of either ion. The mass m* at which such ions are recorded can be related to the mass of the parent ion m_1 and the daughter ion m_2 by equation 4), (34). Ions

$$m^* = \frac{m_2^2}{m_1} \qquad 4)$$

formed during acceleration or deflection are lost and contribute to general background of the instrument. In many instruments of the sector type, the metastable is observed at a slightly higher mass (up to 0.5 mass units) than that calculated by the equation.

The presence of metastable peaks in a mass spectrum is useful in analyzing the fragmentation of a molecule since their presence provides good evidence that the daughter ion arises from the parent in a single step. Beynon (35) has published tables of metastable transitions which alleviate the arithmetic involved in calculating the possible origins of a metastable peak. Alternatively, a computer program may be used to calculate possible transitions (36).

Recently, examples of decompositions occurring with appropriate metastable peaks but probably corresponding to two-step processes, have been observed (37,38). Thus, the presence of a metastable peak corresponding to loss of a unit does not necessarily establish that the unit exists as a structural entity. Alternatively, the absence of an appropriate metastable peak does not necessarily mean that such a transition does not occur. It may be that the rate constant of the fragmentation in question is such that no decompositions occur in the field free region.

Metastables usually have a Gaussian shape, but occasionally they are much broader and have a relatively flat top. Beynon has shown that the increased width of these metastables is caused by the release of a small amount of internal energy of the parent ion as kinetic energy of the fragments (39). Flat-topped metastable peaks have been observed for the loss of NO from o- and p- nitroanilines where the product ions may be stabilized by resonance, and energy released as kinetic energy of the fragments (39).

Thus, it is apparent that the shape and intensity of a metastable peak is a function of the structure of the parent and daughter ion, and ions identical in structure and energy can be identified by identical metastable peaks for their further decomposition. Since a metastable peak

is usually caused by a single transition, complications from competing pathways are absent.

Shannon and McLafferty have used metastable shapes and abundances to classify $C_2H_5O^+$ ions generated from a wide variety of compounds into a few distinct structural types (40). Pike and McLafferty have also suggested that the M-CO ion in the fragmentation of 2-pyrone does not have the same structure as the furan molecular ion since metastable ions for their further fragmentation have different relative abundances (41).

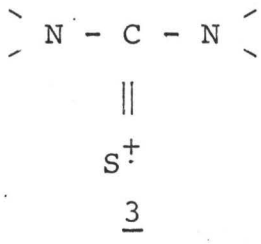
Ionization and appearance potential measurements have also been used extensively in the interpretation of mass spectra. The appearance potential A, of an ion X is defined as being equal to (or greater if the particles are formed with excess energy W) the sum of the dissociation energy D of the bond X-Y and the ionization potential I of X to X^+. The experimental techniques used in obtaining

$$A_X^+ = D_{XY} + I_X + W \qquad 5)$$

ionization and appearance potential values have been discussed in a book by Field and Franklin (42).

The results of ionization potential measurements on ureas and thioureas have provided evidence that the concept of charge localization is indeed valid (43). It was found that successive introduction of methyl groups

into the nitrogen atoms of urea changed the ionization potentials considerably, and this suggested that at least some of the positive charge was localized on the nitrogens. With thiourea, however, successive introduction of methyl groups had very little effect on the ionization potential suggesting that positive charge may be localized on the sulfur atom as in 3, instead of on one of the nitrogen atoms.

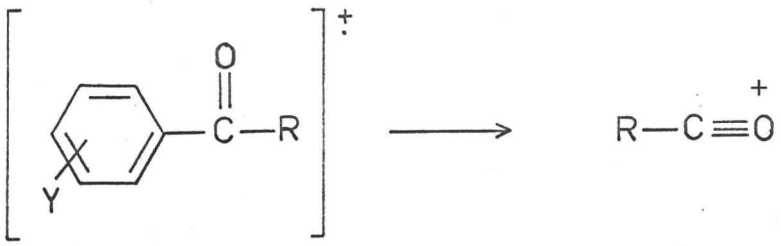


3

Appearance potential measurements were used extensively in the study of the fragmentation of alkylbenzenes (44), and they provided evidence for the intermediacy of a tropylium ion rather than a benzyl ion in their fragmentation.

Another method for gaining insight into mass spectral fragmentations has been developed by Bursey and McLafferty (45,46,47). They have used a kinetic argument for applying free energy relationships to ion abundances in the mass spectra of acetophenones and benzophenones. They have argued that if acyl ions $R - \dot{C} \equiv \overset{+}{O}$ are formed from variously substituted parent ions by a single process and thus have the same energy

distribution, then the rate of further decomposition of the acyl ions will be independent of the substituent Y, and the same in all cases. The ratio of peak intensities



$R = CH_3$ or C_6H_5

RCO^+/M^+ will therefore be a measure of the rate of formation of RCO^+. Bursey and McLafferty found that the observed ratio of ion intensities correlated well with Hammett σ values of the substituents, and concluded that the molecular ions were intact and in their ground state up to the transition state for loss of the acyl ion.

The benzophenone molecule may also fragment by cleavage of the C-R bond with charge retention by the group carrying the substituent. In this case, the substituent influences the rate of further decomposition of the acyl ion, and thus no correlation of acyl ion intensity with Hammett σ values of the substituents was observed at normal ionizing voltages (47). However, further fragmentation of the acyl ion is minimized at low ionizing voltages and a correlation was obtained at 15 eV. From an examination of the relative rates of fragmentation, it

was observed that product stabilization provides an important driving force. In contrast to the fragmentation of benzophenones, it was found (48) that rates of ethylene elimination from substituted phenetoles were independent of the position of the substituent, indicating rearrangement of the molecular ion to a common intermediate before decomposition.

Mass Spectra of Aromatic and Heterocyclic Compounds

The mass spectra of the major classes of organic compounds have been discussed in considerable detail in a recent book by Budzikiewicz, Djerassi, and Williams (49) and the spectra of natural products were discussed in earlier volumes by the same authors (50). A review of the mass spectra of heterocyclic compounds, including naturally occurring heterocycles, was published by Spiteller in 1966 (51).

In this section, the discussion will be limited to those compounds directly related to the work in this thesis; namely aromatic hydrocarbons and heterocyclic compounds. A list of some of these compounds whose spectra have been determined, along with references, is presented in Table I. To keep the number of references within reasonable limits, only those considered most important to this discussion are included.

Table I

Mass Spectra of Aromatic Hydrocarbons and Heterocyclic Compounds

Compound	References
aromatic hydrocarbons	
benzene	52
alkylbenzenes	44, 53, 54, 55
C_7H_8 isomers	56
C_8H_{10} isomers	57
naphthalenes	58
aromatic nitrogen compounds	
β-carbolines	59
imidazoles	60, 61
indoles	2, 62
oxazoles	63
phenazines	64
pteridines	65
purine	65
pyrazines	66
pyrazoles	67
pyridazine	68
pyridines	69, 70, 71, 72, 73
pyrimidines	74, 75, 76
pyrroles	2, 77, 78

Table I (cont'd)

Compound	References
aromatic nitrogen compounds	
quinazolines	79
quinolines	1, 80, 81, 82
isoquinolines	1, 2, 80
quinoline N-oxides	83
tetrazines	84
saturated nitrogen heterocycles	
azabicyclooctanes	85
azasteroids	86
piperidines	87
piperidine alkaloids	88
piperazines	66
pyrrolidines	87, 89
tetrahydroisoquinolines	90, 91
oxygen containing heterocycles	
furans	92, 93, 94
benzofurans	94, 95
chromanes	95, 96
furazans	97
tetrahydrofurans	89, 98, 99
sulfur containing heterocycles	
thiazoles	100

Table I (cont'd)

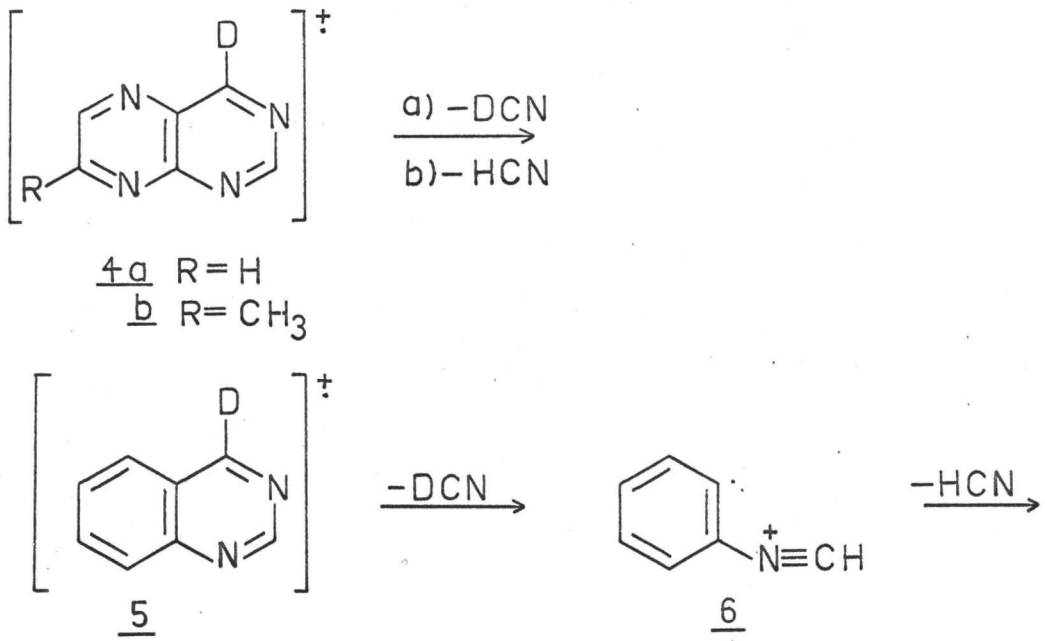
Compound	References
sulfur containing heterocycles	
thiophane	89, 98
thiophenes	101, 102
benzothiophenes	103

The mass spectra of unsubstituted aromatic and heteroaromatic compounds exhibit very intense molecular ion peaks because of the stability of the aromatic system. In general, the only significant fragmentation pathways involve expulsion of a small stable molecule from the molecular ion. Thus, benzene loses C_2H_2 (acetylene) from the molecular ion, and Jennings (52) has shown that the hydrogen atoms in the molecular ion become randomized before or during fragmentation. He postulated that randomization occurs by carbon rearrangements, and that ionized forms of fulvene, prismane and Dewar benzene might be formed as intermediates in the rearrangement.

Similarly, the mass spectrum of pyridine exhibits a fragment ion corresponding to loss of HCN from the molecular ion. Williams and Ronayne (69) have determined the spectra of pyridine-2-d and pyridine-2,6-d, and the results show that hydrogen randomization occurs before loss of HCN. In analogy to the spectrum of benzene, the intermediacy of azafulvene and/or azaprismane ions was postulated (69). C^{13} labelling experiments would be required to confirm the suggestion that skeletal rearrangements occur.

The mass spectra of a number of other nitrogen heteroaromatics have been reported (Table I), and in many cases loss of HCN from the molecular ion is the only important fragmentation. In a few cases, deuterium

labelling has been performed to determine the origin of the HCN which is expelled. Thus, non-specific loss of HCN was observed in the spectrum of imidazole (60). However, the spectra of pteridine-4-d (4a, Scheme 1)(65) and quinazoline-4-d, 5, (79) indicate that initial loss of HCN involves nearly specific loss of C-4 and its hydrogen in both compounds as shown in Scheme 1. Introduction of a 7-methyl group in pteridine, 4b, resulted in loss of HCN instead of DCN. It was suggested that HCN emanates from C-6, and the resulting fragment may be stabilized by the electron releasing methyl group (65).

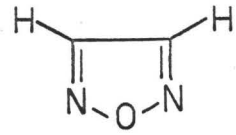


Scheme 1

Quinazoline and pteridine each have more than one nitrogen atom, and successive loss of two molecules of HCN from the molecular ion is observed in the spectra of

both compounds. Pyridazine and tetrazine have two adjacent nitrogen atoms and the major fragmentation process corresponds to expulsion of N_2 rather than HCN (68,84).

Elimination of more than one stable molecule may occur in the fragmentation of compounds containing different heteroatoms. Thus, elimination of CO followed by HCN was observed by Crow et al. (63) in the mass spectra of diphenyloxazoles. The mass spectral fragmentation of furazan, 7, suggests that the N-O bond is prone to cleavage (97), and the base peak corresponds to expulsion of HCN while a peak due to expulsion of NO is also observed. Intense molecular ions, and fragments corresponding to expulsion of RCN (where R = H or CH_3) with charge retention by the sulfur atom are characteristic of the mass spectra of thiazole, 8, and its methyl derivatives (100).



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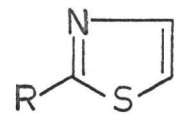


8

Introduction of an alkyl group into an aromatic or heteroaromatic molecule usually alters the fragmentation pattern considerably. In these compounds cleavage of a bond β to the aromatic nucleus is usually the most

important fragmentation process, but other pathways become important if an interaction between the side chain and a heteroatom is possible. A summary of the important features of the mass spectra of alkylated aromatic molecules is presented in the following discussion.

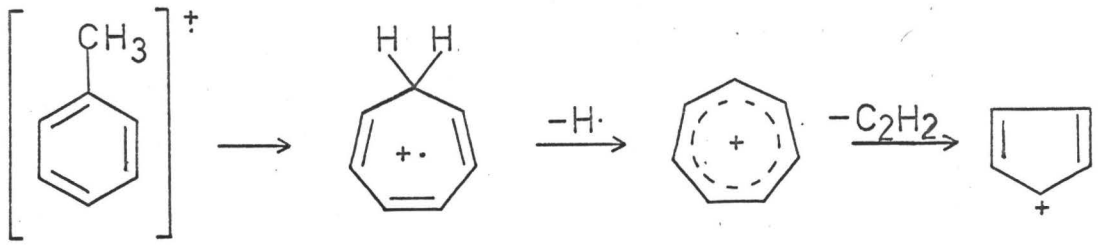
Alkylbenzenes

The mass spectral fragmentations of alkylbenzenes have received considerable attention by Meyerson and coworkers, and by other workers. Particular attention has been paid to the formation and structure of the $C_7H_7^+$ ion which is perhaps the most important fragment ion in the spectra of alkylbenzenes. A summary of the work in this area has been published in a review by Grubb and Meyerson (44).

Extensive deuterium labelling experiments on toluene showed that hydrogen was lost nearly randomly from the ring and side chain positions in formation of the $C_7H_7^+$ ion. In addition, results from deuterium and C^{13} labelling experiments indicated that further expulsion of C_2H_2 from the $C_7H_7^+$ ion could best be explained in terms of a symmetrical ion rather than a benzyl structure. Appearance potential measurements on the formation

of the $C_7H_7^+$ ion were also inconsistent with a benzyl structure.

The results of these experiments led Meyerson to propose that the toluene molecular ion could undergo rearrangement to a symmetrical species as outlined in Scheme 2. The hydrogen atoms in 9 may become equivalent by a series of 1, 2-hydrogen shifts. Loss of H from 9 yields the stable tropylium ion 10 which undergoes further fragmentation by elimination of acetylene to give ion 11.



Scheme 2

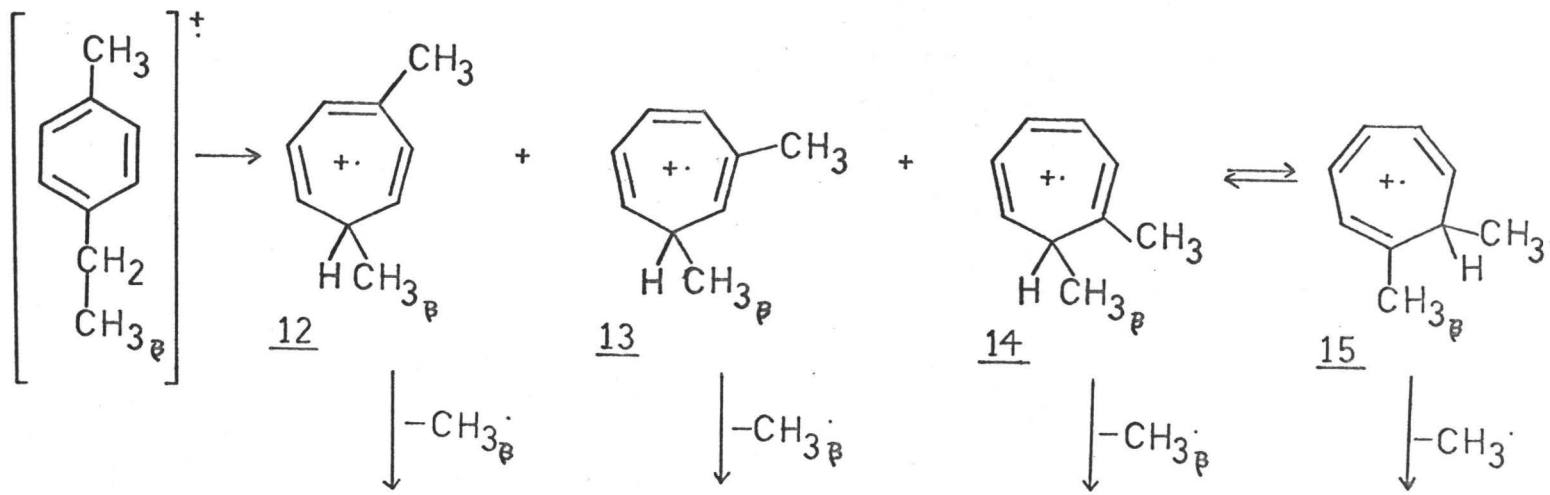
Further studies with ethylbenzenes, benzyl alcohols, and other benzyl derivatives indicated that tropylium ion formation was not limited to toluene. In addition, it was observed that the spectra of cycloheptatriene and other C_7H_8 isomers were remarkably similar to that of toluene (56). It was, therefore, concluded that the C_7H_8 isomers must undergo skeletal

rearrangement to a common ion before fragmentation.

Similar studies on the xylenes indicated that a tropylium ion rather than a tolyl ion was formed on loss of CH_3 from the molecular ion (54). The mechanism of such a rearrangement was not apparent from the labelling evidence available. Other C_8H_{10} isomers have also been found to give similar spectra (57).

In 1964, Meyer and Harrison proposed a detailed mechanism for tropylium ion formation from labelling evidence on ρ-methylethylbenzene (55). They found that the ring methyl and β-methyl were lost in a ratio of 1:5 in the formation of the $C_8H_9^+$ ion. The ratio was found to be independent of electron energy indicating fragmentation from a common intermediate, and appearance potential measurements indicated that the $C_8H_9^+$ ion could best be represented as a methyltropylium ion.

It was proposed that ring expansion of the parent ion to form a dimethylcycloheptatriene ion occurs by transfer of one of the α-hydrogens of the ethyl group to the attached carbon of the ring followed by insertion of the resulting $>CHCH_3$ group between any two carbons of the original benzene ring. This would give three intermediates 12, 13 and 14 in equal probabilities as shown in Scheme 3. Meyer and Harrison further proposed that loss of methyl occurs only from the 7- or methylene position,



Scheme 3

and that rapid intramolecular hydrogen transfer can occur between two positions containing a methyl group when the methyls are adjacent (7-α-hydrogen shift). Such a shift leads to equilibrium between 14 and 15, and to relative abundances of 12, 13, 14 and 15 of 2:2:1:1. Thus, loss of CH_3 from the methylene positions gives 5/6 loss of β methyl and 1/6 loss of ring methyl which is in agreement with the experimental results.

Similar labelling studies on the dimethylethylbenzenes could also be interpreted by assuming that a 7-α-hydrogen shift was much faster than other shifts. No mechanism for insertion of the exocyclic $>CHCH_3$ group was proposed although a possible bicyclic intermediate was suggested. Meyer and Harrison were also able to explain the labelling results on toluene and ethylbenzene by this mechanism, but they noted that it did not appear to explain the labelling results for ρ-xylene.

The analogous formation of a benztropylium ion in the fragmentation of the methylnaphthalenes has also been suggested but no labelling studies have been carried out to substantiate this hypothesis. The spectra of a number of C-12 polyacetylenes have been found to be similar to those of the methylnaphthalenes suggesting formation of common intermediates in their decomposition (58).

Alkylpyridines

The mass spectra of a number of alkylpyridines have been reported by several workers (70, 71, 72). Their characteristic fragmentation patterns will be discussed in some detail since their behaviour is typical of other nitrogen heterocycles.

Biemann has observed that the mass spectra of the three isomeric ethylpyridines differ in the relative abundances of the M-15 peaks (70). This peak is of negligible importance in the spectrum of 2-ethylpyridine, while it is of intermediate abundance in the spectrum of 4-ethylpyridine, and is the base peak in the spectrum of 3-ethylpyridine. Biemann has interpreted these results in terms of relative stability of the carbonium ion formed on loss of the terminal methyl group. In the 2- and 4-isomers, resonance structures can be drawn in which the positive charge is localized at a nitrogen atom with only six electrons, and this is an energetically unfavourable configuration. Such a structure cannot be drawn for the carbonium ion formed on loss of CH_3 from 3-ethylpyridine.

Spiteller, in a review of the mass spectra of heterocyclic compounds has interpreted the above results as evidence against the formation of a ring expanded ion prior to cleavage of the side chain (51). Also, Jennings

et al. (72) noted that the spectra of the monomethylpyridines gave weak M-1 peaks, and they failed to observe a metastable peak for loss of HCN from the M-H ion. These results were also taken as evidence for absence of an azatropylium ion in the fragmentation of methylpyridines (72).

On the other hand, Palmer and Lossing have observed that the appearance potentials of the C_6H_6N (M-1) ions from the three methylpyridines are essentially the same, and they suggested that these ions arise by dissociation of excited molecular ions in which orientational differences are small (73). Formation of an azatropylium ion therefore appeared to be compatible with the appearance potential results.

Stabilization of a fragment ion by interaction of a carbonium ion center with the nitrogen appears to be of importance in the spectra of alkylpyridines and other nitrogen heterocycles. Thus, the spectrum of 2-ethylpyridine (but not the spectra of 3- and 4- ethylpyridines) shows a very intense M-1 peak (the base peak) which has been interpreted in such a manner (16→17, Scheme 4). A McLafferty type rearrangement involving hydrogen transfer to nitrogen with expulsion of an olefin, as shown by the sequence 18→19 in Scheme 4*

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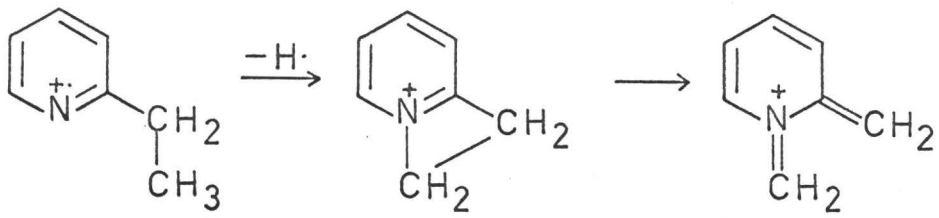
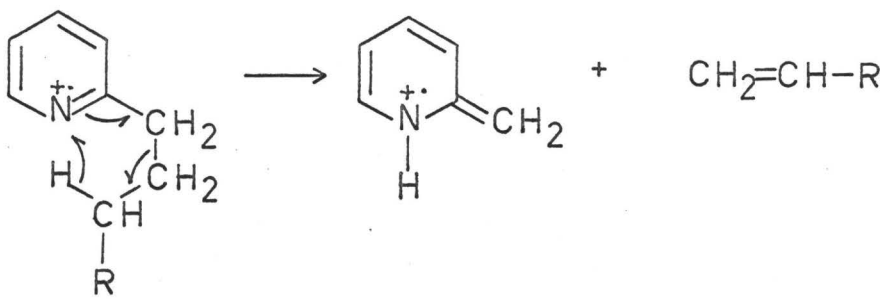
* The single-headed arrows (⇀) shown in Scheme 4 represent a single electron shift (homolytic bond cleavage) while a double-headed arrow(→) represents a two-electron shift (104).

is an important fragmentation pathway in the mass spectra of pyridines and other heterocycles having a three or more carbon chain in the α-position (70).



16 17



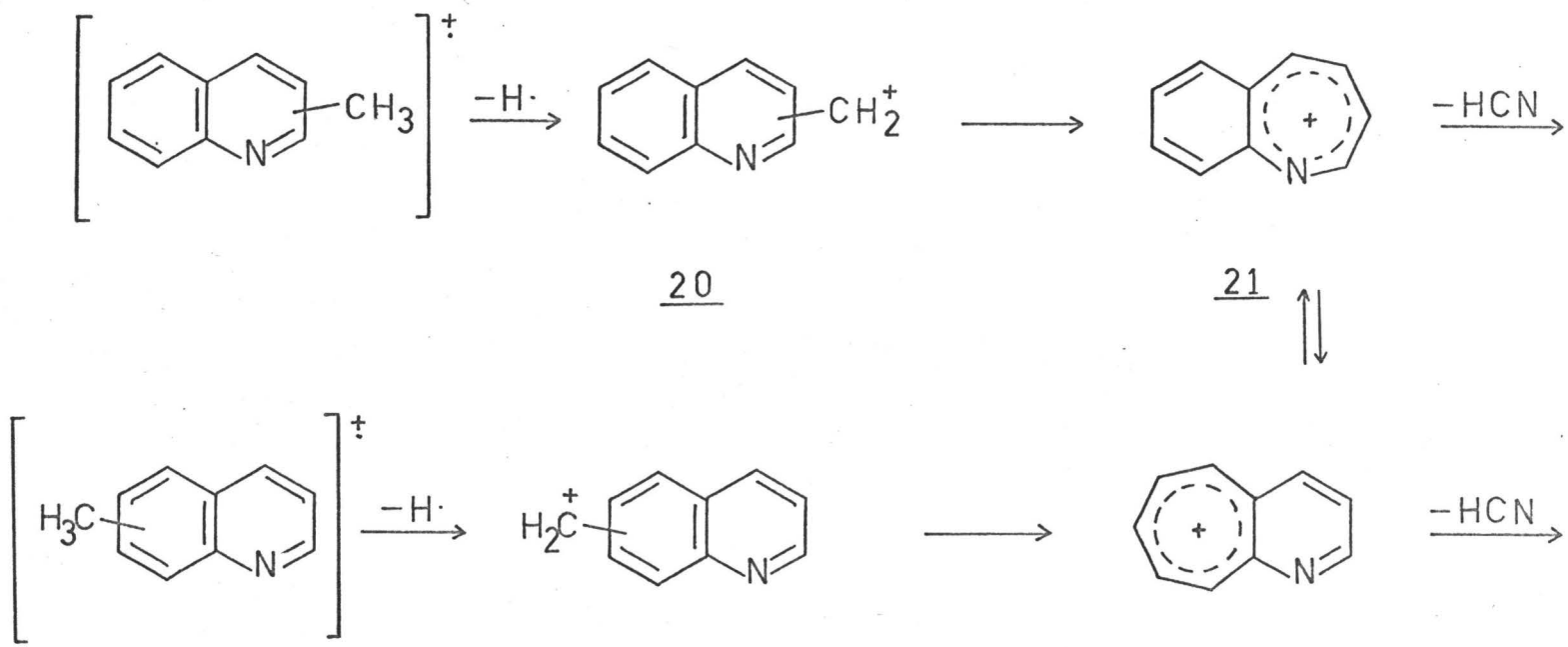
18 19

Scheme 4

Alkylquinolines

The mass spectra of only a few alkylquinolines had been reported in the literature (80,81) when the work for this thesis was initiated, but in 1967 Sample et al. (1) published the results of a study of the mass spectra of some alkylquinolines and isoquinolines. A summary of the results of their study is presented in the following paragraphs.

Sample et al. (1) determined the mass spectra of the seven monomethylquinolines, and they observed that the major fragmentation pathway proceeds through successive loss of H and HCN from the molecular ion. They found that the ratio of peak intensities M-(H+HCN)/M-H was constant for the monomethylquinolines substituted in the pyridine ring, and smaller but also constant for those substituted in the benzene ring. These results were interpreted in terms of expulsion of HCN from a common intermediate, i.e., the extent of formation of the M-(H+HCN) ion from the M-H ion should be independent of the position of the original substituent. Thus, they postulated the formation of a benzazatropylium ion 21 from monomethylquinolines substituted in the pyridine ring, and formation of ion 23 from quinolines substituted in the benzene ring (Scheme 5). A possible rearrangement



Scheme 5

of 23 to 21 was also suggested. The authors had no labelled monomethylquinolines available so they were unable to determine whether rearrangement preceded hydrogen loss as in the spectra of alkylbenzenes, or whether benzyl ions 20 or 22 were initially formed. They noted that the relative abundances of the M-(H+HCN) ions were consistent with either mechanism.

The mass spectral fragmentations of 2,3- and 2,4- dimethylquinolines were also interpreted in terms of initial hydrogen loss with ring expansion, followed by loss of CH_3CN or HCN.

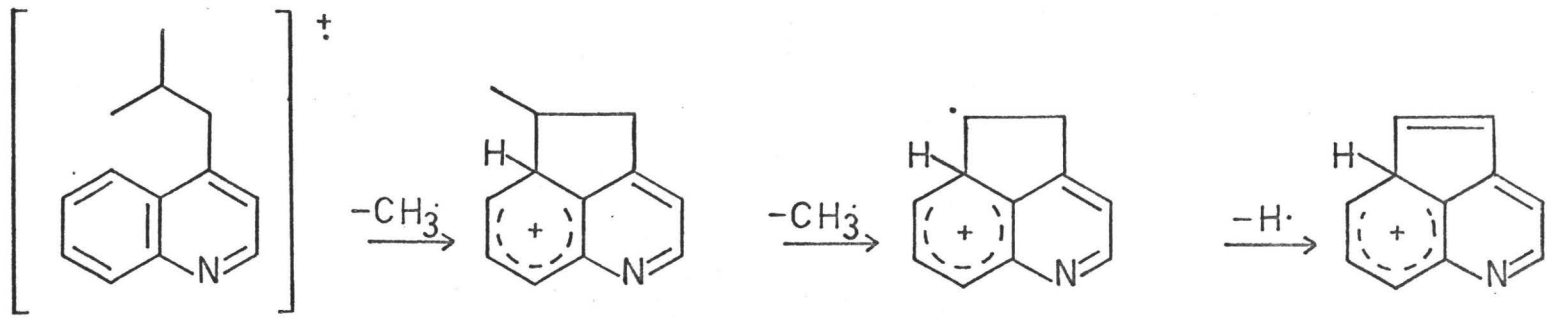
The mass spectra of 2- and 7- ethylquinolines were also discussed in the paper by Sample et al. 2-Ethylquinoline exhibits an intense M-1 peak (the base peak) in its mass spectrum, and a structure analogous to 17 shown in Scheme 4 for the M-1 ion in 2-ethylpyridine was assigned to this ion. A metastable peak corresponding to loss of 28 mass units from the M-1 ion was observed, and thus they were able to account for the formation of at least part of the peak observed at M-29. 7-Ethylquinoline was found to behave analogously to ethylbenzene in that the $M-CH_3$ peak was the base peak in its mass spectrum.

The intense (base peak) M-28 peak in the mass spectrum of 2-n-propylquinoline was interpreted in terms

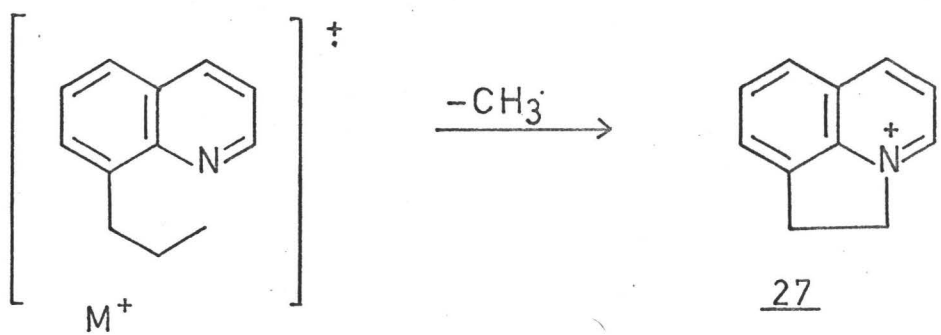
of a McLafferty type rearrangement, analogous to that shown in Scheme 4. This rearrangement was supported by labelling evidence, and it was also noted that alkyl migration to nitrogen does not occur if the γ carbon is tetrasubstituted.

The mass spectra of 4-isobutylquinoline and 8-n-propylquinoline were found to be similar in that the base peak in the spectra of both compounds corresponds to loss of CH_3 from the molecular ion. Sample et al., have suggested that the M-15 ion in 4-isobutylquinoline is stabilized by cyclization to the 5-position ($M^+ \rightarrow$ 24, Scheme 6), and that the M-15 ion in 8-n-propylquinoline is stabilized by cyclization to the nitrogen atom ($M^+ \rightarrow$ 27, Scheme 6). Ion 24 can further fragment by loss of another methyl group to give 25, which then loses H, to give 26 as shown in Scheme 6.

The salient features in the mass spectra of 6- and 7-n-propylquinolines, and 6- and 7-n-butylquinolines were also discussed in the paper by Sample et al. β cleavage was found to predominate in the spectra of the n-propylquinolines, while β cleavage and McLafferty rearrangement were found to be of approximately equal importance in the spectra of the n-butylquinolines. Thus, they note that transfer of a secondary hydrogen is favoured over transfer of a primary hydrogen in this



M^+ 24 25 26



M^+ 27

Scheme 6

McLafferty type rearrangement.

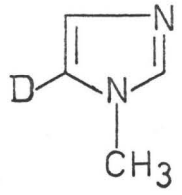
The mass spectra of a number of other quinoline derivatives including oxygenated quinolines (82) and quinoline N-oxides (83) have also been reported. The major fragmentation pathway of the hydroxyquinolines corresponds to loss of CO and then HCN from the molecular ion (82). The mass spectra of 2- and 8- methoxyquinolines differ from the spectra of the remaining isomers in that the former exhibit intense M-1 ions. Stabilization of the M-1 ions by the nitrogen atom is possible in the 2- and 8- isomers only (82). The mass spectra of some quinoline N-oxides have been reported and they show characteristic peaks corresponding to loss of an oxygen atom from the molecular ion (83).

Other Heteroaromatic Compounds

In this section the characteristics of the spectra of other heteroaromatic compounds are discussed. It will be apparent that some compounds show similar spectra to the compounds already discussed, while others show some differences.

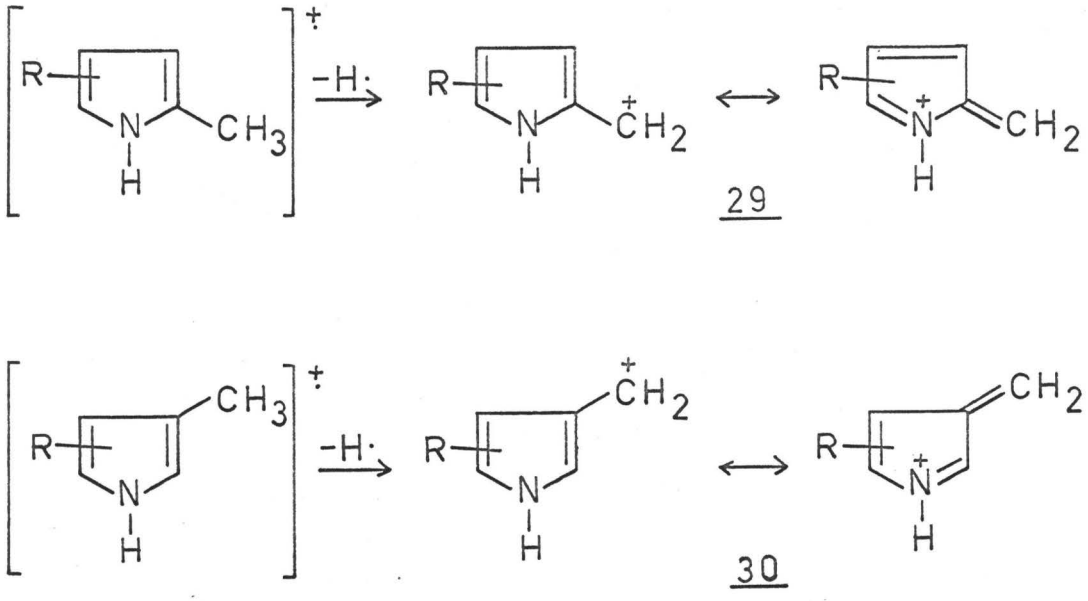
Intense M-1 peaks corresponding to β cleavage are observed in the spectra of the methylimidazoles, and the spectrum of 1-methylimidazole -5-d, 28, shows that some of the hydrogen lost in formation of the M-1 ion

originates from C-5 (60). This could be interpreted in terms of ring expansion before loss of hydrogen.



28

The monomethylpyrroles also exhibit intense M-1 ions in their spectra. However, the M-1 peaks are more intense than the M-15 peaks in the spectra of the dimethylpyrroles which is opposite to that observed in the xylenes. Budzikiewicz et al. have interpreted this apparent anomaly in terms of formation of stable ions 29 and 30, as shown in Scheme 7, rather than ring expansion to a pyridinium ion (77).



Scheme 7

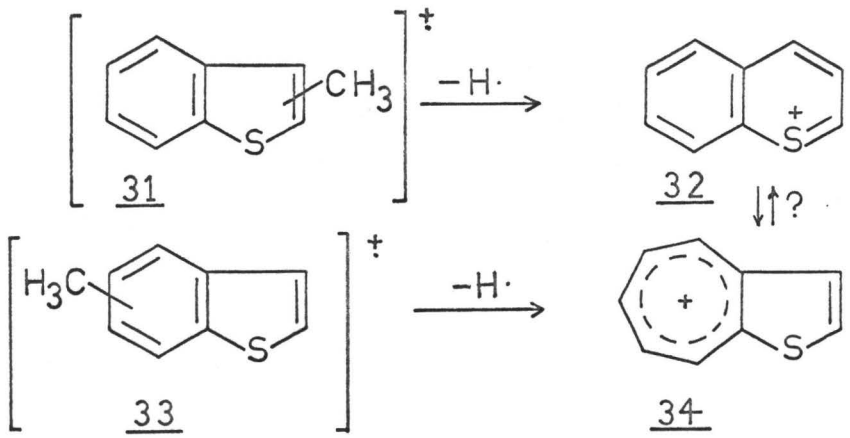
Beynon has determined the mass spectra of a number of alkylindoles and β cleavage, possibly with ring expansion to a quinolinium ion, is again the most important fragmentation process (62).

The mass spectra of the methylpteridines differ from the spectra of the monomethylquinolines in that no M-1 and M-(H+HCN) peaks are observed in the spectra of the former compounds. Rather, intense peaks corresponding to loss of HCN or CH_3CN (depending on the position of the substituent) from the molecular ion are observed (65). Similarly, the loss of CH_3CN or HCN from the molecular ion in the spectra of the methylquinazolines is preferred over loss of H followed by HCN or CH_3CN (79).

The mass spectra of aromatic compounds containing heteroatoms other than nitrogen have also received considerable attention, and in many cases analogies to the corresponding nitrogen compounds may be observed. Thus, the major fragmentation of furan corresponds to loss of CHO from the molecular ion (92), and β cleavage, possibly with ring expansion, is an important fragmentation process in the spectra of the alkylfurans (92)(93) and alkylbenzofurans (94). Stable ion structures analogous to those shown in Scheme 7 can also be drawn for many of the fragment ions formed by β cleavage in the spectra of these

compounds, and thus the ring expansion hypothesis need not necessarily be invoked to explain the abundance of such ions (51).

β cleavage is similarly the most important fragmentation pathway in the mass spectra of the alkylthiophenes (101,102) and alkylbenzothiophenes (103). In a study of the spectra of the methylbenzothiophenes, Porter has observed that the 2- and 3- methyl isomers show nearly identical spectra, and the 4-, 5-, 6- and 7- methyl isomers also show nearly identical spectra (103). He has attributed this to the formation of common ring expanded intermediates 32 and 34 from 31 and 33, respectively, as shown in Scheme 8. He also suggested that 32 and 34 may not have separate identity since they could be readily interconverted. This interpretation is entirely analogous to that proposed by Sample et al. in the fragmentation of the monomethylquinolines (Scheme 5)(1), but no labelling results were available to confirm these interpretations.

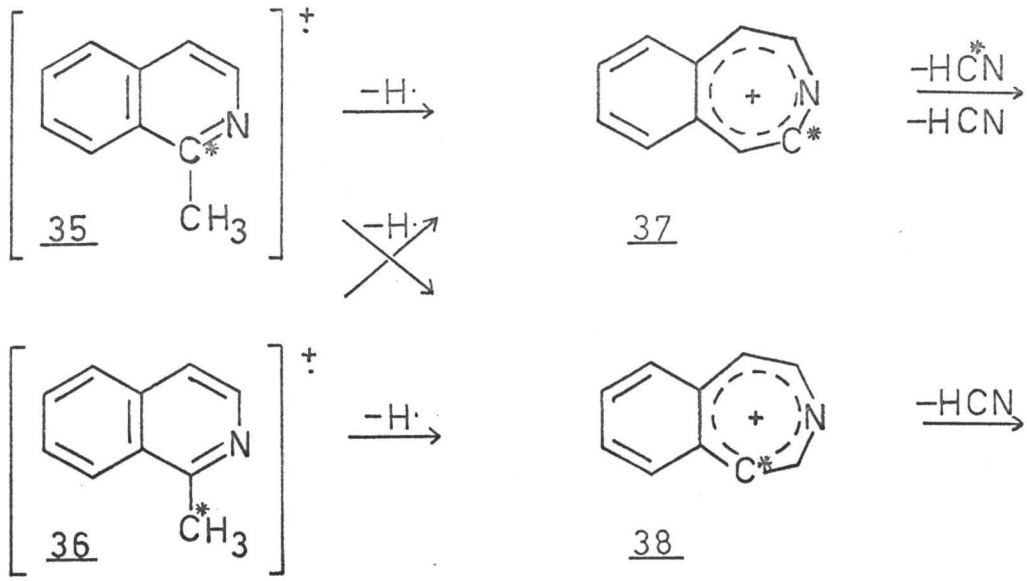


Scheme 8

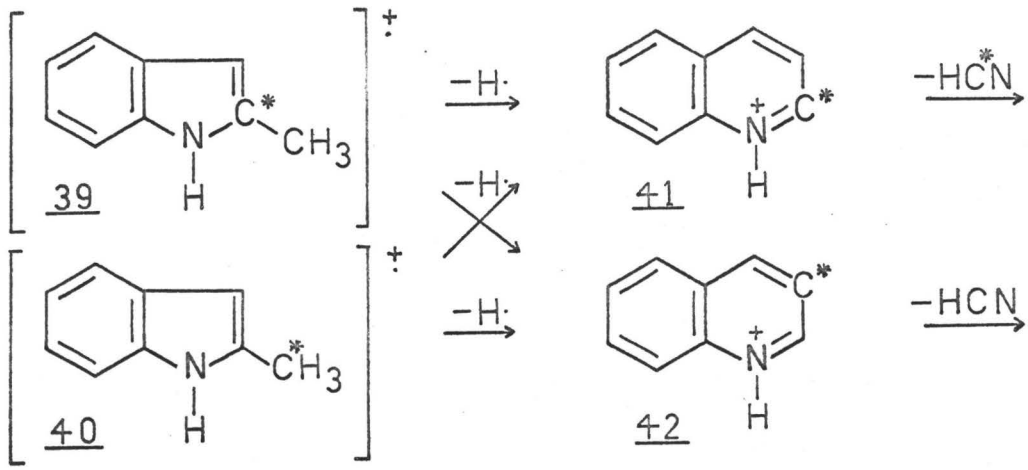
From the preceding discussions, it is seen that β cleavage of alkylated aromatic heterocycles is an important mass spectral fragmentation process, and, in analogy with the spectra of alkylbenzenes, the formation of ring expanded ions seems probable. However, no labelling evidence was available to confirm the existence of such ring expanded ions until early in 1968 when the results of some C^{13} labelling experiments on 1-methylisoquinoline, 1- and 2- methylindoles and N-methylpyrrole were published by Marx and Djerassi (2). Their results which are summarized in the following discussion may be interpreted in terms of the intermediacy of ring expanded ions.

In their study, Marx and Djerassi recorded the mass spectra of 1-C^{13}-methylisoquinoline (35, Scheme 9) and 1-methyl-C^{13}-isoquinoline, 36, and they noted that on loss of H from 35 and 36 two possible ring expanded ions 37 and 38 could be formed. Ion 37 could be formed from 35 by migration of the methyl carbon to the adjacent phenyl carbon, and 38 from 35 by migration of the methyl carbon to nitrogen. Ions 38 and 37 may be formed from 36 by similar mechanisms.

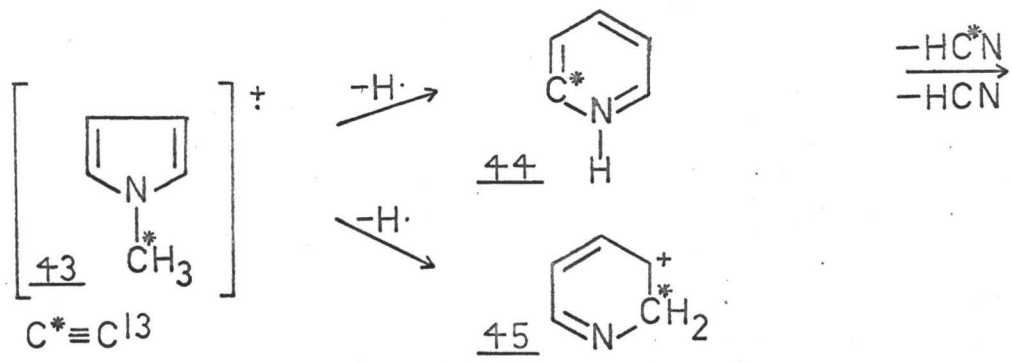
They argued that 37 is symmetrical with respect to nitrogen, and thus its contribution to the fragmentation process will be twice the observed label loss. No loss of label in expulsion of HCN is expected for ion 38.



Scheme 9



Scheme 10



Scheme 11

In compound 35, 26% of the label was lost as HCN, and in compound 36 14% was lost. Thus, they were able to account for 80% of the label in terms of a ring expanded intermediate formed in the manner shown in Scheme 9. No explanation was offered for the remaining 20%. In the ring expansion of methylethylbenzene, it was suggested that the exocyclic carbon could be inserted between any two carbons of the ring (55), and similarly a more complicated mechanism of ring expansion may be operating with the isoquinolines.

In the spectra of the two labelled indoles 39 and 40, the authors were similarly able to account for 86% of the label by assuming that ring expansion proceeded by the two pathways to ions 41 and 42 as shown in Scheme 10. They were unable to account for 14% of the label and suggested that rupture of the phenyl ring might also be involved in the loss of HCN. In both the isoquinoline and indole derivatives, Marx and Djerassi observed that migration of the exocyclic carbon to another carbon is favoured over migration to nitrogen in the formation of the ring expanded intermediates.

The 65% retention of label observed in the spectrum of N-methyl-C^{13}-pyrrole (43, Scheme 11), is incompatible with the formation of a symmetrical ion 44 where 50% loss of label on expulsion of HCN would

be expected. Therefore, at least part of the M-(H+HCN) ion must arise from another pathway (or pathways), and Marx and Djerassi have proposed an alternative pathway involving formation of an unsymmetrical ion 45.

The mass spectrum of N-methyl-C^{13}- indole also gave results which were consistent with ring expansion to a quinolinium ion. Thus, the authors concluded that formation of the M-(H+HCN) fragment in the decomposition of the above compounds is accompanied by a very significant degree of skeletal rearrangement involving migration of the exocyclic methyl group. They recognize that their experimental data have not established the intermediacy of ring expanded ions, but note that their data can most readily be interpreted in terms of such ions or other ring expanded species.

Saturated Heterocycles

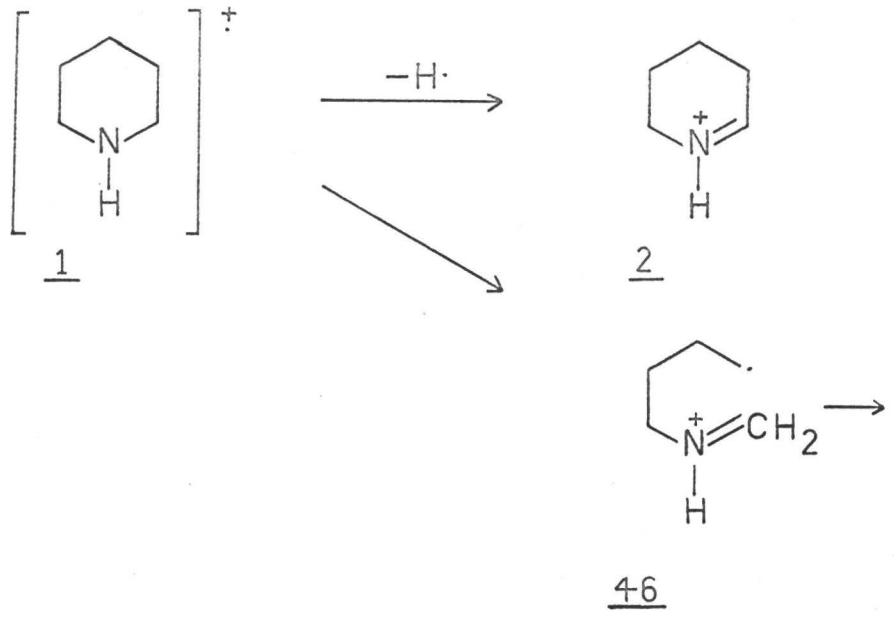
The mass spectra of saturated heterocycles usually differ markedly from their aromatic analogs. In particular, the intense molecular ion peaks which are characteristic of the stable aromatic system become less evident in the spectra of the saturated compounds, and new fragmentation modes become apparent.

The difference in the spectra of the aromatic and

saturated heterocycles may be used to advantage in the identification of an unknown aromatic heterocycle. Thus, if an aromatic heterocycle cannot be identified by its mass spectrum, it may be reduced to the corresponding saturated compound whose spectrum may aid in the determination of the structure. Biemann has shown how the structure of an alkylpyrazine may be elucidated by reducing it to the corresponding piperazine (66).

The mass spectra of a number of saturated nitrogen heterocycles, as illustrated in Table I, have been determined. In most of these compounds, the initial fragmentation process involves cleavage of a bond α to the nitrogen since the nitrogen atom can aid in the stabilization of the positive charge in the resulting fragment. The importance of α cleavage is illustrated in the following discussion.

The M-1 ion is of importance in the mass spectrum of pyrrolidine and piperidine, and deuterium labelling studies have shown that H is lost mainly from the α position (87,89). Thus, the M-1 ion in the spectrum of piperidine may be represented by structure 2 in Scheme 12. Labelling experiments on the N-methyl analogue show that loss of a secondary hydrogen is preferred over loss of a primary hydrogen in formation of the M-1 ion (87).

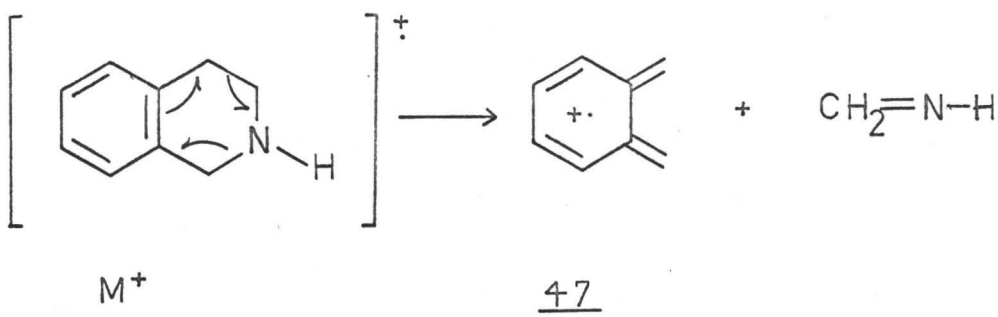


Scheme 12

In addition, the other major fragment ions in the mass spectra of the pyrrolidines and piperidines have been interpreted by assuming that the alternative mode of α cleavage (e.g., 1 → 46, Scheme 12) occurs initially. The mechanisms of further fragmentations were elucidated with the aid of deuterium labelling and high resolution measurements (87).

The mass spectra of a number of 1- substituted 1,2,3,4-tetrahydroisoquinolines have been reported, and the expected α cleavage with loss of the substituent gives rise to the most intense peak in their spectra (90,91). The fragmentation of the parent tetrahydroisoquinoline, its N-methyl, and N-acetyl derivatives have

also been reported by Baldwin et al. (90). 1,2,3,4-Tetrahydroisoquinoline exhibits an intense M-1 peak in its spectrum which is presumably due to α cleavage, and also a peak at M-3 corresponding to further loss of hydrogen with formation of an isoquinolinium ion. However, the base peak in the spectrum of this compound corresponds to loss of CH_2 = N-H from the molecular ion by a retro Diels Alder reaction ($M^+ \rightarrow$ 47, Scheme 13). Intense fragment peaks corresponding to a similar reaction are also observed in the spectra of the N-methyl and N-acetyl derivatives.

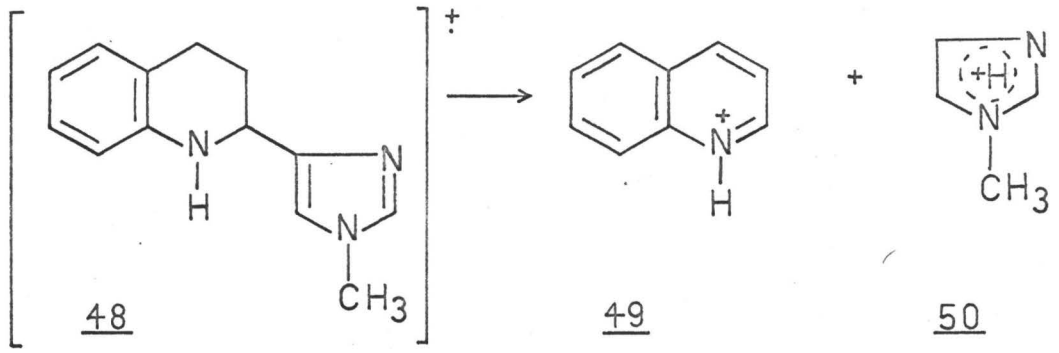


M^+ 47

Scheme 13

An intense M+1 ion due to an ion-molecule reaction has been claimed in the spectrum of N-methyl-1,2,3,4-tetrahydroisoquinoline (90), but closer examination of the spectrum indicates that a counting error may have been made.

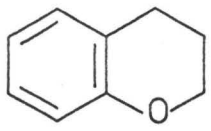
The spectrum of a tetrahydroquinoline derivative 48 has been reported and a major fragmentation pathway involves α cleavage with transfer of two hydrogens to the imidazole nucleus (61). This results in the formation of a stable quinolinium ion 49 and an imidazole ion 50 as shown in Scheme 14.



Scheme 14

The mass spectral behaviour of saturated oxygen heterocycles is similar in many ways to the behaviour of their corresponding nitrogen analogs. Thus, the spectra of tetrahydrofurans (89,98,99) and tetrahydropyrans (99), as well as the spectra of chromanes (95) exhibit intense peaks corresponding to α cleavage. The oxygen atom is, however, less able to tolerate positive charge than is nitrogen, and thus it might be expected that α cleavage would be less important in the spectra of saturated oxygen heterocycles.

An interesting feature of the mass spectrum of chromane, 51, is the presence of a peak at M-15. Willhalm et al. have observed metastables for loss of CH_3 from the molecular ion, and for loss of CH_2 from the M-1 ion (95). Sample (96) has reinvestigated the spectrum since loss



51

of CH_2 is usually a very high energy process. No metastable peak for loss of CH_2 was observed by Sample, and deuterium labelling experiments carried out to determine the origin of the eliminated methyl were inconclusive. Labelling experiments on 2, 2- diphenylchromane gave similar results and Sample suggested that hydrogen scrambling must occur before elimination of the methyl group (96).

DISCUSSION OF RESULTS

The mass spectra of the isomeric monomethylquinolines, most of the dimethylquinolines and some monoethylquinolines and monopropylquinolines have been determined in this investigation. The mass spectra of 1,2,3,4-tetrahydroquinoline, 5,6,7,8-tetrahydroquinoline and several monomethyl-1,2,3,4-tetrahydroquinolines have also been examined. In the following discussion, fragmentation mechanisms, based on the results of a number of deuterium labelling experiments, are proposed to account for the important features in the spectra of these compounds.

Monomethylquinolines

The mass spectra of the seven isomeric monomethylquinolines are shown in Fig. 3 (a-g). The results obtained are similar to those reported by Sample et al. (1). All the compounds exhibit an intense molecular ion peak (the base peak) which is characteristic of the stable aromatic system. The major fragmentation of all the isomers proceeds through the sequence $M^+ \rightarrow M-1 \rightarrow M-28 \rightarrow M-54$, and the presence of appropriate metastable peaks

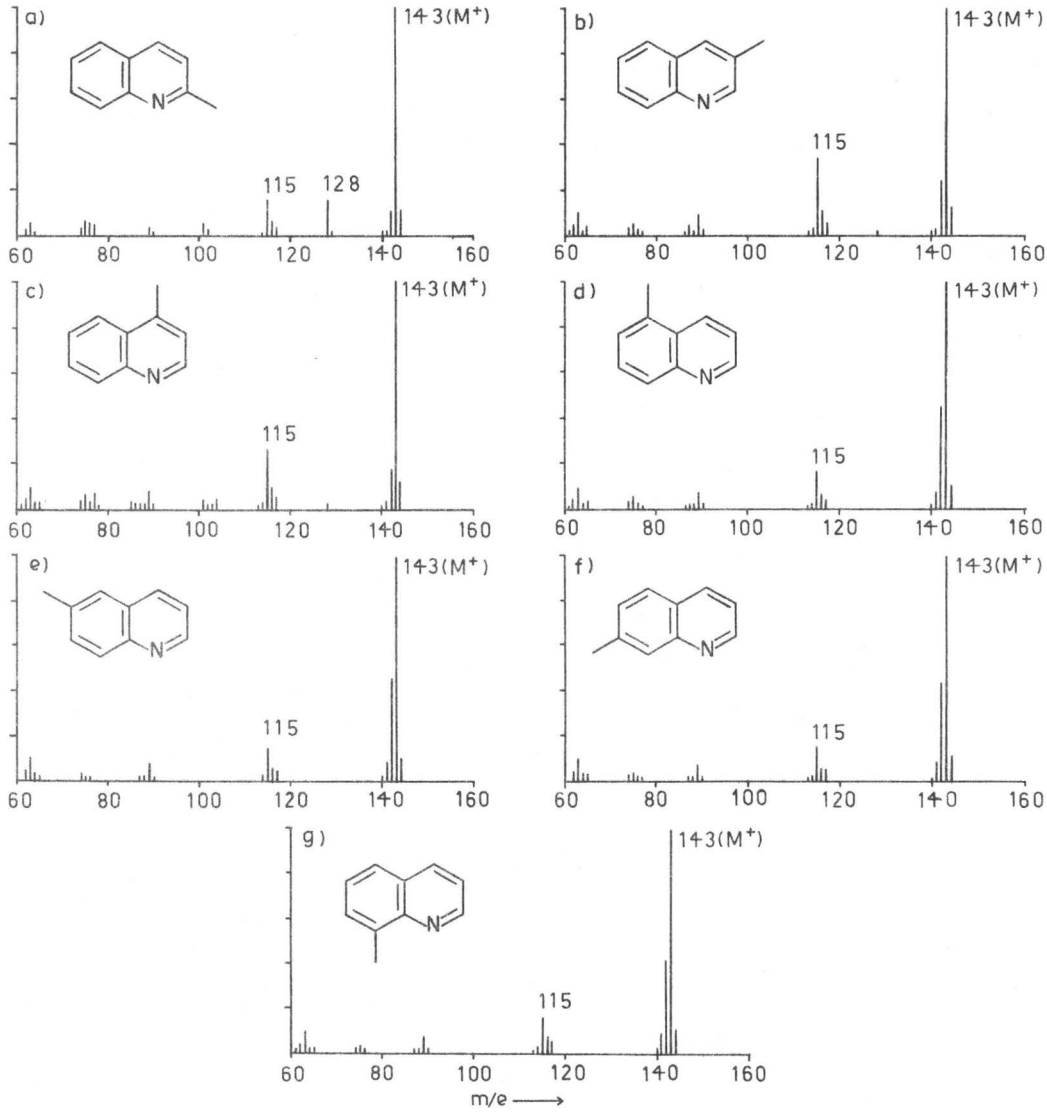


Figure 3. Mass spectra of a) 2-methylquinoline, b) 3-methylquinoline, c) 4-methylquinoline, d) 5-methylquinoline, e) 6-methylquinoline, f) 7-methylquinoline and g) 8-methylquinoline.

(Table II) provide supporting evidence for this sequence.

Table II

Metastable Ions Observed in the Spectra of the Monomethylquinolines

Transformation	Obs.	Calcd.	Obs. in the spectra of:
M→M-1	141	141.0	2-,3-,4-,5-,6-,7-,8-
M→M-15	114.8	114.6	2-
M→M-18	112.3	112.2	2-α-d_3
M→M-27	94.2	94.1	2-,3-,4-
M-1→M-28	93.2-93.3	93.1	2-,3-,4-,5, 6-,7-,8-
M-15→M-42	79.8	79.7	2-
M-28→M-54	69	68.9	2-,3-,4-,5-,6-,7-,8-

Exact mass measurements of the M-28 ion (m/e 115) in the spectra of the 2- and 4- isomers show that its composition is $C_9H_7^+$, and it therefore arises through loss of H+HCN rather than C_2H_4 [calculated for C_9H_7 115.0548 observed 115.0548 (2-methylquinoline) and 115.0548 (4-methylquinoline)]. A similar composition of the M-28 ion is also expected for the other monomethylquinolines. Further fragmentation of the M-28 ion proceeds by loss of acetylene.

In addition to the above fragmentation pathway,

the loss of CH_3 from the molecular ion results in a significant peak in the spectrum of 2-methylquinoline (Fig. 3a). This feature allows the spectrum of 2-methylquinoline to be readily differentiated from the spectra of the other isomers. In the spectrum of the deuterated analogue (Fig. 4a), this peak is shifted nearly quantitatively to M-18 showing that loss of methyl proceeds without significant rearrangement.

Sample et al. noted that the M-28 peak arises by loss of H+HCN, and they observed that the ratio of peak intensities M-(H+HCN)/M-H in the spectra of the monomethylquinolines substituted in the pyridine ring was constant (1). In other words, the extent of HCN loss from the M-H ion is independent of the position of the substituent, and therefore proceeds from a common intermediate. They also noted that this ratio was smaller but also constant for the methylquinolines substituted in the benzene ring. These workers had no deuterated methylquinolines available so they were unable to determine whether rearrangement preceded hydrogen loss as in the spectra of the alkylbenzenes, or whether benzyl ions were initially formed. Therefore, in this study the spectra of a number of labelled monomethylquinolines were determined in an attempt to further elucidate the mechanism of ring expansion.

The labelled monomethylquinolines prepared were: 2-methylquinoline-2-α-d_3, 4-methylquinoline-2-d_1, 8-methylquinoline-8-α-d_1, 8-methylquinoline-8-α-d_3 and 2-methylquinoline-2-α-C^{13}. Their spectra are recorded in Fig. 4a-e, respectively, and the labelling results are summarized in Table III. In the first column, the (M-H)/(M-H)+(M-D) peak intensity ratios in the transformation M→M-H, expressed in terms of the percent label retention ((M-H)/(M-H)+(M-D) × 100), are listed. Similarly, the percent retention of label in the M-(H+HCN) ion is listed in the next column. In the third column is listed the label retention expected for statistical loss of a single hydrogen or deuterium from the ring containing the substituent, and in the last column the calculated label retention for random loss of a single hydrogen or deuterium from the whole molecule is listed. The results shown in Table III are the average of two determinations, and the absolute values obtained in the different determinations usually agreed to within 2%.

Calculation of the label retention in the M-H and M-(H+HCN) ions in the deuterated monomethylquinolines requires the use of some approximations. It therefore seems appropriate to discuss in some detail the method used to calculate the label retention before discussing the implications of the results.

Label retention in the M→M-H process was calculated

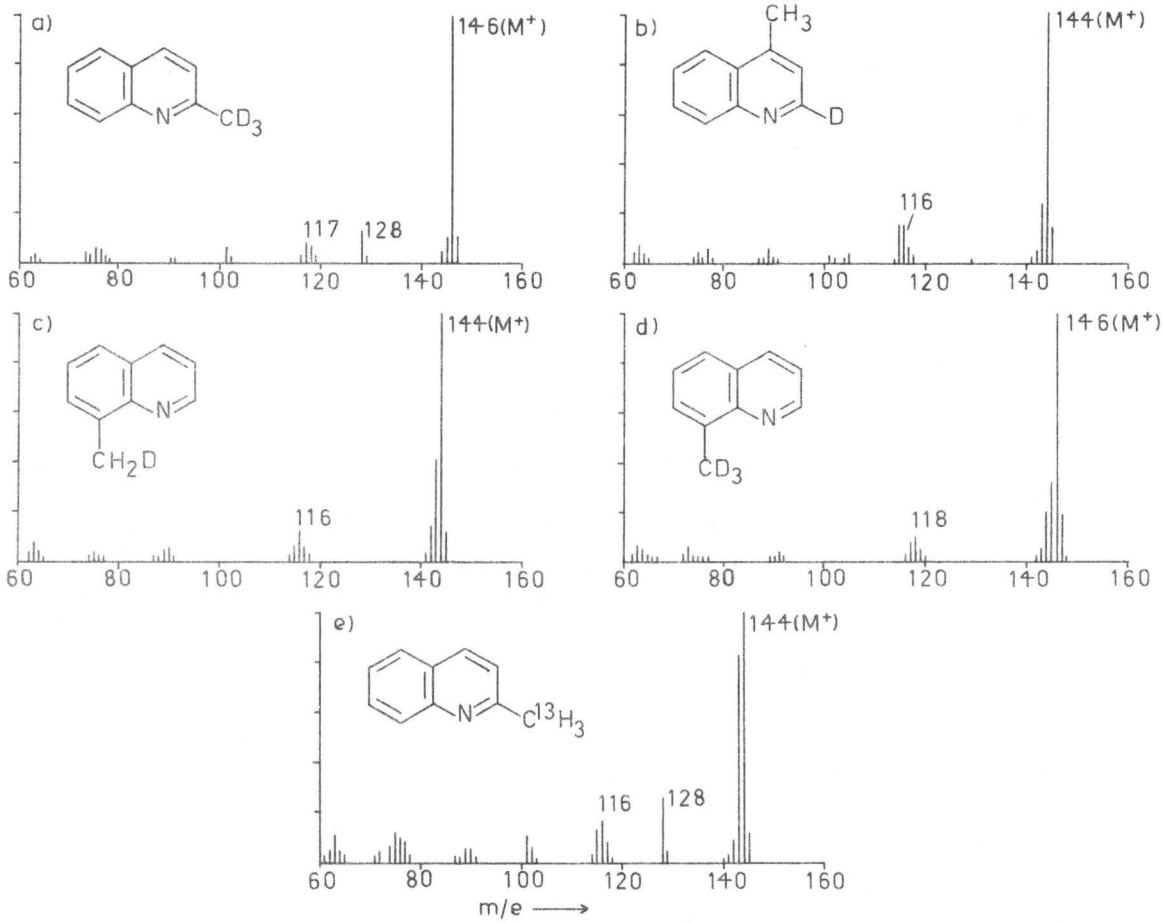


Figure 4. Mass spectra of a) 2-methylquinoline-2-α-d_3, b) 4-methylquinoline-2-d_1, c) 8-methylquinoline-8-α-d_1, d) 8-methylquinoline-8-α-d_3 and e) 2-methylquinoline-2-α-C^{13}.

Table III

Mass Spectra of Labelled Monomethylquinolines

compound	% retention (M-H)	% retention [M-(H+HCN)]	calculated for random loss of H from ring containing substituent	calculated for random loss of H from molecule
2-methylquinoline-2-α-d_3	74		40	67
4-methylquinoline-2-d_1	91	50	80	89
8-methylquinoline-8-α-d_1	89	78	83	89
8-methylquinoline-8-α-d_3	62		50	67
2-methylquinoline-2-α-C^{13}		80		

from the peak intensities at M-H and M-D in the spectra of the labelled compounds by the equation $\frac{(M-H)}{(M-H)+(M-D)} \times 100$. The peak intensities were first corrected for isotopic impurities (determined by low voltage mass spectrometry) and for naturally occurring C^{13}. An additional correction for contributions of the ion corresponding to M-2H at M-D (M-2) in the spectra of the labelled compounds was also required, and it was estimated by the following procedure. The peak at m/e 140 (M-3H) in the spectrum of the undeuterated compound is found at m/e 140 [M-(D+2H)] and 141(M-3H) in the spectrum of a monodeuterated analogue, while the peak at m/e 141(M-2H) in the undeuterated compound is observed at m/e 141 [M-(H+D)] and 142 (M-2H) in the deuterated species. Therefore, if the sum of the relative intensities of the peaks at m/e 140 and 141 in the deuterated compound is subtracted from the sum of the peak intensities at m/e 140 and 141 in the undeuterated compound, then the difference corresponds to M-2H ions contributing at M-2 in the labelled compound. The M-2H contribution may then be subtracted from the total M-2 intensity to give the M-D contribution. The correction for the compounds containing three deuteriums was similar to that described above, except that the peak at M-5 [M-(2D+H)] was also considered in the correction.

An alternative method of calculating label retention which was not used in this investigation, and which does not require the above correction, uses the ratio I_2/I_1, where I_2 is the intensity of the M-H peak in the spectrum of the labelled compound and I_1 is the M-H peak intensity in the spectrum of the unlabelled analogue. The use of this method depends on the assumption that introduction of the label has no effect on the total yield of the fragment ion in question (54). In the spectra of the labelled monomethylquinolines, however, an apparent isotope effect results in the sum of the peak intensities at M-H and M-D being slightly less than the M-H peak intensity in the unlabelled analogues.

This isotope effect could presumably arise through a combination of two effects. The first is a simple isotope effect favouring loss of hydrogen over a chemically equivalent deuterium. This would result in the observed M-H/M-D ratio being greater than the ratio of chemically equivalent hydrogens to deuteriums actually present in the molecular ion. Thus, the calculated label retention would be higher than in the absence of such an effect, and this is a possible source of error in the results shown in Table III.

A second effect which should not affect the M-H/

M-D ratios may be a consequence of the relative rates of hydrogen and deuterium transfers in the anticipated rearrangement process. The favoured transfer of hydrogen over deuterium observed in the McLafferty rearrangement (32) may be interpreted in terms of the relative rates of hydrogen and deuterium transfer. A similar effect in the monomethylquinolines would result in a lower rate of rearrangement and fragmentation, and a consequent lowering of fragment ion intensity in the deuterated compounds.

The peak at m/e 116 in the spectra of the monomethylquinolines labelled with a single deuterium (or C^{13}) corresponds to retention of label in the M→M-(H+HCN) process, and the peak at m/e 115 corresponds to loss of label. However, peaks of appreciable intensity at masses 113, 114, 116 and 117 as well as at 115 in the spectra of the unlabelled methylquinolines (Fig. 3) contribute at m/e 115 and 116 in the labelled compounds, and corrections for these contributions have been made as described in the following paragraphs.

The peak at m/e 115 in the spectrum of the labelled derivative corresponds not only to loss of label in the M→M-(H+HCN) process (I_3), but also to a partial shift of the m/e 114 peak found in the spectrum of the unlabelled analogue. The latter contribution was estimated by sub-

tracting the sum of the peak intensities at m/e 113 and 114 in the labelled derivative from the sum of the peak intensities at m/e 113 and 114 in the unlabelled compound. Similarly, the peak at m/e 116 in the spectrum of the labelled derivative corresponds to retention of label in the M→M-(H+HCN) process (I_4) and also to a contribution from the m/e 116 peak in the spectrum of the unlabelled compound. The latter contribution was estimated by subtracting the sum of the peak intensities at m/e 117 and 118 in the labelled derivative from the sum of the peak intensities at m/e 116 and 117 in the unlabelled compound. The label retention in the M→M-(H+HCN) process may then be calculated from the ratio

$$\frac{I_4}{I_3 + I_4} .$$

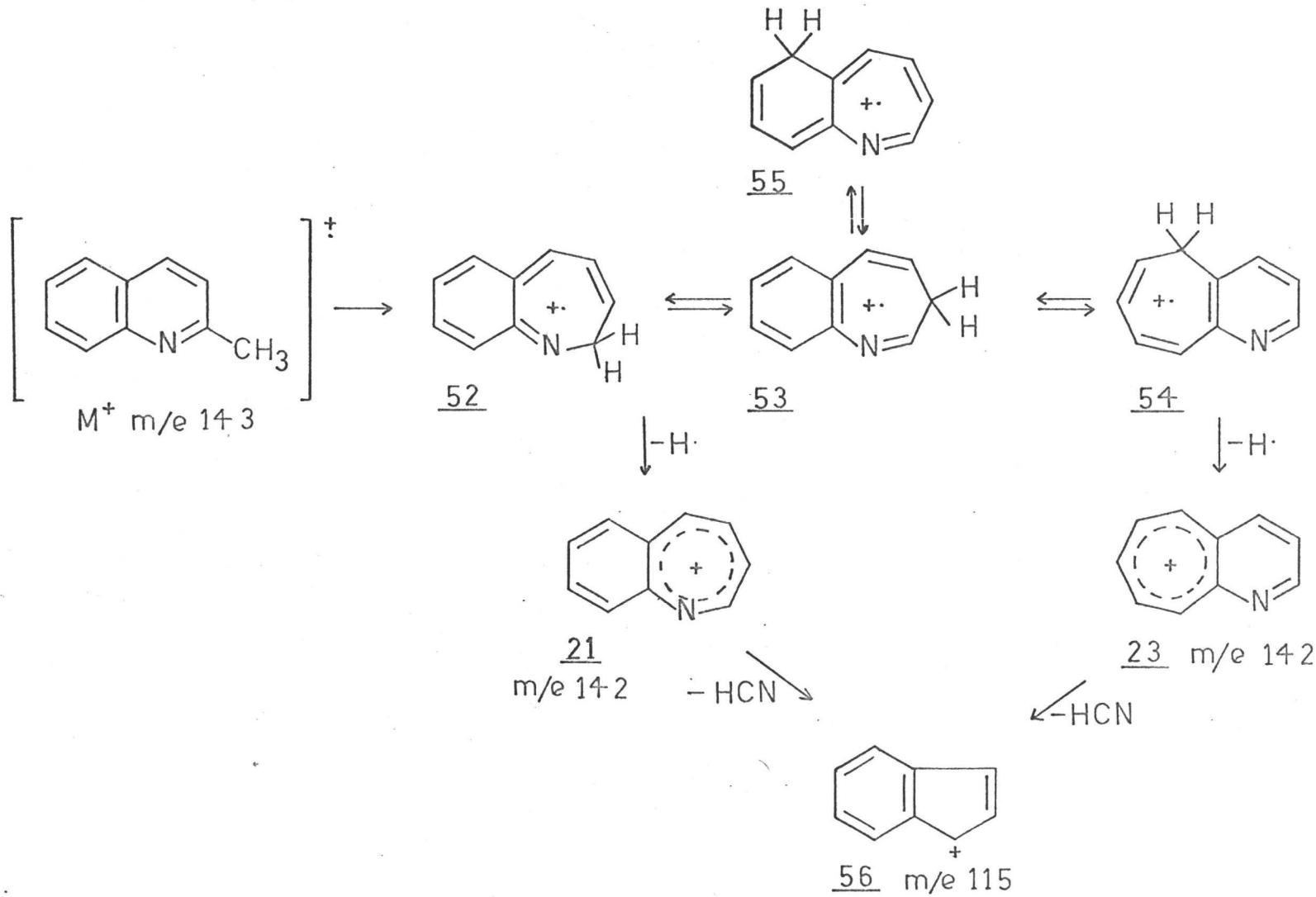
Calculation of the label retention in the M-(H+HCN) ion in compounds containing more than one deuterium requires further assumptions and was therefore not attempted.

It was found that the relative ion yields in this region of the spectra were about 10% lower in the labelled derivatives than in the unlabelled compounds because of the isotope effect. Therefore, the peak abundances in this region of the labelled derivatives were multiplied by a factor such that the relative

intensities of the peaks become equivalent in both the unlabelled and labelled compounds.

Examination of the results listed in Table III shows that extensive hydrogen rearrangement occurs before or during formation of the M-H ion. The results are not compatible with formation of a simple benzyl ion by loss of a methyl hydrogen, nor are they compatible with a simple ring expansion and randomization of the hydrogens in the ring containing the methyl substituent. They are more in accord with a randomization of all nine hydrogens in the molecule.

In the light of these results, it is tempting to assume that ring expanded species are indeed formed in the fragmentation of methylquinolines. A possible mechanism to account for the hydrogen scrambling is shown in Scheme 15. As depicted in the scheme, a methylquinoline substituted in the pyridine ring is first ionized and then undergoes ring expansion to a species which may be represented as a benzazacycloheptatriene ion 52. The hydrogens may become randomized through a series of 1,2-hydrogen shifts (52→53, etc.). Rearrangement to cycloheptatriene ions represented by ion 54 accounts for hydrogen loss in the benzene ring. Alternative structures, represented by ion 55, could also account for randomization in the benzene ring, and there-



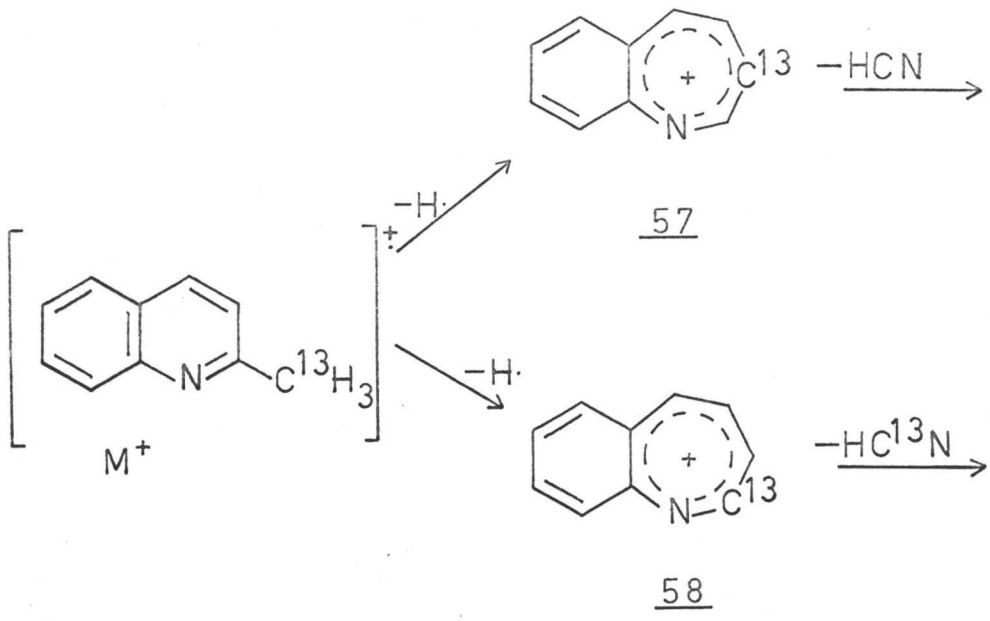
Scheme 15

fore ring expansion in the ring other than that containing the substituent need not necessarily be invoked. Loss of hydrogen (possibly from the methylene position as suggested for the methylethylbenzenes (55)) from the ring expanded molecular ions may then result in formation of an azatropylium ion 21 and a tropylium ion 23. The results for the monomethylquinolines substituted in the benzene ring may be explained in a similar manner; in these compounds initial ionization and ring expansion may result in a cycloheptatriene type ion represented as ion 54.

The observed label retention in the M-(H+HCN) ion, 56, also shows that considerable hydrogen rearrangement has taken place. In the spectrum of 4-methylquinoline-2-d, 50% of the deuterium is retained in the M-(H+HCN) ion while random loss from the molecule in this process requires 78% retention. Thus, the C-2 hydrogen is lost preferentially over the remaining hydrogens which suggests that the C-2 hydrogen is not completely randomized over the molecule before loss of HCN. The label retention in the 8-α-d_1 derivative is about 78% while random loss from the molecule in the M→M-(H+HCN) process requires 78% retention. This result is therefore in accord with a complete randomization of the hydrogens in the molecule before loss of HCN, and it shows that hydrogens in the

benzene ring do indeed participate in the loss of HCN.

The deuterium labelling results on the monomethylquinolines, therefore, suggest that formation of ring expanded species before loss of hydrogen is likely, but they do not suggest a mechanism for the ring expansion process. However, the ring expansion of 2-methylquinoline may be visualized as proceeding by the sequence shown in Scheme 16. If the exocyclic carbon was C^{13} enriched, then two possible ions, 57 and 58, could be formed on ring expansion. Insertion of the exocyclic carbon between the C-2 to C-3 bond would give ion 57, and insertion between the N to C-2 bond would result in ion 58. The spectrum of 2-methylquinoline-2-α-C^{13} (Scheme 16) was therefore determined and 80% retention of C^{13} was observed on loss of HCN. This would suggest that the pathway to ion 57 predominates if such a mechanism is indeed adequate. In 2-methylquinoline-2-C^{13} (which was not prepared in this investigation) insertion of the exocyclic carbon between the C-2 to C-3 bond would result in ion 58, and 80% loss of label should be observed on loss of HCN (assuming that the phenyl carbon adjacent to the nitrogen does not participate in expulsion of HCN).



Scheme 16

The labelling results of Meyer and Harrison on the methylethylbenzenes suggest that formation of the tropylium ion occurs by insertion of the exocyclic carbon between any two carbon-carbon bonds in the original molecule (55). Thus, it is also conceivable that ring expansion in 2-methylquinoline may proceed by insertion of the exocyclic carbon between any two carbon-carbon or carbon-nitrogen bonds in the pyridine ring, or perhaps even between any two bonds in the molecule. Since the carbon-nitrogen and various carbon-carbon bond strengths in the 2-methylquinoline molecule differ from one another, it would be difficult to predict the results of C^{13} labelling experiments on a

statistical basis only. The results of the single C^{13} labelling experiment in this study therefore cannot be used to confirm or disprove that ring expansion occurs by random insertion of the exocyclic carbon.

However, Marx and Djerassi have recently published the results of a study in which they determined the spectra of the 1-methylisoquinolines labelled in the C-1 and in the exocyclic methyl positions, and they were able to account for 80% of the label by a mechanism similar to that shown in Scheme 16 (2). Therefore, this simple mechanism appears to be adequate to account for ring expansion in the isoquinoline series and possibly can be applied to the methylquinolines. The result obtained in this study is in accord with those of Marx and Djerassi in that insertion of the exocyclic carbon between a carbon-carbon bond is favoured over insertion between a carbon-nitrogen bond.

It has been observed that the relative abundance of the M-1 ion in the spectrum of toluene is much greater than the M-1 intensities in the spectra of the methyl-pyridines which suggests that formation of a tropylium ion from toluene is a lower energy process than formation of an azatropylium ion from the methylpyridines. Thus, the azatropylium ion may be a higher energy species than the tropylium ion. (The appearance potential of the

tropylium ion from toluene is about 0.5 eV less than that of the azatropylium ion from the methylpyridines.)

By analogy, the initial ring expanded ion formed from the methylquinolines substituted in the benzene ring may be a lower energy species than that from the methylquinolines substituted in the pyridine ring. This could explain the greater M-(H+HCN)/ M-H peak intensity ratio in the quinolines substituted in the pyridine ring since HCN would be more readily eliminated from a higher energy species.

In summary of this section, it appears that the labelling results on the monomethylquinolines may be readily explained in terms of formation of ring expanded ions before loss of hydrogen. Although the structures shown in Scheme 15 are consistent with the experimental results, it does not necessarily follow that such species actually exist. A considerable amount of evidence is available to suggest that fragmentation of many organic molecules occurs in the lowest electronic state of the ion, but a large amount of excess energy is probably present in the form of vibrational energy. Therefore, the ground state structures (shown in Scheme 15) for the molecular and fragment ions of the monomethylquinolines may not adequately represent the actual structures of the more energetic species formed on electron bombardment.

An alternative structure for the M-1 ion in the spectra of the monomethylquinolines might be a linear polyacetylene type ion in which the hydrogens become randomized. Thus, Alpin and Safe note that the spectra of some C_{12} polyacetylenes are nearly identical with the spectra of the methylnapthalenes (58). They suggest that the acetylenes rearrange to the stable benztropylium cation but a possible equilibrium between the cyclic and open chain species cannot be excluded. On the other hand, Meyerson's C^{13} labelling studies on toluene suggest that an open chain species does not contribute significantly in the fragmentation of toluene.

The intermediacy of azafulvene or azaprismane type ions could also be postulated to account for the labelling results on the monomethylquinolines. The intermediacy of such species has been proposed to account for the hydrogen scrambling observed in pyridine where ring expansion is impossible (69), but their possible intermediacy in systems where ring expansion is possible does not seem to have been seriously considered.

Other peaks in the mass spectra of the monomethylquinolines are of low intensity and the mechanism of their formation does not appear to be straightforward. Peaks at M-26 (m/e 117) and M-27 (m/e 116) are of interest, however, since they complicate the calculation of label

retention in the M-(H+HCN) ion in the labelled derivatives. Exact mass measurements show that the M-26 ion in both the 2- and 4-methylquinolines arises through loss of C_2H_2 rather than CN. [calculated for C_8H_7N 117.0578, observed 117.0585 (2-methylquinoline) and 117.0581 (4-methylquinoline)]. The labelling studies suggest that the loss of C_2H_2 is not specific.

The peak at m/e 116 (M-27) in the spectra of the 2- and 4- methyl isomers consists of two ions in addition to the C^{13} isotope peak of the m/e 115 ion. In the spectrum of 2-methylquinoline the peak corresponding to loss of C_2H_3 is about four times the intensity of the M-HCN peak (calculated for C_8H_6N 116.0500, observed 116.0509; calculated for C_9H_8 116.0626, observed 116.0631), while the $M-C_2H_3$ and M-HCN peaks are of nearly equal intensity in the spectrum of the 4-methyl isomer (observed 116.0508 and 116.0632, respectively). The difference in relative intensities of the two peaks in the 2- and 4- isomers seems reasonable since elimination of HCN from 4-methylquinoline requires less rearrangement and should, therefore, occur to a greater extent than elimination of HCN from 2-methylquinoline. The labelling experiments suggest that considerable hydrogen rearrangement occurs prior to loss of HCN but the results are difficult to interpret since the M-27 peak is a doublet.

The most intense fragment ion in the spectrum of quinoline corresponds to loss of HCN, and since competing reactions appear to be less important than in the methylquinolines, the mechanism of HCN elimination from quinoline should be easier to interpret. The mechanism might then be applied to direct loss of HCN from the monomethylquinolines. With this aim in mind, the spectrum of quinoline-2-d was recorded and about 60% of the deuterium was found to be retained on loss of HCN. This is reasonably close to the 67% retention expected from randomization of the hydrogens in the pyridine ring, and is also in accord with the results reported for pyridine where the hydrogens become randomized before loss of HCN (69). In analogy to the mechanism proposed to account for the scrambling in pyridine (69), the intermediacy of benzazafulvene and/or benzazaprismane ions could be postulated to account for the scrambling observed in the quinoline system. Since ring expansion is impossible in pyridine and it still shows an intense M-HCN peak, there is no reason to suppose that ring expansion occurs in the direct elimination of HCN from either quinoline or the methylquinolines. Further labelling studies with C^{13} would be required to determine whether carbon rearrangement does indeed occur in elimination of HCN from the pyridine and quinoline systems.

The M-HCN ion in the spectra of the monomethylquinolines is a radical ion, and it is likely that this ion loses H to give an even electron species. The contribution of this pathway to the M-28 peak is probably small since the M-HCN peak is of low intensity relative to the M-28 peak.

Dimethylquinolines

In this study, the mass spectra of 18 of the 21 isomeric dimethylquinolines were determined. The relative intensities of the major fragment ions as well as the $M-(CH_3+HCN)/M-CH_3$ peak intensity ratios are listed in Table IV, and the spectra of four representative isomers are recorded in Fig. 5a-d. Sample et al. recorded only the spectra of 2,3- and 2,4-dimethylquinoline (1). They discussed the formation of ions at M-1, M-28 and M-42 in these compounds, but failed to mention the peak at M-15 which is present in the two compounds and which is prominent in the spectra of all the dimethylquinolines examined in this study. It was implied that the M-42 ion in the 2,3- and 2,4- isomers formed through loss of CH_3CN from the M-1 ion.

The results of this work indicate that the major pathway to the M-42 ion proceeds through the sequence

Table IV

Mass Spectra of Dimethylquinolines

	M+	M-H	$M-CH_3$	$M-(H+HCN)$	$M-(CH_3+HCN)$	$\frac{M-(CH_3+HCN)}{M-CH_3}$
2,3	100	22	12	6	25	2.1
2,4	100	14	8	5	14	1.8
2,6	100	33	9	3	10	1.1
2,7	100	26	12	4	12	1.0
2,8	100	28	10	4	10	1.0
3,4	100	38	40	10	17	0.42
3,5	100	34	22	6	8	0.36
3,6	100	34	20	6	8	0.40
3,7	100	34	20	8	10	0.50
3,8	100	30	16	4	6	0.38
4,6	100	31	16	4	6	0.38
4,8	100	26	14	5	5	0.36
5,6	100	34	86	6	8	0.09
5,7	100	40	47	5	6	0.12
5,8	100	52	34	3	4	0.12
6,7	100	38	45	5	6	0.13
6,8	100	32	34	4	4	0.12
7,8	100	54	30	10	4	0.13

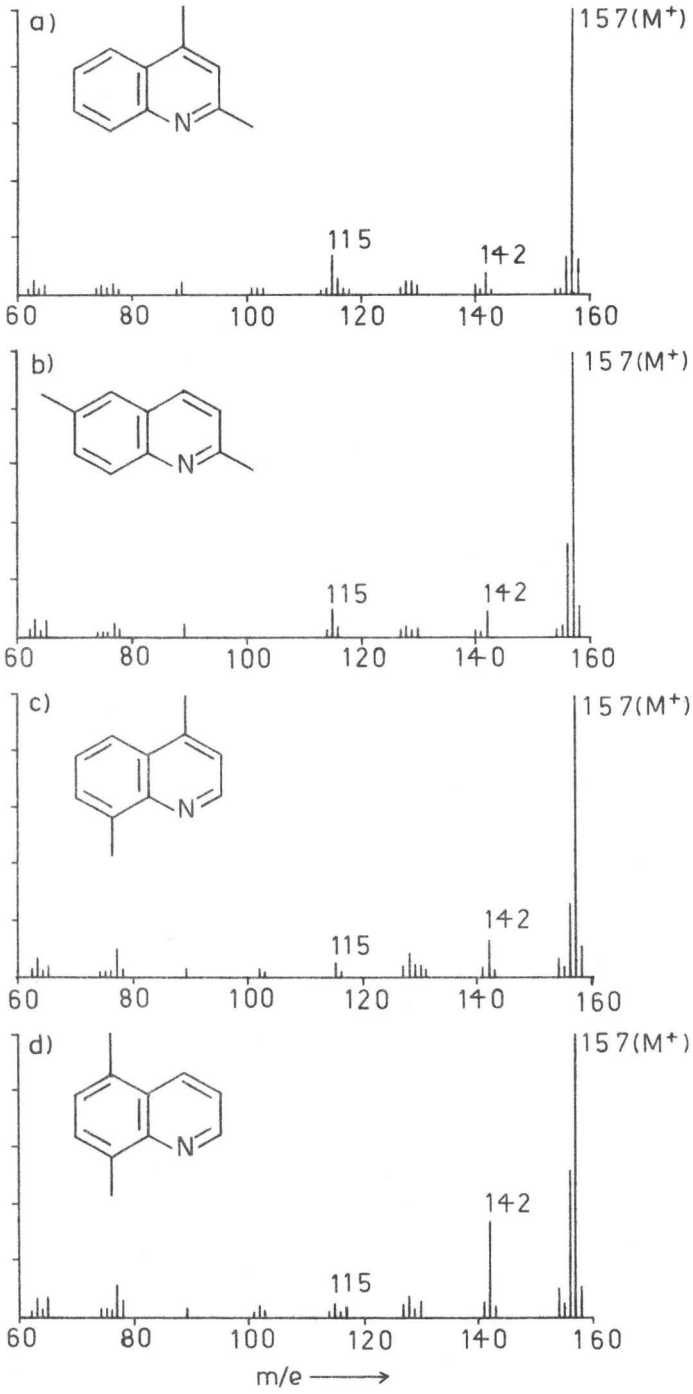


Figure 5. Mass spectra of a) 2,4-dimethylquinoline, b) 2,6-dimethylquinoline, c) 4,8-dimethylquinoline and d) 5,8-dimethylquinoline.

$M \rightarrow M-CH_3 \rightarrow M-(CH_3+HCN)$ although the transformation $M-H \rightarrow M-(H+CH_3CN)$ may contribute in the 2- substituted dimethylquinolines. The former sequence is supported by the presence of metastable peaks corresponding to the two transformations in the spectra of all the isomers which were examined (Table V). Moreover, the loss of acetonitrile from M-H in a single step, as suggested by the earlier workers, in any but the 2- substituted dimethylquinolines would require extensive rearrangement.

Table V

Metastable Ions Observed in the Spectra of Dimethylquinolines

Transformation	Calcd.	Obs.	Obs. in the spectra of
M→M-1	155.0	155.0	all isomers
M→M-15	128.4	128.6	all isomers
M-1→M-28	106.7	106.8	all isomers
M-1→M-29	105.0	105.0	all isomers
M-15→M-42	93.1	93.2	all isomers
M→M-41	85.7	86.0	2,3-,2,4-,2,6-,2,7-,2,8-
M-42→M-66	68.9	69.0	all isomers

Another possible route to the M-42 ion, namely

$M \rightarrow M-CH_3CN \rightarrow M-(CH_3CN+H)$ is also likely in all the 2-substituted dimethylquinolines. Thus, a metastable peak at m/e 86.0 corresponding to the transition $M \rightarrow M-CH_3CN$ has been observed in the spectra of these isomers, and the M-41 peak is more intense than expected of an isotope peak of M-42. The $M-CH_3CN$ species is a radical ion and further loss of H to form an even electron ion is likely.

Examination of the $M-(CH_3+HCN)/M-CH_3$ ratios in Table IV shows that the dimethylquinolines can be divided into four groups in order of decreasing ratios, namely, i) 2,3- and 2,4-dimethylquinoline, ii) other 2-substituted dimethylquinolines, iii) 3,4-dimethylquinoline and dimethylquinolines with a methyl group in each ring but excluding those in ii), and iv) dimethylquinolines having both methyl groups in the benzene ring. The order parallels that observed with the monomethylquinolines where the M-1 ion formed from methylquinolines with a substituent in the pyridine ring exhibits a greater tendency to eliminate HCN than the M-1 ion from methylquinolines substituted in the benzene ring. These differences are useful in the partial identification of an unknown dimethylquinoline by mass spectrometry.

The presence of peaks at M-1 and M-15 in the spectra of all the dimethylquinolines is reminiscent of

the behaviour of the xylenes. Results of labelling studies on the xylenes show that extensive rearrangement, possibly to a ring expanded ion, occurs before loss of H or CH_3 (54). Similarly, it seems likely that CH_3 loss from the dimethylquinolines occurs from a rearranged (possibly ring expanded) species since the monomethylquinolines (2-methylquinoline excepted) show little tendency to lose methyl. Even the dimethylquinolines with methyl groups in different rings exhibit fairly intense M-15 peaks in their spectra which indicates that a significant degree of interaction occurs between the two rings.

It was anticipated that deuterium labelling experiments on the dimethylquinolines might be useful in further elucidating their fragmentation mechanisms, and that analogies to the labelling results on the xylenes could perhaps be drawn. With this aim in mind, several labelled dimethylquinolines were prepared and their spectra determined. The spectra of these compounds (at least one example from each of the four groups of dimethylquinolines mentioned earlier) are recorded in Fig. 6a-e, and the results are summarized in Table VI. In Table VI the $M-CH_3/M-CD_3$ peak intensity ratios and the label retention in the process M→M-H are listed for the various labelled compounds. The procedure used for calculating label

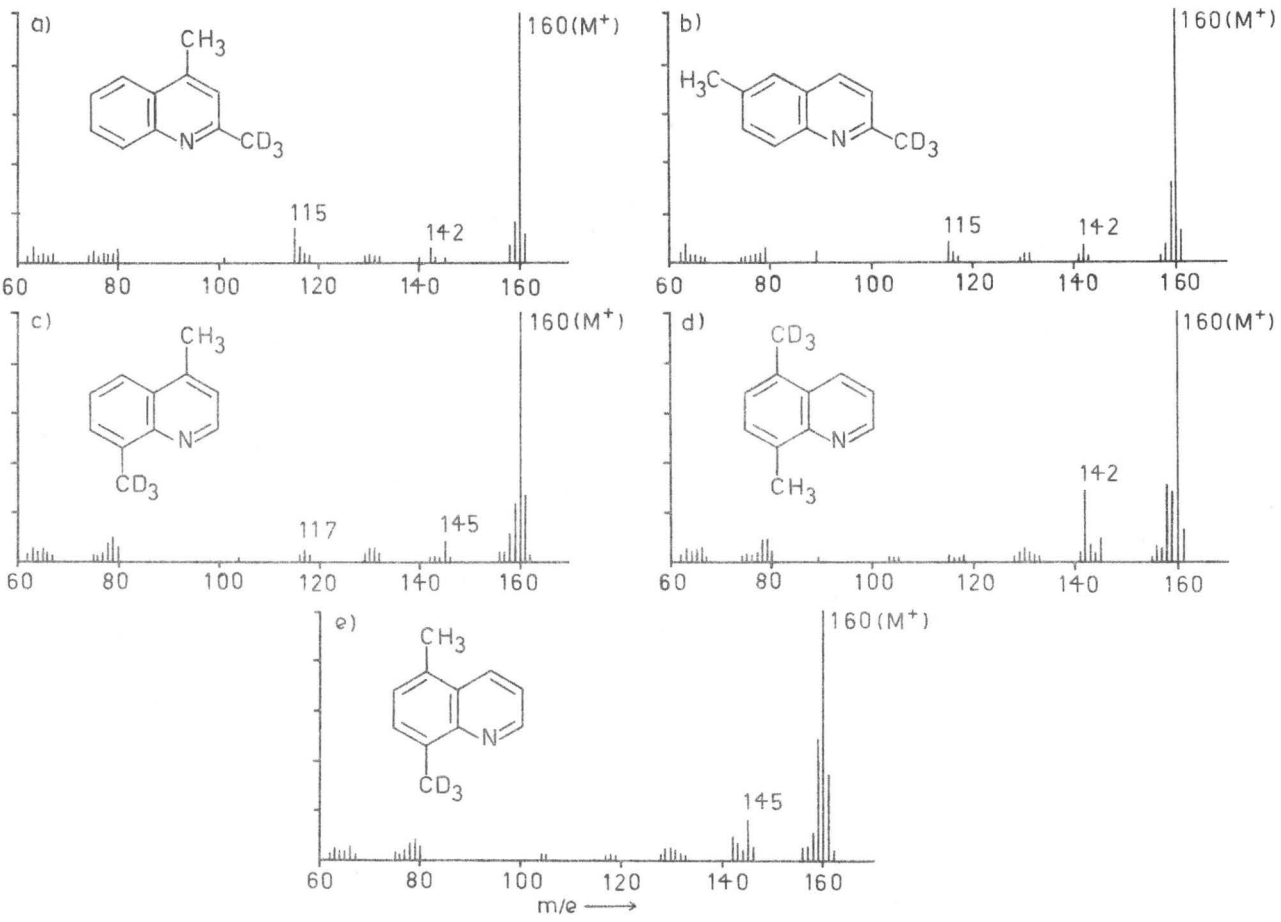


Figure 6. Mass spectra of a) 2,4-dimethylquinoline-2-α-d_3, b) 2,6-dimethylquinoline-2-α-d_3, c) 4,8-dimethylquinoline-8-α-d_3, d) 5,8-dimethylquinoline-5-α-d_3 and e) 5,8-dimethylquinoline-8-α-d_3.

retentions was similar to that described for the monomethylquinolines.

Table VI

Mass Spectra of Labelled Dimethylquinolines

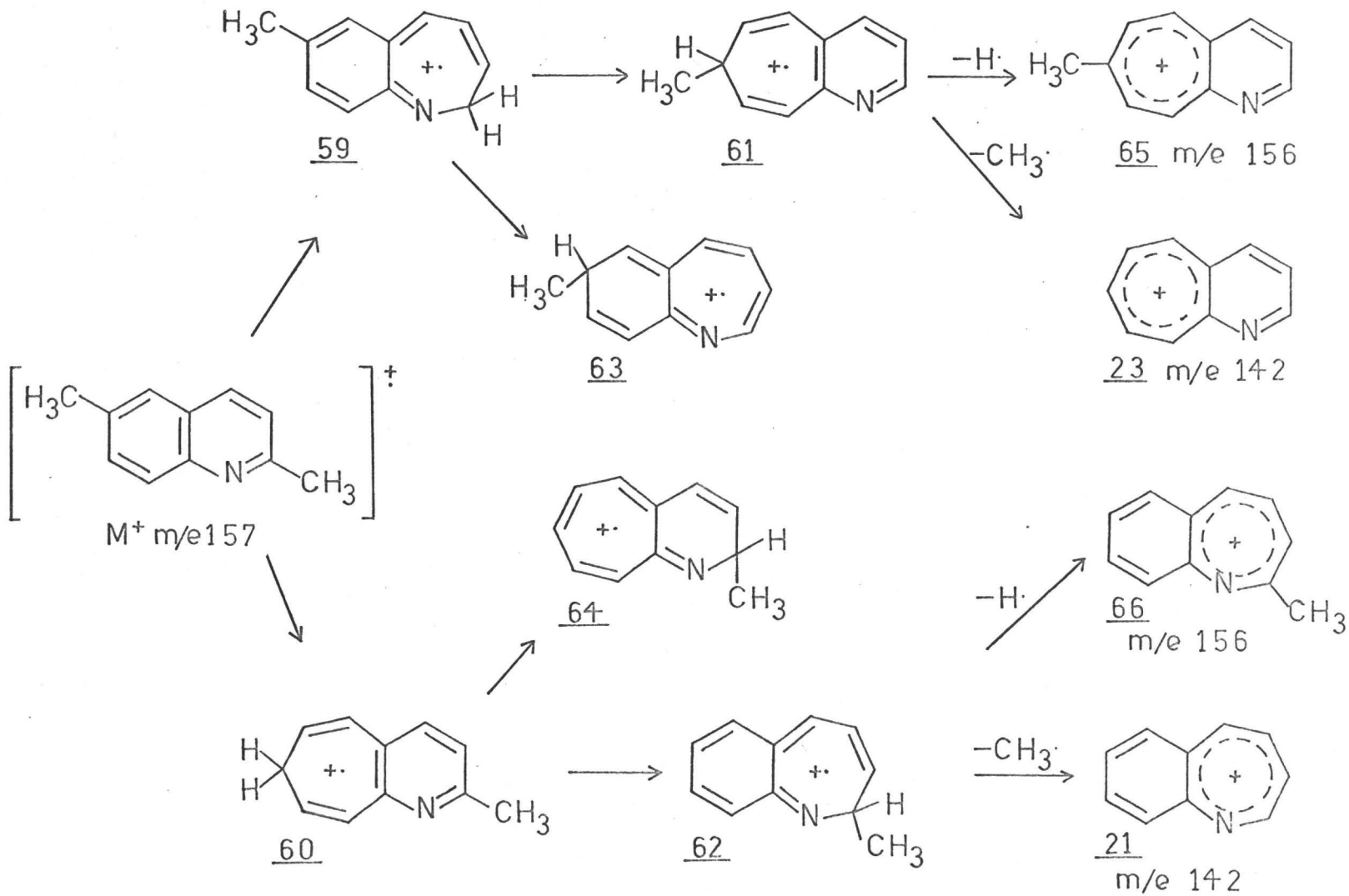
Compound	$M-CH_3/M-CD_3$	% retention (M→M-H)
2,4-dimethylquinoline-2-α-d_3	1:2.5	77
2,6-dimethylquinoline-2-α-d_3	1:5	85
4,8-dimethylquinoline-8-α-d_3	4:1	64
5,8-dimethylquinoline-5-α-d_3	1:3	40
5,8-dimethylquinoline-8-α-d_3	2:1	86

Preliminary examination of the results in Table VI shows that the two methyl groups in the labelled compounds are not lost with equal facility, nor does the hydrogen loss in the M→M-H process appear to be random from the molecule. Complete randomization of three deuteriums and eight hydrogens in the molecule would result in 73% retention of label. That the two methyl groups are not lost equally readily is not surprising since the dimethylquinoline molecule is not a symmetrical system.

Comparison of the spectra of the undeuterated and deuterated dimethylquinolines (Fig. 5 and 6) shows that

some scrambling occurs on loss of methyl from the labelled derivatives. In other words, the methyl group lost does not consist entirely of the original methyl hydrogens. The extent of scrambling appears to vary among the isomers but a quantitative estimation is difficult because of contributions from peaks observed at M-16 and M-17 in the spectra of the undeuterated compounds. In all cases, the scrambling appears to be considerably less than that observed in the spectra of the xylenes where the data indicated that one of the methyl hydrogens has a 50:50 chance of exchanging with a ring hydrogen before loss of methyl (54).

In the dimethylquinolines, ionization and ring expansion may result in formation of two ring expanded ions since there are two exocyclic methyl groups which may participate in the ring expansion process. Thus, ions represented by structures 59 and 60 may be formed from ring expansion involving the C-2 and C-6 methyl groups, respectively, in 2,6-dimethylquinoline (Scheme 17). Loss of methyl does not involve extensive scrambling of the methyl and side chain hydrogens so it appears that equilibration between ions 59 and 60 is relatively unimportant. Since a simple phenyl-methyl cleavage is not observed in the monomethylquinolines (2-methylquinoline excepted) further rearrangement of ions 59 and 60 to ions



Scheme 17

61 and 62, respectively, might be postulated. Alternatively, ions 59 and 60 may rearrange to 63 and 64 respectively, by a series of 1,2-hydrogen shifts. Formation of 63 and 64 requires less skeletal rearrangement than does formation of ions 61 and 62. In either case, both H and CH_3 may be lost from a methylene position. Expulsion of H or CH_3 from 61 may lead to ions 65 or 23, respectively, while loss of H or CH_3 from 62 leads to 66 or 21 respectively. The extent to which H and CH_3 is lost from each of the rearranged ions would be difficult to estimate without a knowledge of the relative energies of the reactant and product ions.

The results from the spectra of the monomethylquinolines suggest that ring expansion in the benzene ring is a lower energy process than ring expansion in the pyridine ring. Thus, ion 60 may be a lower energy species and should be more abundant than the higher energy species 59. Rearrangement and loss of methyl from 61 (or 63) results in expulsion of the 6-methyl while the 2-methyl is lost from ion 62 (or 64). If it is assumed that CH_3 is lost with equal facility from 61 or 62, then a greater loss of the 2-methyl should be observed since ion 62 is formed in greater abundance than 61. The spectrum of 2,6-dimethylquinoline-2-α-d_3 shows that loss of the C-2 methyl is favoured over loss of methyl from C-6 by a ratio of about 5:1. Thus, the

favoured loss of methyl from C-2 in the spectrum of 2,6-dimethylquinoline may be explained by assuming that two separate ring expansion processes occur and that one is favoured energetically over the other.

The spectrum of 4,8-dimethylquinoline-8-α-d_3 shows that loss of methyl from C-4 is favoured over loss of methyl from C-8 and this may similarly be explained by assuming that ring expansion involving the C-8 methyl is favoured over ring expansion involving the C-4 methyl. Loss of the C-2 methyl is favoured over loss of the C-4 methyl in the spectrum of 2,4-dimethylquinoline-2-α-d_3 which suggests that ring expansion involving the C-4 methyl may be slightly favoured over ring expansion involving the C-2 methyl. Simple α-cleavage of the 2-methyl group (in analogy with loss of CH_3 from 2-methylquinoline) may also contribute to the favoured loss of the 2-methyl in the 2- substituted dimethylquinolines.

The spectra of the labelled 5,8-dimethylquinolines show that loss of the C-5 methyl is favoured over loss of the C-8 methyl which suggests that the two possible ring expanded ions 67 and 68 (Scheme 18) are not formed in equal abundance, or that loss of methyl from the two ions does not occur with equal facility. It should be noted that the M-CH_3/M-CD_3 peak intensity ratios in the

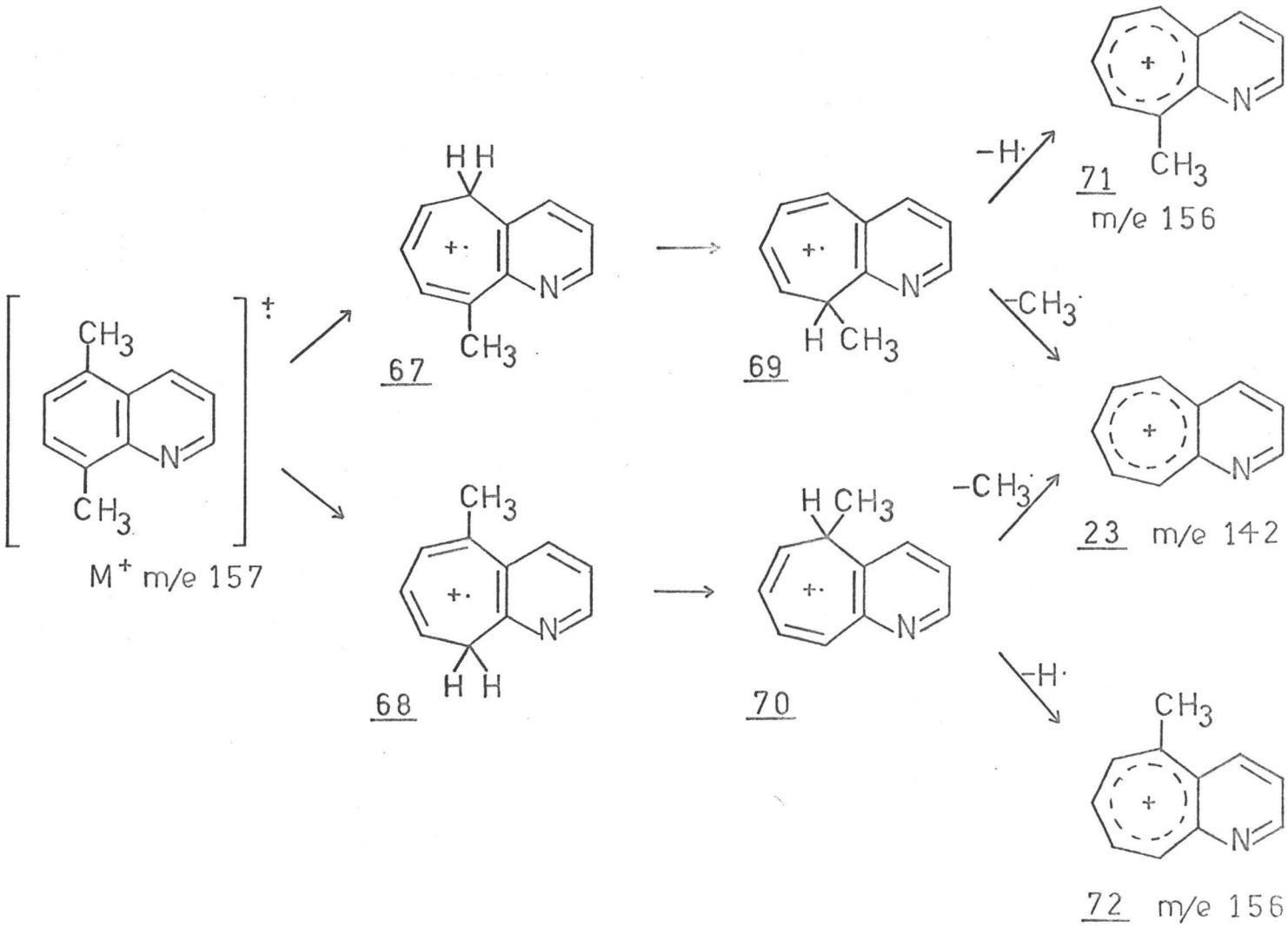
two labelled 5,8-dimethylquinolines are not the inverse of one another as might be expected. The difference could be attributed to a mass effect in which the heavier CD_3 is lost more readily than CH_3. A similar effect is observed in the spectrum of 2-isopropylquinoline-2-β-d_3 (Fig. 8c) where the two methyl groups are equivalent.

In Scheme 17 it is proposed that both H and CH_3 are lost from the same intermediates. A correlation should therefore be observed between the label retention in the M→M-H process and the M-CH_3/M-CD_3 ratios in the spectra of the deuterated compounds. Randomization of all nine hydrogens in the molecule appears to occur before loss of H in the spectra of the monomethylquinolines, while in the dimethylquinolines only the ring and side chain hydrogens participating in the ring expansion process will be randomized. The hydrogens in the remaining methyl group will be lost in the transformation M→M-CH_3. Thus, in the spectrum of 2,6-dimethylquinoline-2-α-d_3 ring expansion and rearrangement by the sequence $M^+ \rightarrow \underline{60} \rightarrow \underline{62}$ will result in 100% retention of label in the M→M-H process, while ring expansion involving the C-2 methyl should result in a randomization of the three methyl deuteriums and the five ring hydrogens. Since the former sequence (in which 100% retention of deuterium is observed) appears

to predominate then a high retention of deuterium should be observed, and such is actually the case. The results on 2,4-dimethylquinoline-2-α-d_3 are also roughly in accord with loss of H from two ring expanded intermediates.

Similarly, the M-CH_3/M-CD_3 peak intensity ratios in the spectrum of 4,8-dimethylquinoline-8-α-d_3 suggest that ring expansion involving the C-8-methyl occurs to a greater extent than expansion at the C-4 methyl. Ring expansion at C-8 with randomization of the three deuteriums and five hydrogens should result in 62.5% retention of label on loss of H, while ring expansion to the C-4 methyl results in 100% retention of label. For example, if 80% of the H lost originates through ring expansion involving the C-8 methyl, and 20% by ring expansion involving the C-4 methyl, then the expected label retention would be 0.8 x 62.5 + 0.2 x 100 = 70%. The 64% retention of label observed in the spectrum of 4,8-dimethylquinoline-8-α-d_3 is relatively close to this value.

Ionization and ring expansion of 5,8-dimethylquinoline may result in formation of two ring expanded species 67 and 68 as shown in Scheme 18. It would be expected that ring expansion involving the C-5 and C-8 methyls should occur to about the same extent since the spectra of 5- and 8-monomethylquinolines are nearly



Scheme 18

identical. However, ions 67 and 68 are not identical in structure and they are therefore not necessarily formed in equal abundance. Rearrangement of ions 67 and 68 to ions 69 and 70, respectively, might be proposed since H and CH_3 may be lost from a methylene position (55). Loss of H or CH_3 from 69 yields 71 or 23, respectively, while loss of H or CH_3 from 70 results in 72 or 23.

The labelling results show that loss of the C-5 methyl is favoured over loss of the C-8 methyl in the transformation M→M-15, and this might suggest that ring expansion to ion 68 occurs more readily than ring expansion to 67. However, if ion 68 is more abundant than ion 67, then loss of a C-8 methyl hydrogen in the process M→M-H should occur to a greater extent than loss of a hydrogen from the C-5 methyl, and this is contrary to the labelling results. Alternatively, the position of the methyl group in the rearranged molecular ions 69 and 70 may influence the manner in which they fragment, and the relative stabilities of the fragment ions 71, 23 and 72 may also influence the fragmentation of 69 and 70. Thus, ion 69 may fragment preferably by loss of H (some of which may originate from the C-5 methyl), while loss of the C-8 methyl may be less important. On the other hand, ion 70 may fragment mainly by loss of the 5-methyl, while expulsion of H (which originates from the ring and

C-8 methyl) may be less important.

From the above discussion, therefore, the favoured loss of methyl from C-5 does not appear too unreasonable, nor is the 86% retention of label observed in the transformation M→M-H in the 8-α-d_3 derivative unreasonable. However, the low M-H/M-D peak intensity ratio in the 5-α-d_3 derivative cannot be explained by this mechanism. The result for this compound suggests that some loss of H from the C-5 methyl may occur before ring expansion, or H may be lost from the methylene position in the ring expanded species 67 before complete randomization has occurred. A slight preference for loss of the methyl hydrogens over ring hydrogens has been observed in the spectrum of toluene (105), but it is much smaller than that observed in the 5-α-d_3 derivative. No explanation is offered to account for the anomalous behaviour of this compound.

To account for the labelling results on the dimethylquinolines, it has been suggested that loss of H and CH_3 may proceed from two possible ring expanded ions, and that one of the ions may be favoured energetically over the other. If this is the case, then formation of the lower energy species should predominate to an even greater extent when the energy of the ionizing electrons (the ionization voltage) is decreased. In other words,

the $M-CH_3/M-CD_3$ peak intensity ratios in the spectra of the labelled dimethylquinolines should depend on the ionization voltage. If, on the other hand, methyl is lost from a single species, then the $M-CH_3/M-CD_3$ peak intensity ratios should be independent of the ionization voltage.

To show that loss of methyl may indeed originate from two species of different energy, the spectra of some of the deuterated compounds were determined at varying electron energies, and the results are summarized in Table VII. The ionizing voltages shown in Table VII are those registered by the ionization gauge and do not necessarily represent the absolute values. The repeller voltages were maintained at a constant value (2V) for all the readings.

Table VII

Dependence of $M-CH_3/M-CD_3$ Ratios on Ionizing Voltage

ionizing voltage	$M-CH_3/M-CD_3$ 4,8-dimethyl-quinoline-8-α-d_3	5,8-dimethyl-quinoline-5-α-d_3	5,8-dimethyl-quinoline-8-α-d_3
80	4.5	0.33	1.8
20	6.3	0.34	2.0
16	8.4	0.33	2.2
14	9.1	0.31	2.3
12.5	9.1	0.29	2.4
11.5	9.1	0.27	2.5
11	-	0.27	-

The results in Table VII show that the $M-CH_3/M-CD_3$ peak intensity ratios depend on the energy of the ionizing electrons in all the compounds examined. In the spectrum of 4,8-dimethylquinoline-8-α-d_3, the $M-CH_3/M-CD_3$ peak intensity ratio increases from about 4.5 at 80 eV to 9.1 at 11.5 eV, and this is in accord with the lower energy process (ring expansion in the benzene ring with expulsion of the C-4 methyl) occurring to a greater extent relative to the higher energy process at lower ionizing voltages. The change in $M-CH_3/M-CD_3$ ratios in the spectra of the labelled 5,8-dimethylquinolines is considerably less dramatic, but the results from both compounds suggest that expulsion of the C-5 methyl requires somewhat less energy than expulsion of the C-8 methyl group.

Further fragmentation of the M-1 and M-15 ions in the spectra of the dimethylquinolines appears to proceed by loss of HCN. Expulsion of CH_3CN from an α-methylazatropylium ion (ion 66) may also occur. The extent of hydrogen scrambling in the M-(H+HCN) and M-(CH_3+HCN) ions in the spectra of the deuterated compounds is difficult to estimate because of the adjacent peaks found in the spectra of the unlabelled compounds. The M-(CH_3+HCN) peak (m/e 115) in the spectra of 2,4- and 2,6-dimethylquinoline is found mainly at m/e 115 in the

spectra of the labelled derivatives since most of the label is lost as CD_3. In the spectrum of 4,8-dimethylquinoline-8-α-d_3 most of the methyl is lost as CH_3, and peaks at m/e 117 and 118 which may arise through loss of DCN and HCN, respectively, from M-CH_3 are observed. Therefore, little information regarding the existence of ring expanded intermediates is obtained on examination of the M-(H+HCN) and M-(CH_3+HCN) ions in the spectra of the labelled dimethylquinolines.

The M-(CH_3+HCN)/M-CH_3 peak intensity ratios in the spectra of the dimethylquinolines may be explained in a similar manner to the M-(H+HCN)/M-H ratios in the spectra of the monomethylquinolines. Thus, ring expansion in the benzene ring is a lower energy process than ring expansion in the pyridine ring, and expulsion of HCN from the lower energy species should occur to a lesser extent than from a higher energy ion. The higher values in the 2,6-,2,7- and 2,8-dimethylquinolines relative to the other dimethylquinolines with a substituent in each ring may be a consequence of a significant contribution to the M-42 ion by the transformations M→M-CH_3CN→M-(CH_3CN+H) and M-H→M-(H+CH_3CN).

In the above discussion an attempt has been made to justify the labelling results on the dimethylquinolines in terms of expulsion of H and CH_3 from ring

expanded ions. Although most of the labelling results and the low voltage studies appear to be compatible with fragmentation by mechanisms similar to those described in this discussion, it does not necessarily follow that such mechanisms adequately represent the fragmentation. It is likely that excess energy in the form of vibrational energy is present in the molecular and fragment ions, and their structures may, therefore, be considerably different from the ground state structures shown in Schemes 17 and 18. It appears that further studies on the mechanism of rearrangement and fragmentation of the xylenes would be useful. The information gained on the more simple molecules could perhaps be profitably applied to the fragmentation of the dimethylquinolines.

Ethylquinolines

The mass spectra of 2-,3-,4-,6- and 8-ethylquinoline, 2-ethylquinoline-2-α-d_2, 2-ethylquinoline-2-β-d_3 and 8-ethylquinoline-8-β-d_3 are recorded in Fig. 7. Examination of Fig. 7 shows that the spectra of the 2- and 8- isomers are similar, but differ from the spectra of the 3-,4- and 6- isomers in the relative intensities of peaks at M-1 and M-15. Thus, it is apparent that the fragmentation of the 2- and 8- isomers is strongly

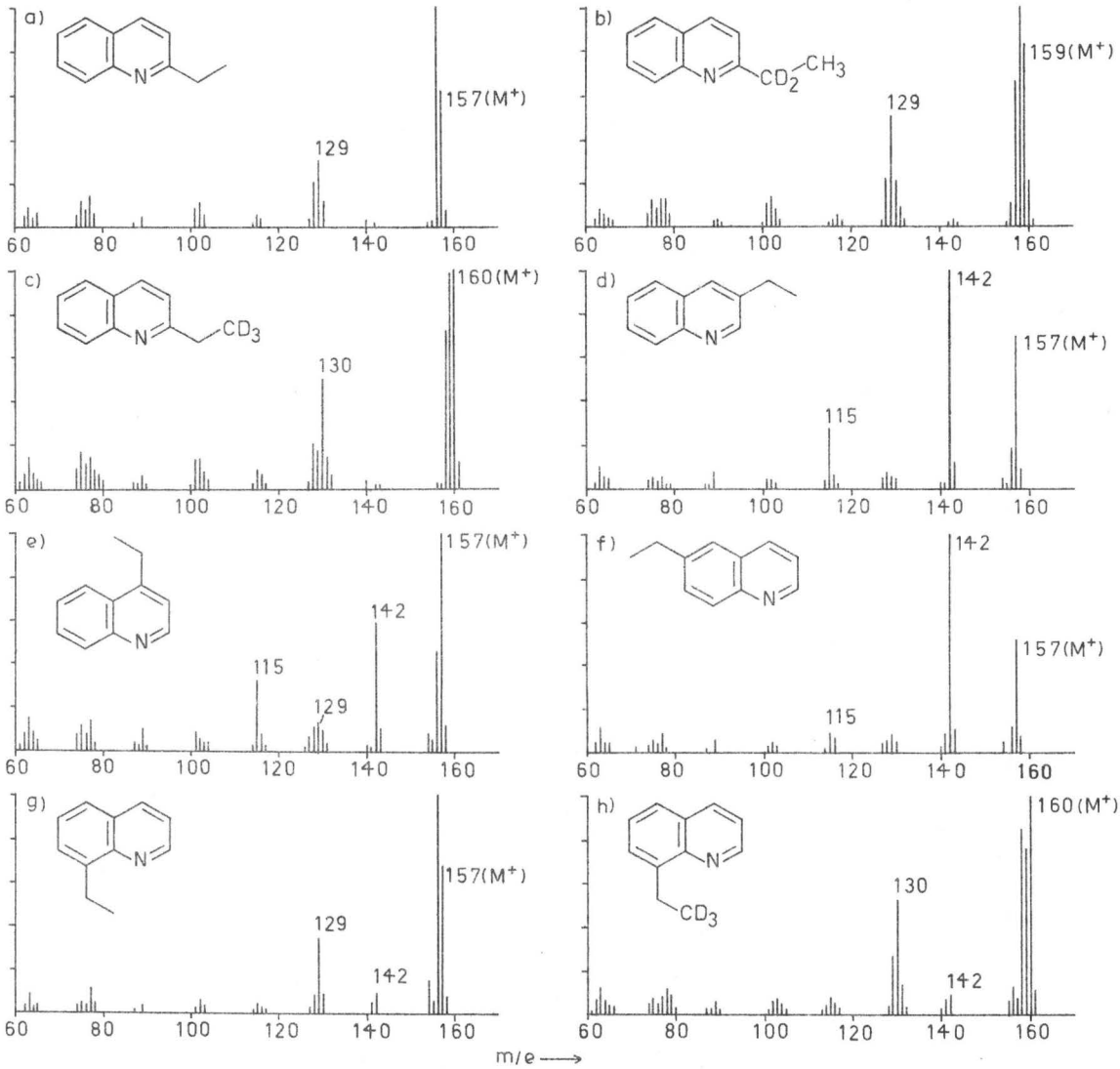
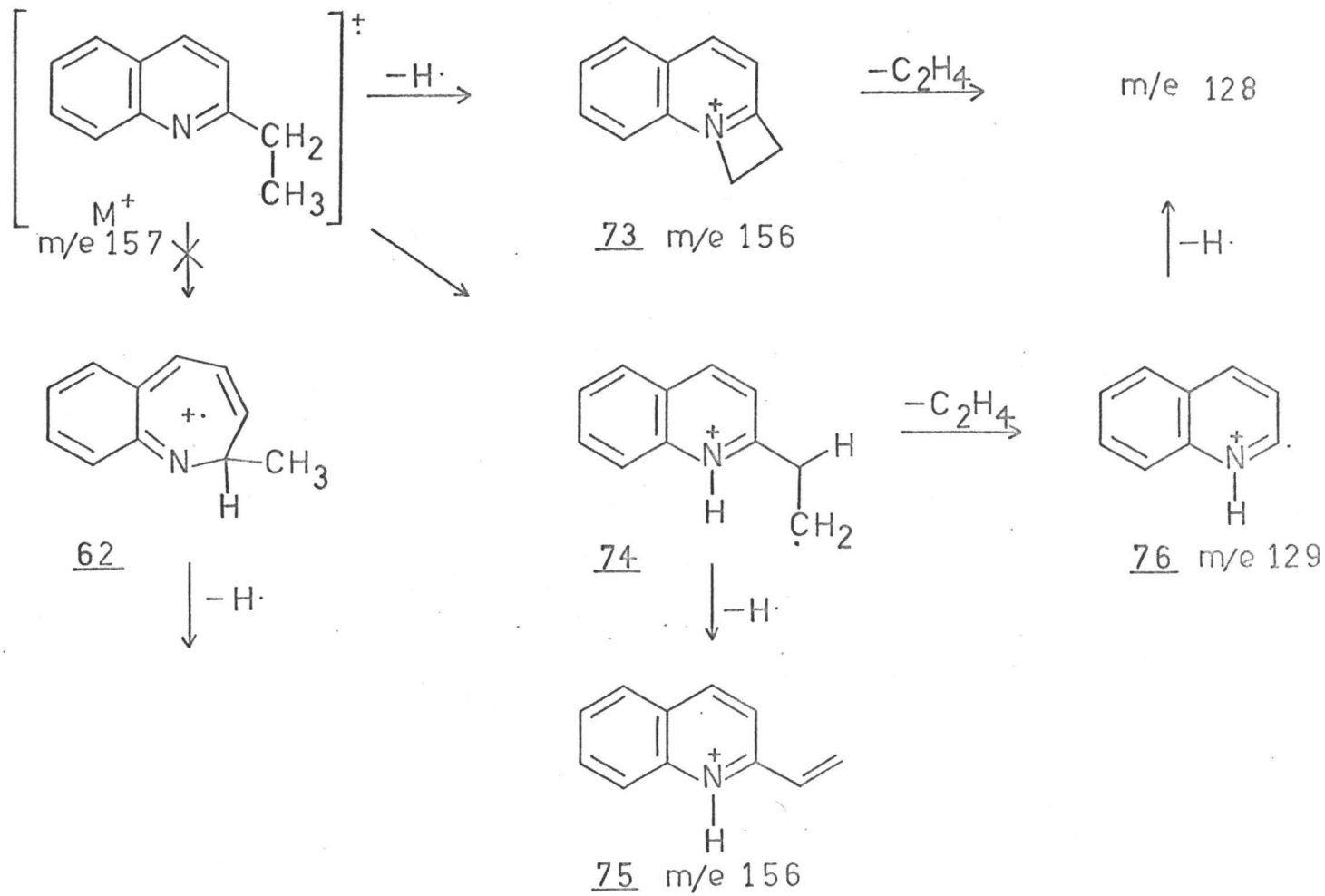


Figure 7. Mass spectra of a) 2-ethylquinoline, b) 2-ethylquinoline-2-α-d_2, c) 2-ethylquinoline-2-β-d_3, d) 3-ethylquinoline, e) 4-ethylquinoline, f) 6-ethylquinoline, g) 8-ethylquinoline and h) 8-ethylquinoline-8-β-d_3.

influenced by the proximity of their alkyl side chains to the nitrogen.

The spectra of 2-ethylquinoline, 2-ethylquinoline-2-α-d_2 and 2-ethylquinoline-2-β-d_3 are recorded in Fig. 7a-c respectively. The spectra of the labelled derivatives show that hydrogen is lost from both the α- and β- carbons in formation of the M-1 ion. Calculations based on the spectra of the labelled compounds show that about 40% of the hydrogen lost originates in the methyl group, and about 40% in the methylene group. The remainder may be the result of a random loss from the nucleus, or there may be an isotope effect favouring loss of H from the side chain. Examination of the spectrum of the 2-α-β-d_5 compound would be required to determine if hydrogen were lost from the nucleus.

The sequence shown in Scheme 19 ($M^+ \rightarrow$ 73) accounts for the hydrogen loss from the β-carbon. In this sequence, a β-hydrogen is lost and the resulting radical is stabilized by cyclization to the nitrogen. This mechanism was earlier proposed to account for the intense M-1 ion observed in the spectra of 2-ethylpyridine (51) and 2-ethylquinoline (1). A second mechanism involving transfer of a β-hydrogen to nitrogen giving ion 74 (Scheme 19), followed by elimination of an α-hydrogen yielding ion 75 is proposed to account



Scheme 19

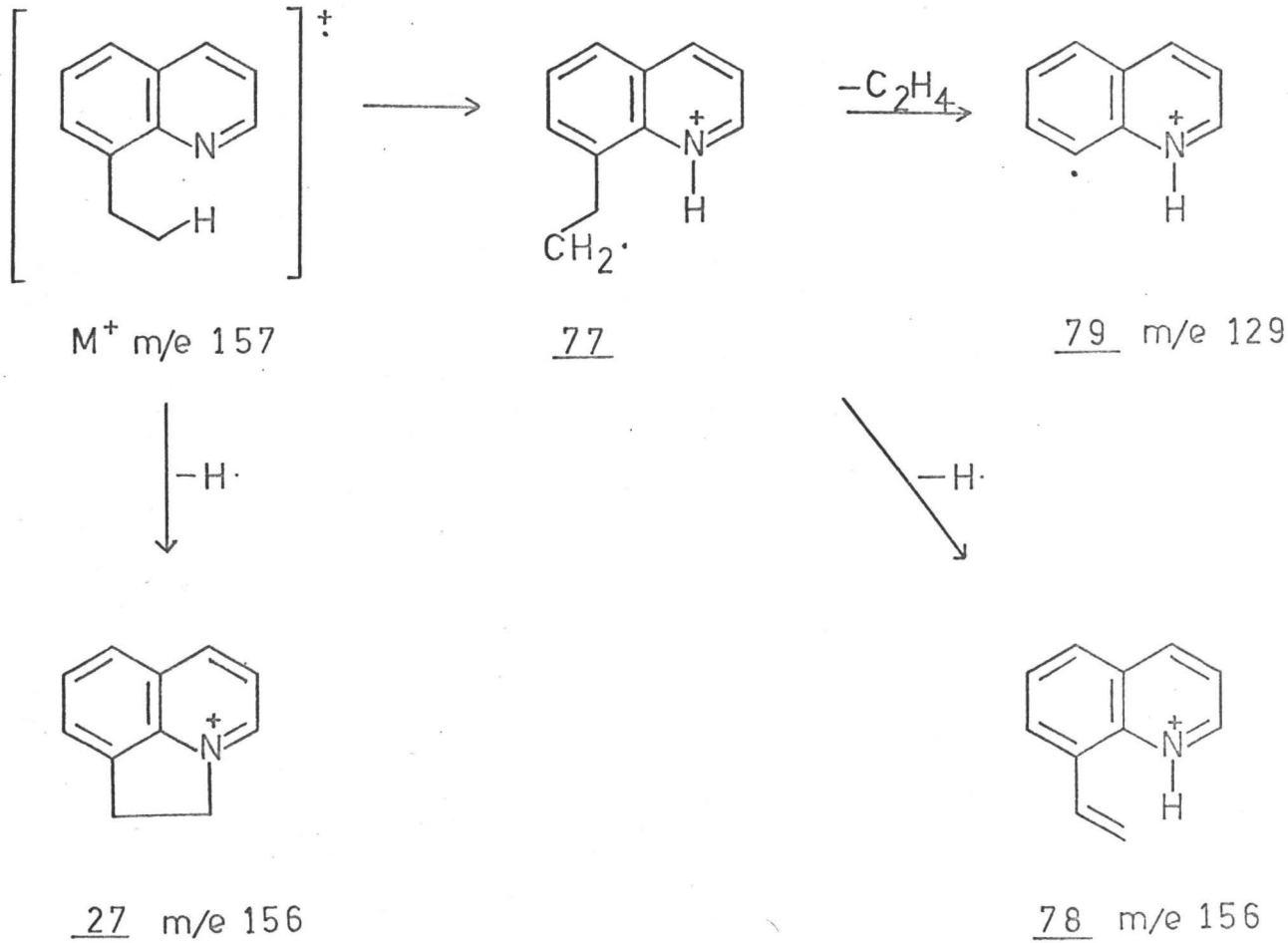
for loss of hydrogen from the α position.

Formation of a ring expanded ion 62 followed by loss of H is an alternative mechanism to account for loss of α-hydrogen. However, an intense M-15 ion (observed in the spectra of the 3-,4- and 6- isomers) would be expected in the spectrum if such a ring expanded species were formed. In addition, random loss of H from the six ring positions and the two α-hydrogens, in analogy with the spectra of the monomethylquinolines, would be expected from a ring expanded ion. This would result in only 15% loss of label in the spectrum of the 2-α-d_2 compound while the observed loss is about 40%.

Other peaks of significant intensity in the mass spectrum of 2-ethylquinoline are found at M-27, M-28 and M-29. The peak at M-28 in the unlabelled compound is shifted to M-30 in the spectra of both the deuterated 2-ethylquinolines. Thus, loss of ethylene from the rearranged molecular ion 74 resulting in ion 76 is a convenient representation of this fragmentation. The M-29 ion in the spectrum of 2-ethylquinoline may arise by loss of C_2H_4 from ion 73, by loss of H from the M-28 ion 76, or by α-elimination of the ethyl group (by analogy with loss of the methyl group from 2-methylquinoline). A significant contribution from the first of these pathways is suggested by the presence of a metastable peak corresponding to the transformation M-1→M-29. In the spectrum of the β-d_3 ana-

logue, the peak is shifted to M-31 and M-32. The M-32 ion is expected for α-cleavage or for loss of $CD_2{=}CH_2$ from ion 73. The M-31 peak suggests a significant contribution from the pathway in which H is lost randomly from ion 76. The spectrum of 2-ethylquinoline-2-α-d_2 is compatible with any of these mechanisms.

The mass spectra of 8-ethylquinoline and 8-ethylquinoline-8-β-d_3 are shown in Fig. 7g and h, respectively. The spectra of the 2- and 8-ethylquinolines are similar but may be differentiated by the more intense M-15 peak in the latter. The most intense fragment ions in the spectrum of 8-ethylquinoline are observed at M-1 and M-28, and the labelling results indicate that these ions are formed by mechanisms similar to those proposed for the corresponding peaks in 2-ethylquinoline. Thus, the spectrum of the deuterated compound shows that about 55% of the M-1 ion originates through loss of a β-hydrogen ($M^+ \rightarrow$ 27, Scheme 20), and the remainder may be derived from the α-carbon through the sequence $M^+ \rightarrow$ 77 $\rightarrow$ 78. Ring expansion with loss of H is an alternative mechanism. The M-28 ion, represented as ion 79, appears to originate from the rearranged molecular ion 77 through loss of ethylene since it is shifted almost quantitatively to M-30 in the spectrum of the deuterated compound. A metastable peak corres-



Scheme 20

ponding to the transition m/e 157→129 is observed at m/e 105.0 in the spectrum of the unlabelled compound.

The loss of methyl yielding the M-15 ion is specific since the peak is quantitatively shifted to M-18 in the spectrum of the 8-β-d_3 analogue. An anomaly in the spectrum of the deuterated compound is the relatively intense peak at M-31. No explanation is offered to account for the presence of this peak, although a small amount of an impurity in the sample is a possibility.

The mass spectra of the 3-, 4- and 6-ethylquinolines (Fig. 7d, e and f), and the 7- isomer recorded by Sample et al. (1) differ considerably from the spectra of the 2- and 8- isomers. Loss of 15 mass units accounts for the major fragment ion in the spectra of the former compounds while loss of H and ethylene are relatively less important processes. Thus, the ethylquinolines in which the alkyl side chain cannot interact with the nitrogen exhibit spectra which are similar to those of the ethylbenzenes.

It is noteworthy that the ratio of peak intensities M-(CH_3+HCN)/M-CH_3 in the spectrum of 4-ethylquinoline is greater than in the spectrum of 3-ethylquinoline, and this is consistent with ring expansion occurring after loss of methyl. Thus, loss of methyl before ring

expansion from 4-ethylquinoline results in a carbonium ion of higher energy than does loss of methyl from 3-ethylquinoline, and HCN would be more readily eliminated from the higher energy species. However, the results of studies on the ethylbenzenes and the results of this work on the mono- and dimethylquinolines would suggest that ring expansion should occur before loss of methyl. Alternatively, ring expansion and loss of methyl may be a concerted reaction in which the relative energy of the carbonium ion is still reflected at the transition state for loss of methyl. Thus, ring expansion presumably accompanies loss of methyl in the spectra of the ethylquinolines, but the timing of the ring expansion process is not evident from the results described in this section.

The spectrum of 6-ethylquinoline (Fig. 7f) is similar to that of 3-ethylquinoline, but the two may be differentiated by the $M-(CH_3+HCN)/M-CH_3$ peak intensity ratios. Elimination of HCN from the M-15 ion is a more favourable process when the ethyl group is in the 3- or 4- position than when it is in the benzene ring, and this behaviour is analogous to that observed in the spectra of the mono- and dimethylquinolines.

The more intense M-1 ion in the spectrum of 4-ethylquinoline relative to that observed in the 3-,

6- or 7- isomers may be a consequence of radical stabilization by cyclization to the 5- position as suggested by other workers (1) for 4-isobutylquinoline. However, no labelling experiments have been carried out to test this hypothesis. If the proposed cyclization is indeed important, then the spectrum of 5-ethylquinoline should also show a more intense M-1 ion due to cyclization to the 4- position. An alternative explanation for the more intense M-1 peak is that the competing pathway (loss of CH_3) appears to be a higher energy process than in the 3-, 6- and 7- isomers.

In Table VIII the metastable peaks observed in the spectra of the ethylquinolines are recorded. They support the mechanisms proposed for the fragmentation of these compounds.

Table VIII

Metastable Ions Observed in the Spectra of Ethylquinolines

Transformation	Calculated	Obs. in the spectra of
M→M-1	155.0	2-,3-,4-,6-,8-
M→M-2		2-α-d_2,2-β-d_3,8-β-d_3
M→M-15	128.4	3-, 4-,6-
M→M-28	106.0	8-
M→M-30	105.6	2-β-d_3
M-1→M-29	105.0	2-,8-
M-2→M-32	103.6	2-β-d_3
M-15→M-42	93.1	3-,4-,6-,8-
M-29→M-56	79.7	2-,8-

In summarizing the spectra of the ethylquinolines, it appears that the 2- and 8- isomers may be differentiated from one another and from the other isomers by mass spectrometry. The remaining isomers fragment in a similar manner, but show sufficient differences that mass spectrometry alone is useful in their identification. The importance of charge stabilization in the product ion in determining the course of fragmentation is also dramatically illustrated by the spectra of the various ethylquinolines.

The ethylquinolines may also be differentiated from the isomeric dimethylquinolines by mass spectrometry. Thus, the intense M-1 peaks in the spectra of the 2- and 8-ethyl isomers, and the intense M-15 peaks in the 3- and 6- isomers readily differentiate them from any of the dimethylquinolines. The spectrum of 4-ethylquinoline may also be differentiated from the spectra of the dimethylquinolines by the relative intensities of peaks at M-1, M-15 and M-42.

Propylquinolines

In Fig. 8 the mass spectra of 2-, 3-, 4-, 6- and 8-n-propylquinoline and 2-isopropylquinoline are recorded. The spectra of 2-isopropylquinoline-2-β-d_3

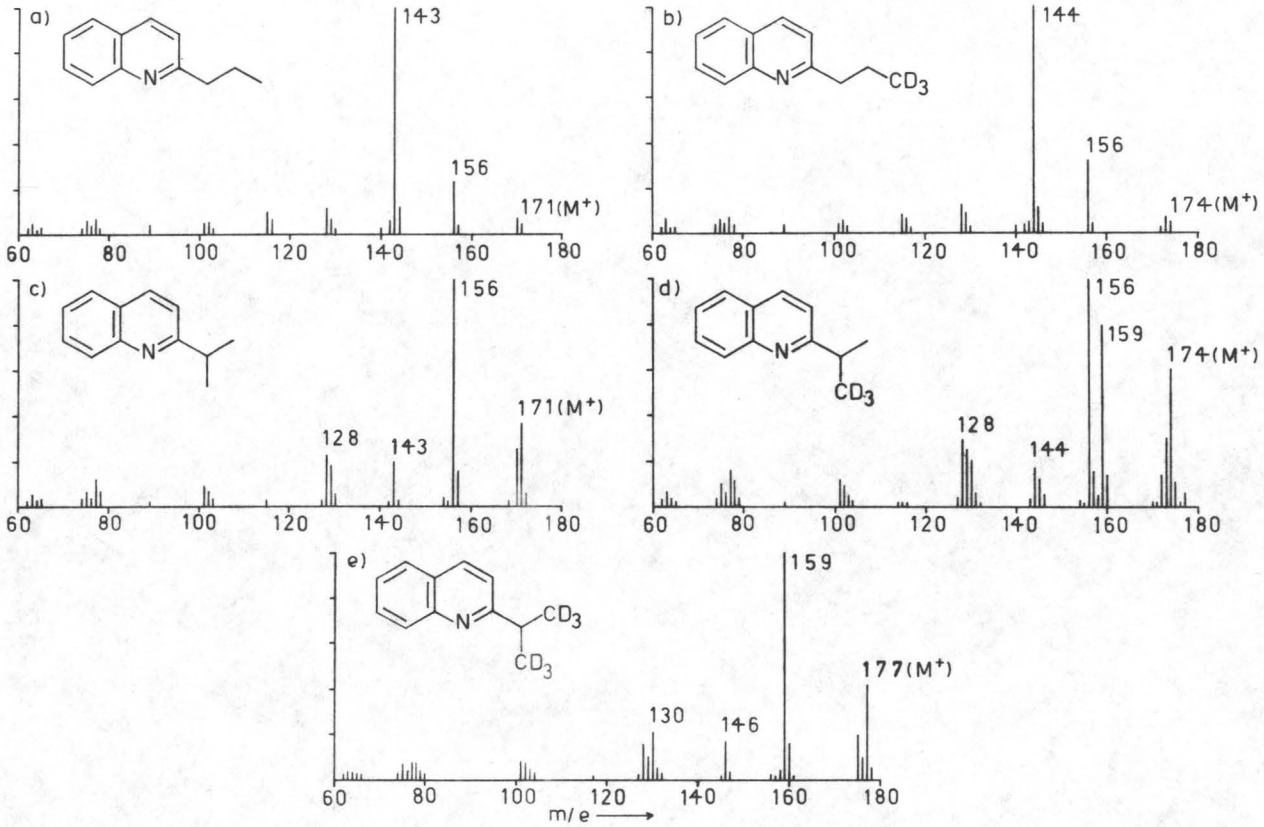


Figure 8. Mass spectra of a) 2-n-propylquinoline, b) 2-n-propylquinoline-2-γ-d_3, c) 2-isopropylquinoline, d) 2-isopropylquinoline-2-β-d_3 and e) 2-isopropylquinoline-2-β-d_6.

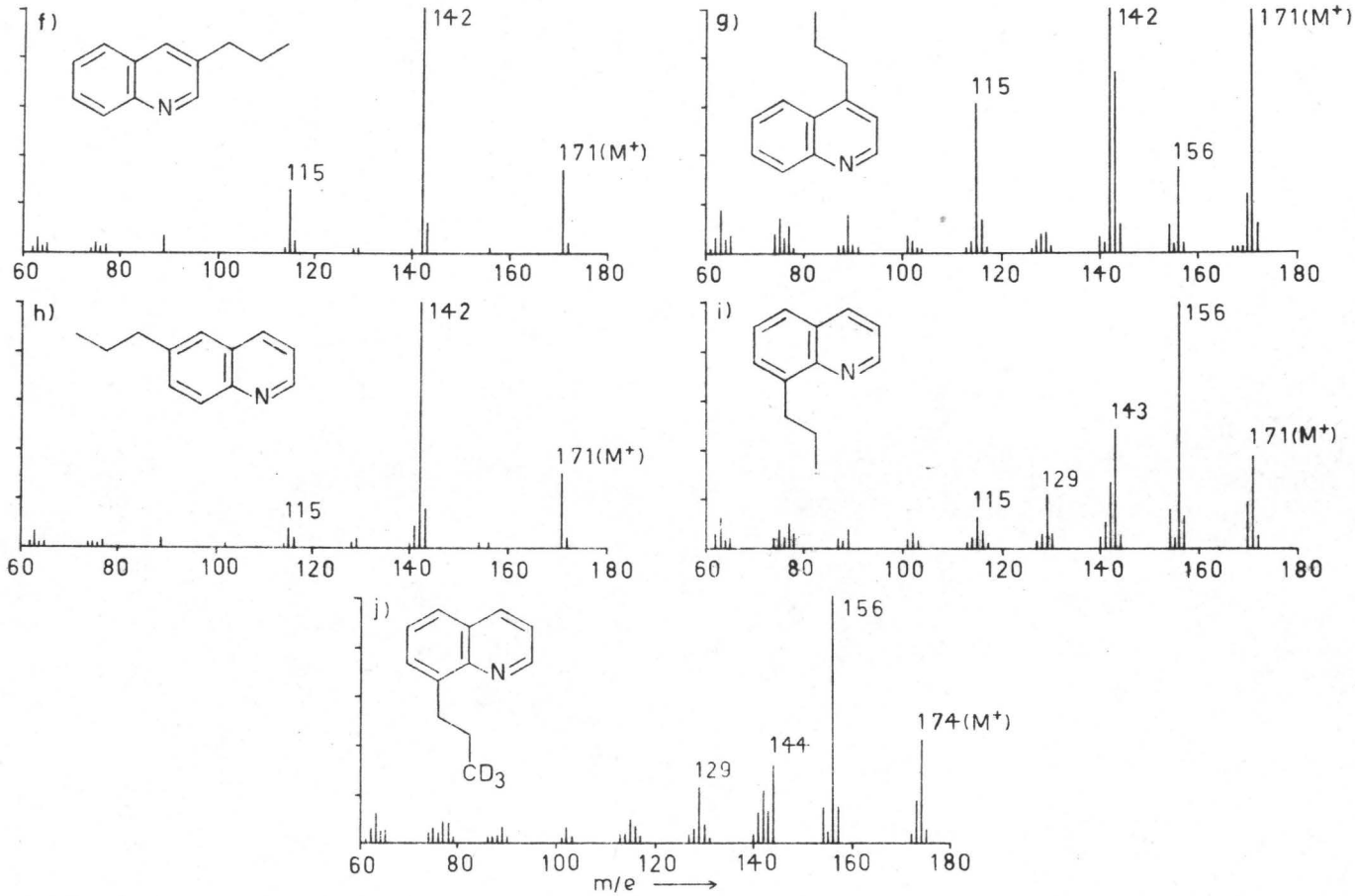
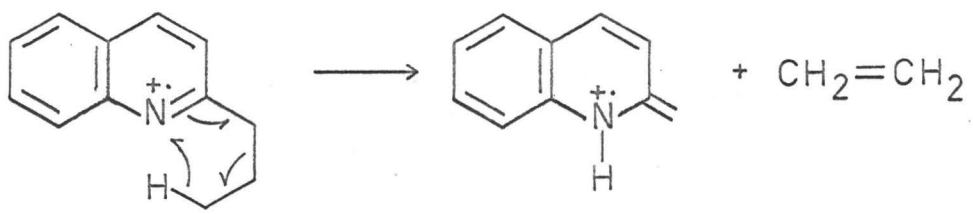


Figure 8. Mass spectra of f) 3-n-propylquinoline, g) 4-n-propylquinoline, h) 6-n-propylquinoline, i) 8-n-propylquinoline and j) 8-n-propylquinoline-8-γ-d_3.

2-isopropylquinoline-2-β-d_6, 2-n-propylquinoline-2-γ-d_3 and 8-n-propylquinoline-8-γ-d_3 were determined to aid in elucidation of the fragmentation mechanisms of the respective parent compounds, and they are also recorded in Fig. 8. Examination of Fig. 8 shows that the spectra of 2- and 8-n-propylquinoline differ considerably from the spectra of the 3-,4- and 6-n-propyl isomers, and this is expected in analogy with the spectra of the ethylquinolines.

By far the most intense peak in the mass spectrum of 2-n-propylquinoline (Fig. 8a) is found at m/e 143, (M-28) and this peak is shifted quantitatively to m/e 144 in the spectrum of the 2-γ-d_3 derivative (Fig. 8b). Thus, the M-28 ion may be visualized as originating through a McLafferty type rearrangement ($M^+ \rightarrow$ 80, Scheme 21). A similar mechanism, based on the same labelling experiments, was also proposed by Sample et al. (1).

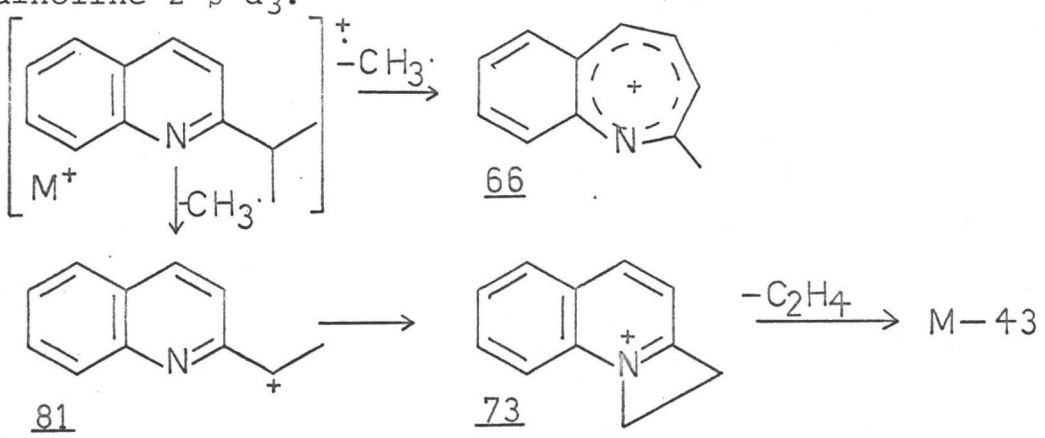


M^+ m/e 171 80 m/e 143

Scheme 21

The spectrum of 2-isopropylquinoline (Fig. 8c) may be readily differentiated from that of 2-n-propylquinoline by the relative intensities of peaks at M^+, M-1, M-15 and M-28. Since no γ hydrogen is present in 2-isopropylquinoline, the McLafferty rearrangement is impossible and other fragmentation modes become important.

The base peak in the spectrum of 2-isopropylquinoline is found at M-15, and the spectrum of the 2-β-d_3 derivative (Fig. 8d) shows that CH_3 is lost without rearrangement in the side chain. The M-15 ion could be represented by a ring expanded species 66, Scheme 22, but ions 81 or 73 might be better representations since a metastable peak is observed for the transformation M-15→M-43. Loss of C_2H_4 from 73 has already been proposed to account for the transformation M-1→M-29 observed in the spectrum of 2-ethylquinoline. A mass effect in which loss of the heavier CD_3 is favoured over loss of CH_3 (by a factor of about 1.4) is observed in the spectrum of 2-isopropylquinoline-2-β-d_3.



Scheme 22

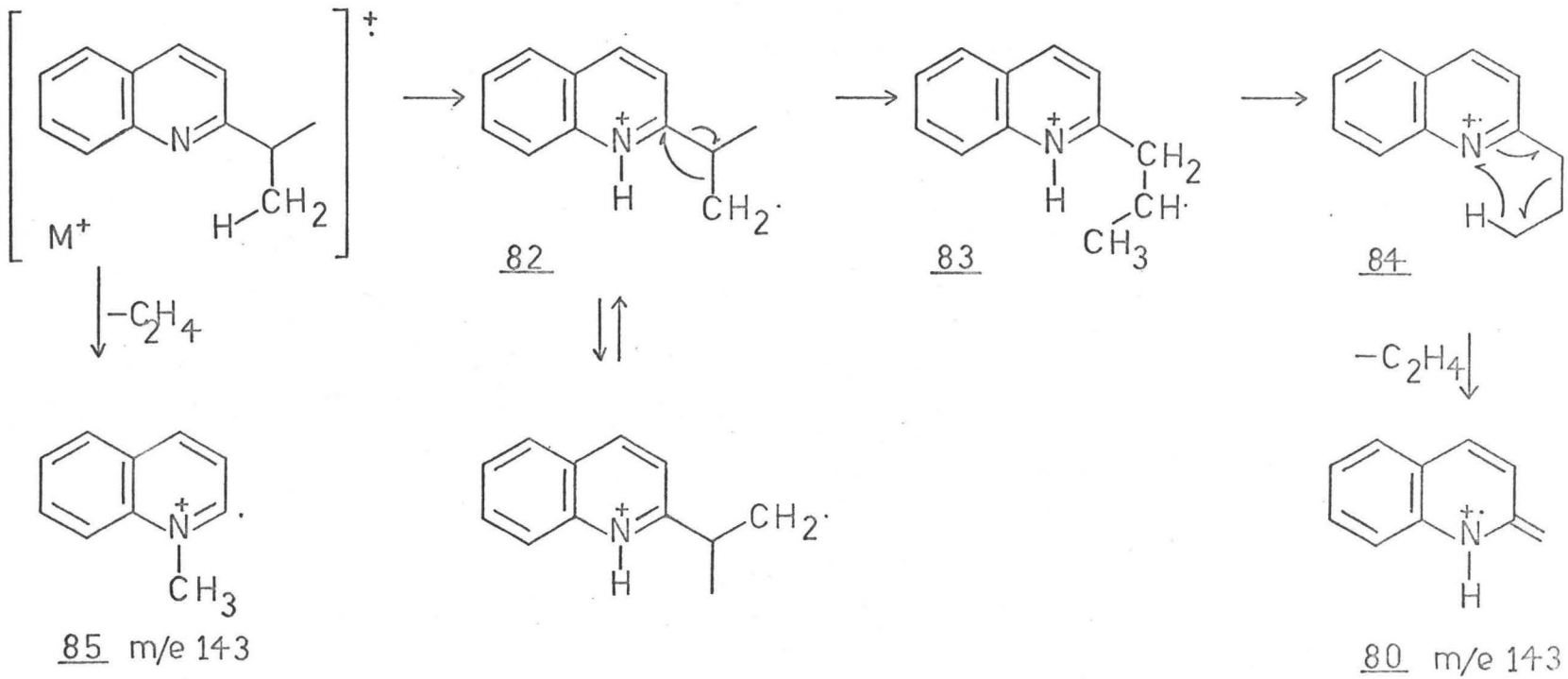
The results of the labelling experiments on 2-isopropylquinoline (Fig. 8d and e) suggest that the origin of peaks at M-1 and M-42 can be accounted for by mechanisms similar to those proposed for peaks at M-1 and M-28, respectively, in 2-ethylquinoline (Scheme 19). Thus, the M-1 peak is partly shifted (about 70%) to M-2 in the spectrum of the 2-β-d_6 derivative and the M-42 ion (m/e 129) is shifted to M-47 (m/e 130) in the spectrum of the 2-β-d_6 compound. The peak at M-43 arises partly through the sequence outlined in Scheme 22, while any of the transformations M-1→M-43, M-42→M-43 or M→M-43 (in analogy with mechanisms proposed to account for the M-29 peak in the spectrum of 2-ethylquinoline) are also possible.

An interesting feature in the spectrum of 2-isopropylquinoline is the presence of a peak of significant intensity at M-28. The presence of an appropriate metastable peak indicates that the 28 mass units are lost in a single step, and this suggests that the M-28 ion arises through the transformation M→M-C_2H_4 rather than M→M-H→M-(H+HCN). In the spectrum of the 2-β-d_6 derivative the peak is shifted quantitatively to M-31 (M-C_2HD_3) which shows that loss of H+HCN does not contribute to the M-28 ion. Peaks are observed over the region M-28 to M-31 in the spectrum of the 2-β-d_3 compound but the M-29 (M-C_2H_3D) and M-30 (M-$C_2H_2D_2$) ions predominate.

Since the spectrum of isopropylbenzene does not exhibit a peak of significant intensity at M-28, it appears that the nitrogen atom plays an important part in the fragmentation.

A plausible mechanism to account for the M-28 peak is outlined in Scheme 23. In the first step, a β hydrogen is transferred to the nitrogen with formation of ion 82. Rearrangement of ion 82 through ion 83 may then result in a 2-n-propylquinoline molecular ion 84, which can lose the 28 mass units by the usual McLafferty type rearrangement. The labelling results are compatible with this mechanism which predicts a loss of C_2HD_3 in the spectrum of the 2-β-d_6 derivative and a loss of $C_2H_2D_2$ or C_2H_3D in the 2-β-d_3 compound. (In the 2-β-d_3 compound a loss of $C_2H_2D_2$ would be observed if H were involved in the initial hydrogen transfer, while C_2H_3D would be lost if D were involved.) The less intense peaks at M-28 and M-31 in the spectrum of the 2-β-d_3 compound may be the result of partial scrambling of the β-hydrogens which could occur in ion 82.

An alternative mechanism to account for the M-28 ion involves methyl migration to the nitrogen with loss of C_2H_4 ($M^+ \rightarrow$ 85, Scheme 23). However, the labelling results require that hydrogen rearrangement occurs before loss of methyl. Again, the intermediacy of ion 82 could



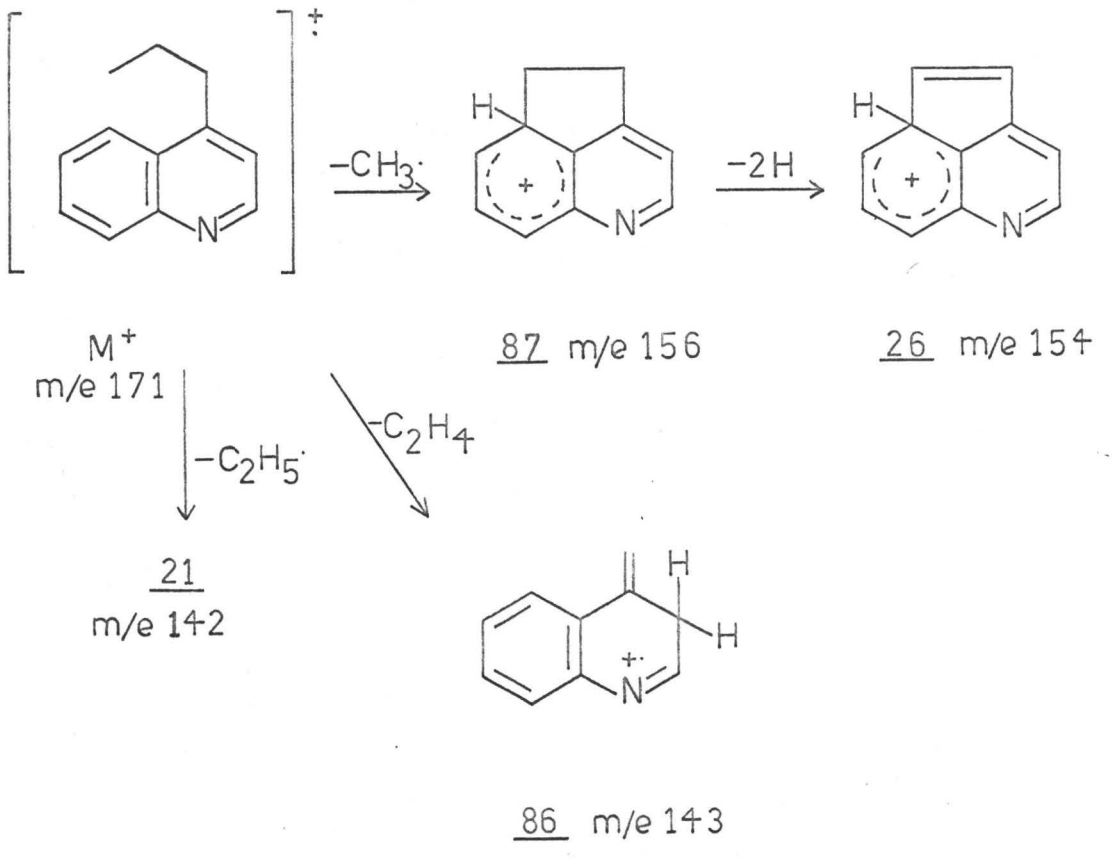
Scheme 23

be proposed. Methyl migrations in organic mass spectrometry are relatively rare but a similar methyl migration to nitrogen has been reported in the spectra of some dimethylaminopyrimidines (76).

The mass spectra of 3- and 6-n-propylquinolines (Fig. 8f and 8h) are similar in that the ion arising by β-cleavage forms the base peak in both their spectra. However, the two are readily differentiated by the fact that elimination of HCN from the m/e 142 ion in the propylquinolines substituted in the pyridine ring is favoured over elimination of HCN from the m/e 142 ion in the propylquinolines substituted in the benzene ring. β-cleavage with hydrogen rearrangement (McLafferty rearrangement) is of little importance in the spectra of 3- and 6-n-propylquinoline.

The spectrum of 4-n-propylquinoline (Fig. 8g) is dominated by peaks originating from β-cleavage with hydrogen rearrangement (ion 86, Scheme 24) and by simple β-cleavage. The greater importance of the rearrangement process relative to the 3- and 6- isomers may be the result of β-cleavage in the 4-position being a higher energy process than in the 3- and 6- positions. Peaks at M-15, represented by ion 87, and M-17, ion 26, may be due to stabilization of the fragments by cyclization to C-5 as shown in Scheme 24, but no labelling experiments

were carried out to show that the hydrogens lost in the sequence 87 → 26 originate from the α- and β- positions. The mechanism outlined in Scheme 24 is analogous to that proposed to account for the fragmentation of 4-isobutylquinoline (1).



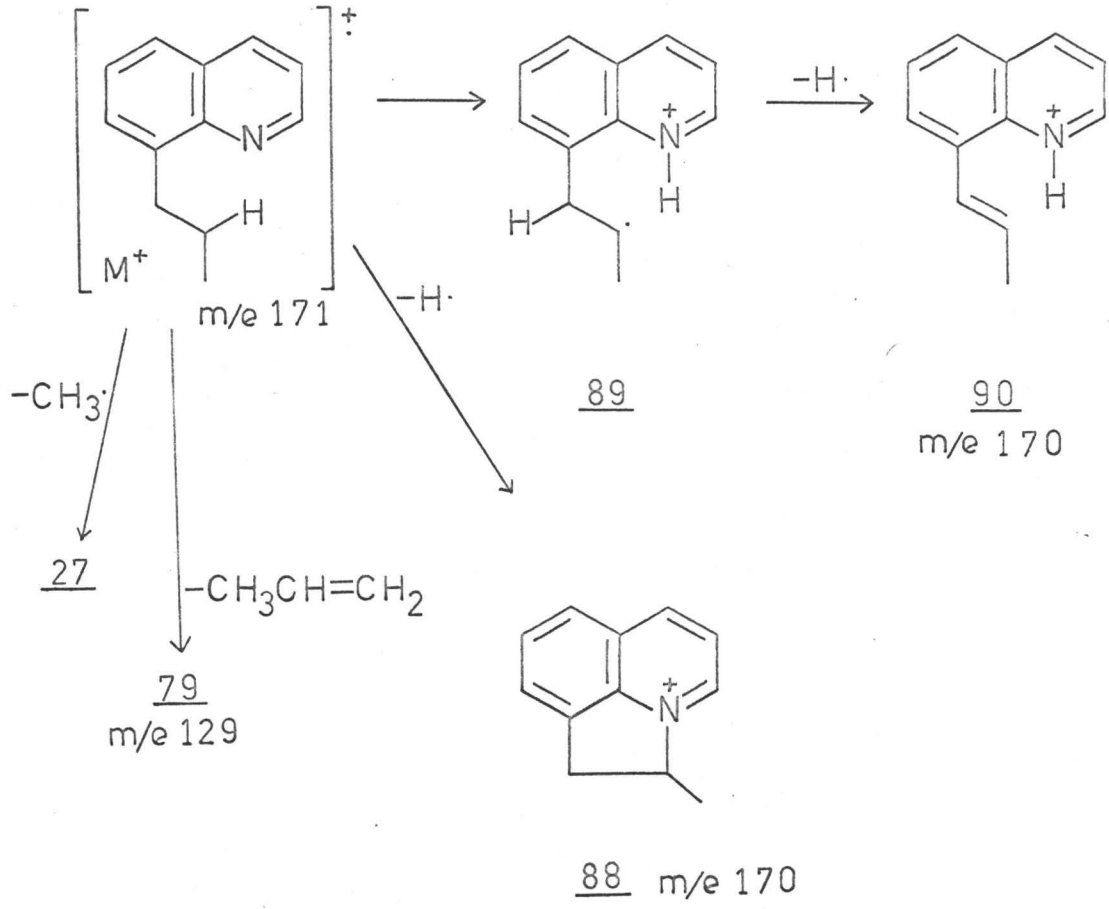
Scheme 24

The spectrum of 8-n-propylquinoline (Fig. 8i) is similar to that recorded by Sample et al.(1) but examination of the spectrum of the 8-γ-d_3 derivative (Fig. 8j) in this study has been useful in clarifying the fragmentation. The base peak in the spectrum of the undeuterated compound arises from loss of CH_3 from the molecular ion, and the peak is shifted quantitatively to M-18 in the 8-γ-d_3 analogue showing that the terminal methyl is lost. The M-15 ion may, therefore, be represented by ion 27 as suggested earlier (1).

The labelling results show that only a small portion (about 25%) of the M-1 ion originates through loss of a terminal hydrogen. Thus, loss of a β-hydrogen with formation of ion 88, Scheme 25, appears to be more favourable than loss of a γ hydrogen with cyclization to the nitrogen. Loss of an αH through the sequence $M^+ \rightarrow 89 \rightarrow 90$ (as in the 2- and 8-ethylquinolines) is also possible.

The peak at m/e 143 in the spectrum of 8-n-propylquinoline is partially shifted (with some scrambling) to m/e 144 in the spectrum of the deuterated compound, and this evidence is consistent with a McLafferty type rearrangement. Simple β-cleavage with ring expansion to give ion 23 accounts for the peak at m/e 142 in the spectrum of the unlabelled compound since it remains at m/e 142 in the 8-γ-d_3 analogue. The peak found at m/e 12[illegible]

possibly originates by transfer of a β-hydrogen to nitrogen followed by loss of propylene, in analogy with the rearrangement involving expulsion of ethylene observed in the spectra of 2- and 8-ethylquinolines.



Scheme 25

The metastable peaks observed in the spectra of the propylquinolines are listed in Table IX. They support the fragmentation mechanisms proposed for these compounds.

Table IX

Metastable Ions Observed in Spectra of Propylquinolines

Transformation	Calcd.	Observed in the Spectra of:
M→M-1	169.0	4-,8-n-propyl
M→M-15	142.3	2-isopropyl
M→M-28	119.6	2-,4-n-propyl, 2-isopropyl
M→M-29	117.9	3-,4-,6-n-propyl
M-15→M-43	105.0	2-isopropyl
M-29→M-56	93.1	2-,3-,4-,6-,8-n-propyl

From the results described in this section, it is seen that the isomeric propylquinolines show sufficient differences in their mass spectra that mass spectrometry should be useful in their identification. It might be expected that the spectrum of 5-n-propylquinoline would exhibit a relatively intense M-15 peak (in analogy with the spectrum of 4-n-propylquinoline) and thus it could be differentiated from the spectra of the 6- and 7- isomers.

As in the spectra of the ethylquinolines, charge stabilization in the product ion plays an important role in determining the fragmentation of the propylquinolines.

1,2,3,4-Tetrahydroquinoline

The mass spectra of 1,2,3,4-tetrahydroquinoline, and its 1-d_1,2,2-d_2, 3,3-d_2 and 4,4-d_2 derivatives are recorded in Fig. 9a-e, respectively. An intense molecular ion peak, and an intense M-1 peak (the base peak) characterize the spectrum of 1,2,3,4-tetrahydroquinoline. The spectrum of 1,2,3,4-tetrahydroquinoline-2-2-d_2 shows that about 70% of the hydrogen lost in formation of the M-1 ion originates from C-2. Loss of an α-hydrogen resulting in the stable ion 91, Scheme 26,is expected by analogy with the spectra of other cyclic amines. The labelling results suggest that the remainder of the hydrogen may be lost randomly from the rest of the molecule. Ring expansion involving C-4 with random loss of hydrogen to give a substituted tropylium ion 92 is a possible route to account for the hydrogen loss from positions other than C-2 and C-3. The peak at M-3 may be represented as a quinolinium ion 49, and it presumably arises from aromatization of ion 91.

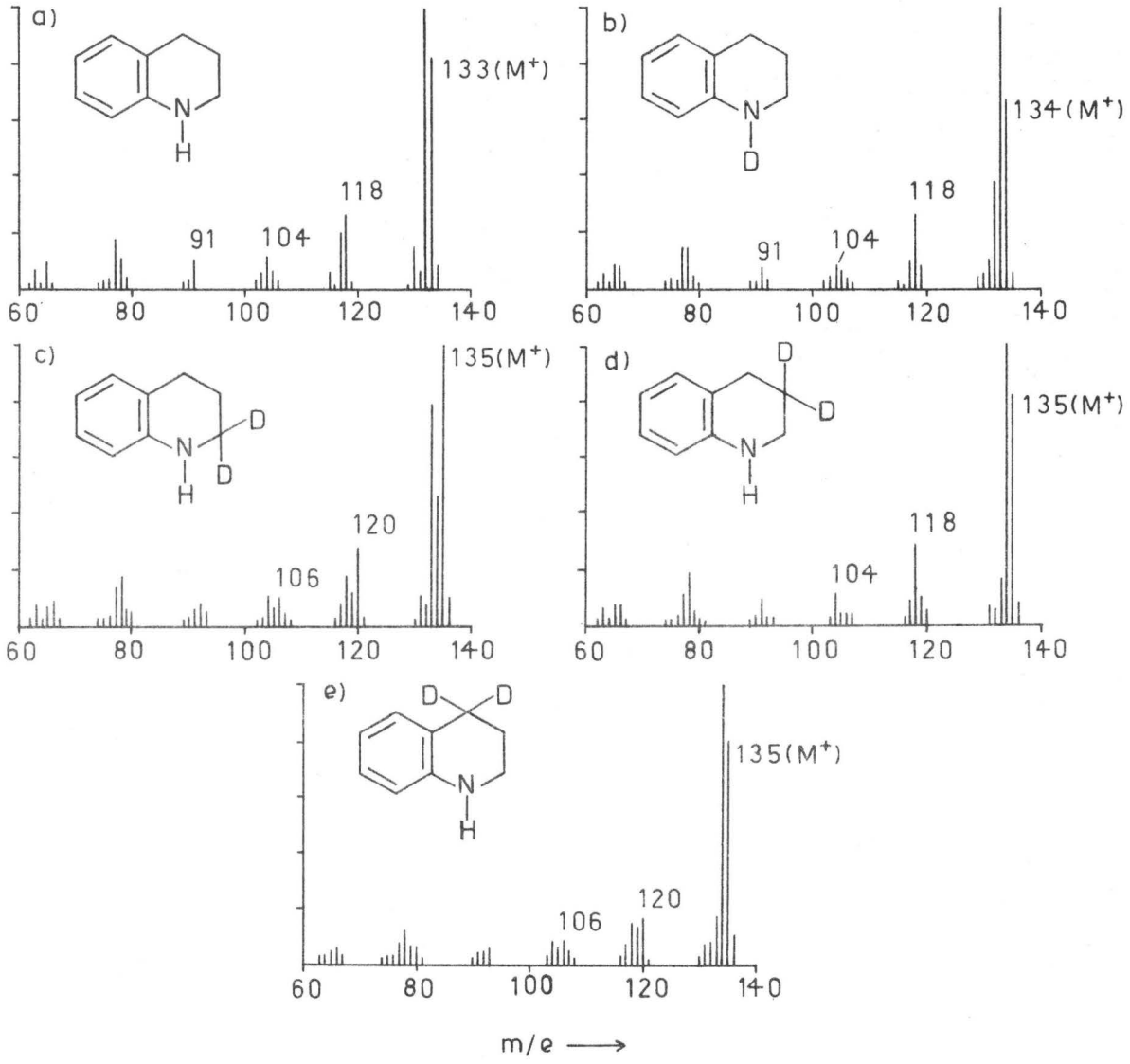
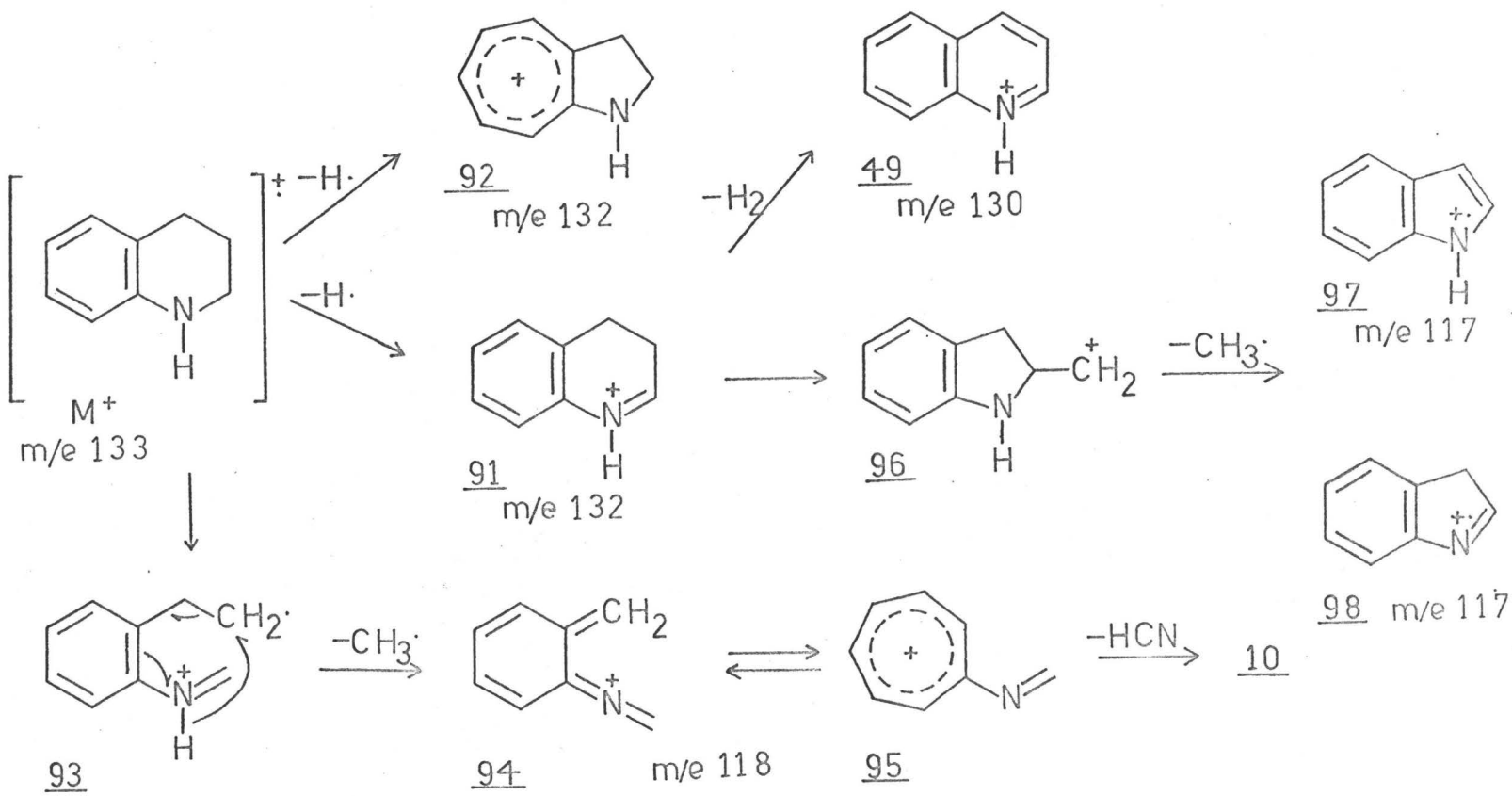


Figure 9. Mass spectra of a) 1,2,3,4-tetrahydroquinoline, b) 1,2,3,4-tetrahydroquinoline-1-d_1, c) 1,2,3,4-tetrahydroquinoline-2,2-d_2, d) 1,2,3,4-tetrahydroquinoline-3,3-d_2 and e) 1,2,3,4-tetrahydroquinoline-4,4-d_2.


M+
m/e 133
-H·
-H·
92
m/e 132
91
m/e 132
-H2
49
m/e 130
96
-CH3·
97
m/e 117
98 m/e 117
93
-CH3·
94
m/e 118
95
-HCN
10

Scheme 26

Peaks at M-15 (m/e 118) and M-16 (m/e 117) are also of significant intensity in the spectrum of 1,2,3,4-tetrahydroquinoline, and exact mass measurements show that they originate through loss of the elements CH_3 and CH_4, respectively (calculated for C_8H_8N 118.0657, observed 118.0655; calculated for C_8H_7N 117.0578, observed 117.0577). The peak at M-15 is partially shifted (about 70%) to M-16 in the spectrum of the 1-d_1 analogue, and to M-16 and M-17 in the 3,3-d_2 derivative. These results indicate that the major portion of the M-15 peak arises from loss of C-3 and its hydrogens as well as the hydrogen on the nitrogen. The mechanism proposed in Scheme 26 involves initial α cleavage to give ion 93, followed by transfer of hydrogen from the nitrogen to the radical centre at C-3, and finally loss of CH_3. The resulting ion may be represented by structures 94 or 95.

A similar mechanism supported by labelling experiments has been proposed to account for the M-15 peak found in the spectrum of piperidine (87). C-3 and its associated hydrogens are lost in both compounds; in piperidine the third hydrogen is transferred from C-6 while in tetrahydroquinoline the third hydrogen is transferred from nitrogen.

The M-16 peak in the spectrum of 1,2,3,4-tetra-

hydroquinoline may arise either by loss of H from M-15 or by loss of CH_3 from M-1. The latter pathway is supported by the presence of a metastable peak at m/e 103.9 (calcd. 103.7) and probably represents the major route. Examination of the spectra of the labelled compounds has helped to elucidate its mode of formation but the results are complicated by some apparent hydrogen scrambling. From the spectra of the labelled compounds, it is observed that the M-16 peak is not appreciably shifted in the 2,2-d_2 derivative, that it is partially shifted (about 40%) to M-17 in the 1-d_1 derivative, to M-17 and M-18 in the 3,3-d_2 derivative and to M-17 in the 4,4-d_2 compound. The 3,3-d_2 compound appears to show the greatest shift, suggesting that C-3 is lost accompanied by three hydrogens from among the 1-,3- and 4- positions. A possible mechanism shown in Scheme 26 involves initial ring contraction of ion 91 to ion 96. Hydrogen transfer from C-4 or the nitrogen followed by loss of a methyl radical would yield ions 97 or 98, respectively. The driving force for this rearrangement may lie in the formation of the stable indole system.

This mechanism implies that both the hydrogens from C-3 are lost. However, the spectrum of the 3,3-d_2 derivative shows that both CH_2D and CD_2H are lost from

the M-1 ion in this compound. Thus, it appears that some hydrogen scrambling in the 1-,3- and 4- positions occurs before loss of methyl from the M-1 ion.

Other peaks in the spectrum of 1,2,3,4-tetrahydroquinoline are of relatively low intensity and their formation is difficult to interpret with the aid of the deuterated compounds alone. However, exact mass measurements on some of these peaks have aided in the interpretation of their formation. The peak at m/e 115 (M-18) appears to arise from the M-1 ion since a metastable peak is observed at m/e 100.3 for the transformation m/e 132→m/e 115 (calcd. 100.2). The exact mass of the m/e 115 ion corresponds to a C_9H_7 species (calculated for C_9H_7, 115.0548, observed 115.0547), and the elements NH_3 are therefore lost from the M-H ion. The results of the labelling experiments do not suggest a simple mechanism for this transformation.

Metastable peaks observed for the transformations m/e 132→105 and m/e 130→103 suggest that peaks at m/e 105 and m/e 103 originate through loss of HCN from the M-1 and M-3 ions respectively. The exact mass of the m/e 105 ion does indeed correspond to expulsion of the elements H+HCN (calculated for C_8H_9 105.0704, observed 105.0698). The peak at m/e 104 is a doublet composed of C_7H_6N (calculated 104.0500, observed 104.0500) and C_8H_8 ions

(calculated 104.0626, observed 104.0623) in approximate relative abundance of 2:1, respectively. Thus, the C_7H_6N ion corresponds to loss of C_2H_5 while the C_8H_8 ion may originate through loss of H from the m/e 105 ion.

The peak at m/e 91 ($C_7H_7^+$) may be represented as a tropylium ion 10, and it is probably derived from ion 94 or 95 through loss of HCN since a metastable peak corresponding to the transformation m/e 118→m/e 91 is observed at m/e 70.2.

A number of metastable peaks are observed in the spectrum of 1,2,3,4-tetrahydroquinoline and they support many of the proposed fragmentation mechanisms. The most intense metastable peaks in the spectrum are recorded in Table X.

Table X

Metastable Ions Observed in the Spectrum of 1,2,3,4-Tetrahydroquinoline

Transformation	Calcd.	Observed
M→M-1	131.0	131.0
M-1→M-16	103.7	103.9
M-1→M-18	100.2	100.3
M-1→M-28	83.6	83.6
M-3→M-30	81.7	81.7
M-15→M-42	70.2	70.2

Methyl-1,2,3,4-tetrahydroquinolines

In Fig. 10a-b the mass spectra of N-methyl-1,2,3,4-tetrahydroquinoline and its N-α-d_3 derivative are recorded, while the spectra of the corresponding N-methyl-1,2,3,4-tetrahydroisoquinolines are recorded in Fig. 10c-d. The mass spectra of 2-,3-,4- and 6-methyl-1,2,3,4-tetrahydroquinolines are shown in Fig.11a-d respectively.

The mass spectrum of N-methyl-1,2,3,4-tetrahydroquinoline is similar to that of the parent compound in that they both show intense molecular ion and M-1 peaks. In the former compound, there are two α-positions from which hydrogen could be lost in formation of the M-1 ion, but the spectrum of the labelled analogue shows that little, if any, of the hydrogen is lost from the N-methyl carbon. This is expected on the basis of earlier studies on N-methylpiperidine where loss of a secondary hydrogen (from C-2) is favoured over loss of a primary hydrogen (87).

Peaks at M-15, M-16 and M-17 are also of significant intensity in the spectrum of N-methyl-1,2,3,4-tetrahydroquinoline. The M-16 ion appears to arise through loss of CH_3 from the M-1 fragment since a metastable peak corresponding to the transformation m/e 146→131 is observed at m/e 117.8. A metastable peak is also observed for the transformation M-16→M-17 showing that

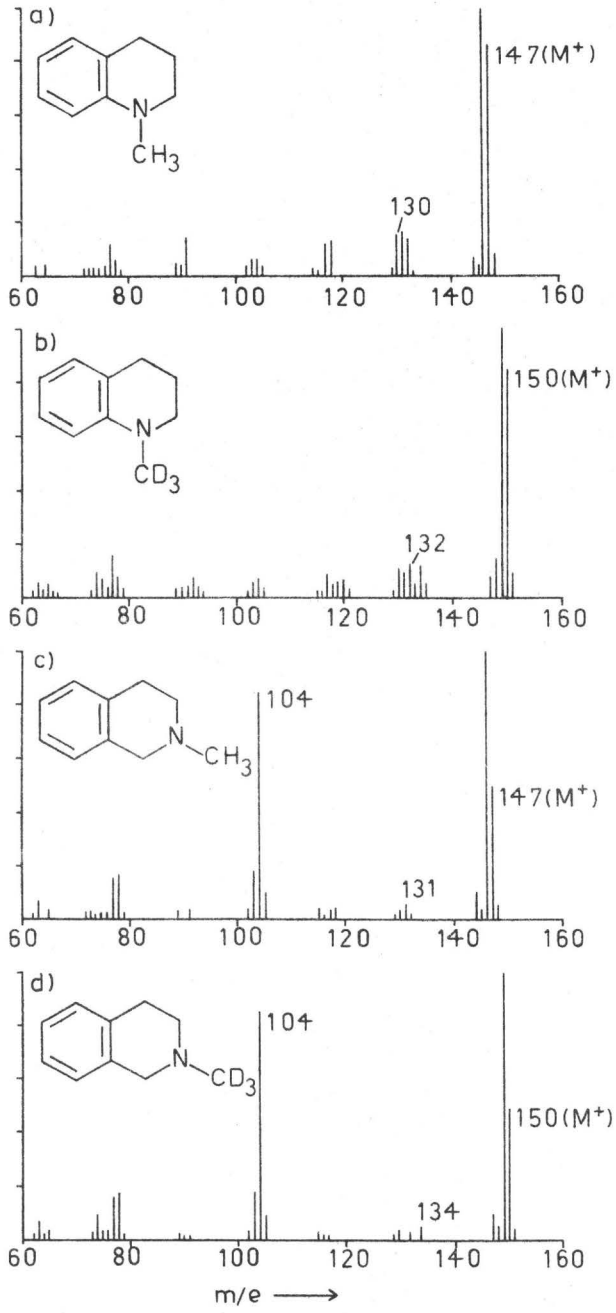


Figure 10. Mass spectra of a) N-methyl-1,2,3,4-tetrahydroquinoline, b) N-methyl-1,2,3,4-tetrahydroquinoline-N-α-d_3, c) N-methyl-1,2,3,4-tetrahydroisoquinoline and d) N-methyl-1,2,3,4-tetrahydroisoquinoline-N-α-d_3.

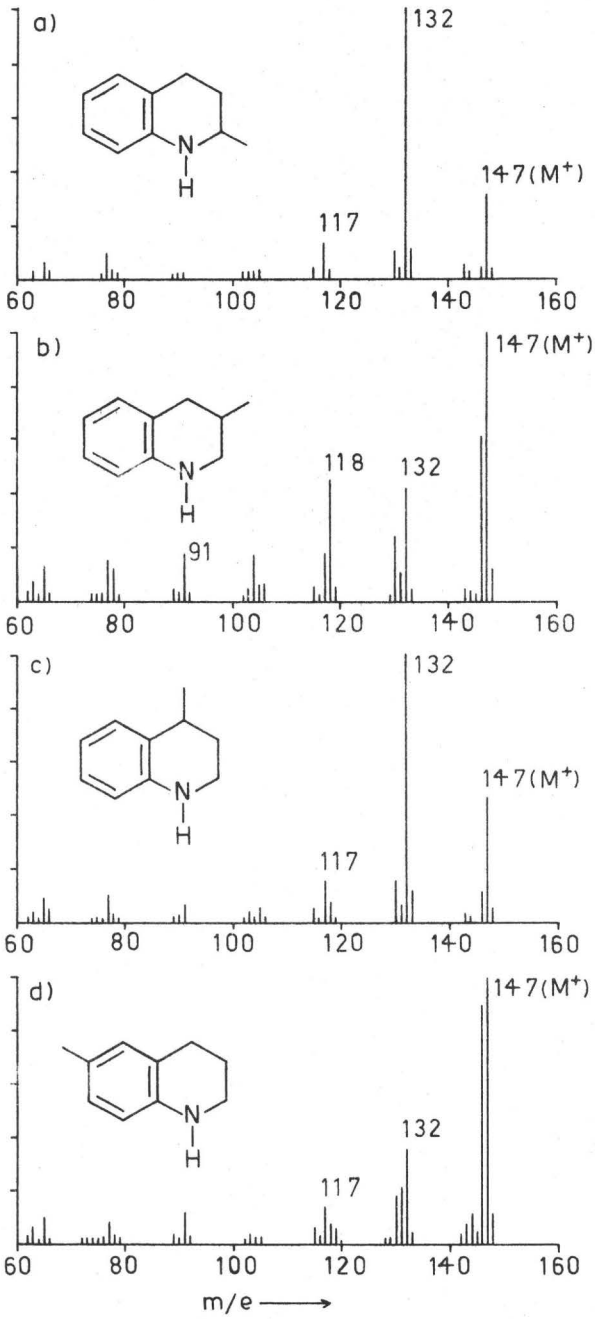
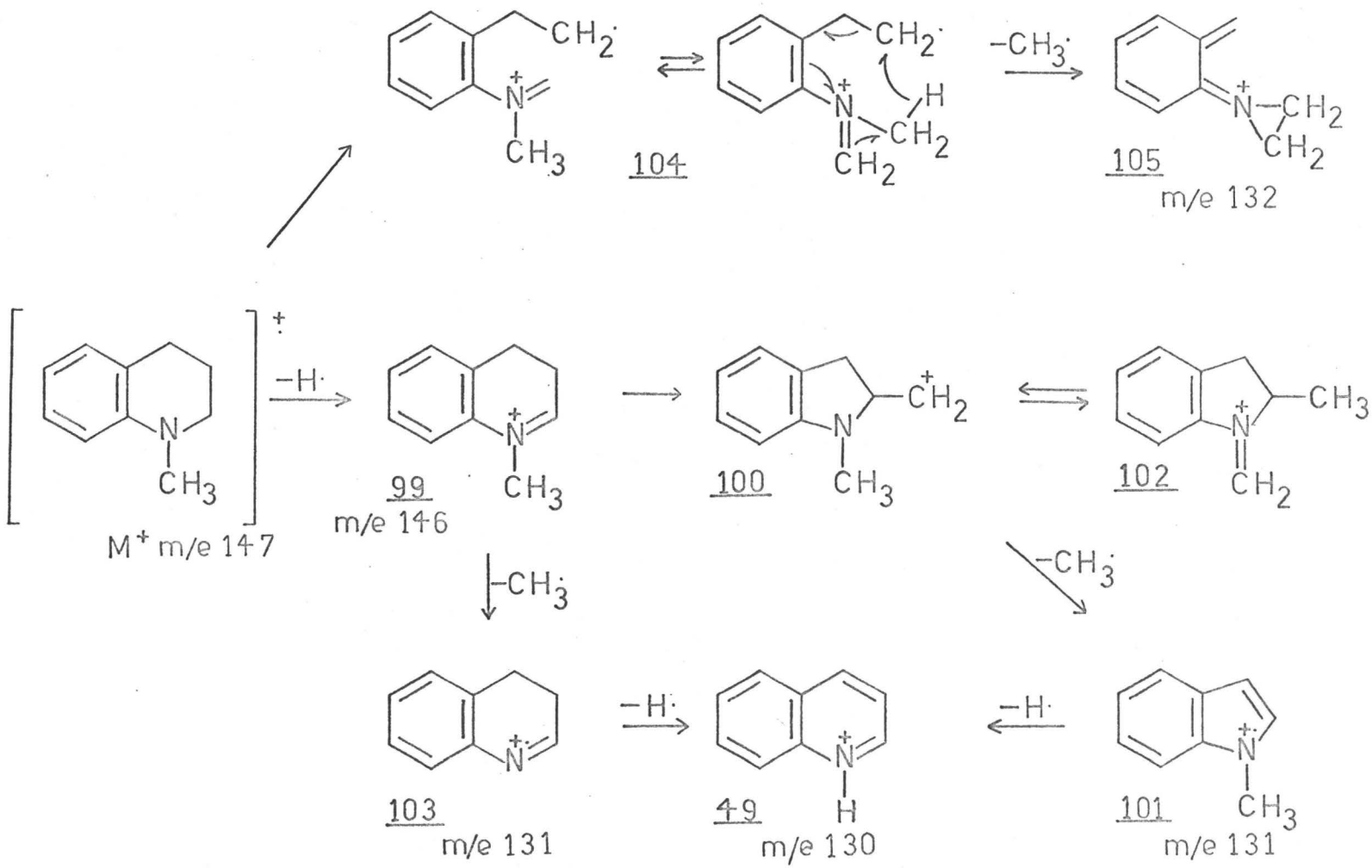


Figure 11. Mass spectra of a) 2-methyl-1,2,3,4-tetrahydroquinoline, b) 3-methyl-1,2,3,4-tetrahydroquinoline, c) 4-methyl-1,2,3,4-tetrahydroquinoline and d) 6-methyl-1,2,3,4-tetrahydroquinoline.

the M-17 ion arises, in part at least, through loss of hydrogen from the M-16 ion. In the spectrum of the N-α-d_3 analogue the peaks are observed over the region M-15 to M-20, while metastable peaks corresponding to the transformations m/e 149→134, 149→133 and 149→131 are observed at m/e 120.5, 119.0, and 115.2 respectively. Thus, the M-16 peak in the spectrum of the undeuterated compound is found mainly at m/e 131, 133 and 134 in the spectrum of the labelled derivative.

To account for the M-16 peak in the spectrum of N-methyl-1,2,3,4-tetrahydroquinoline, an initial ring contraction of ion 99 to ion 100, as shown in Scheme 27, is proposed. Hydrogen transfer from C-4 followed by loss of methyl leads to an N-methylindole molecular ion 101. An equilibrium between ions 100 and 102 is proposed to account for loss of CH_2D as well as CH_3 from 99 in the deuterated compound. This ring contraction mechanism is analogous to that proposed for the sequence M-1→M-16 in the spectrum of the parent tetrahydroquinoline. Direct loss of the N-methyl group from 99 also appears to contribute to the M-16 ion since loss of CD_3 from M-1 is observed in the spectrum of the labelled derivative. Ions 101 and 103 may then lose H to give the M-17 ion (m/e 130) which is represented as a quinolinium ion 49.


M+ m/e 147
99
m/e 146
100
102
103
m/e 131
49
m/e 130
101
m/e 131
104
105
m/e 132
-H·
-CH3·

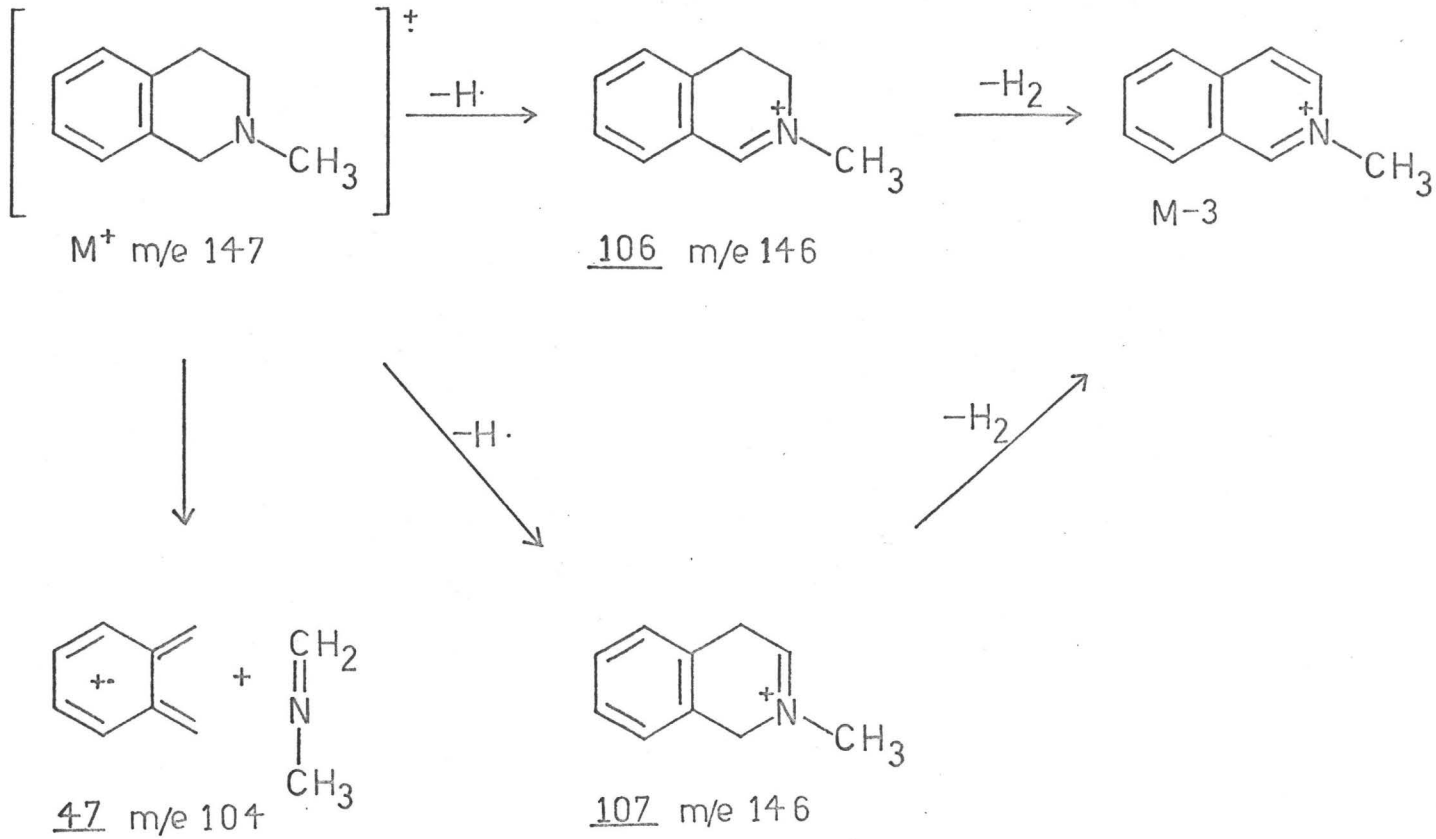
Scheme 27

The sequence $M^+ \rightarrow \underline{104} \rightarrow \underline{105}$ shown in Scheme 27 is suggested to account for the M-15 peak in the spectrum of N-methyl-1,2,3,4-tetrahydroquinoline, and it appears to be compatible with the spectrum of the deuterated analogue which exhibits peaks at M-15 and M-16. The hydrogen transfer from the N-methyl carbon with loss of methyl is similar to the mechanism proposed for loss of CH_3 in the parent tetrahydroquinoline. Direct loss of the N-methyl group is usually a high energy process and does not occur to a significant extent in the spectrum of N-methylpiperidine (87).

Baldwin et al. (90) have recorded the spectrum of N-methyl-1,2,3,4-tetrahydroisoquinoline. They report that the molecular ion peak is the base peak in the spectrum of this compound, and that a relatively intense peak caused by an ion-molecule reaction is observed at M+1. The spectrum of N-methyl-1,2,3,4-tetrahydroisoquinoline examined in this study (Fig. 10c) is similar to that recorded by Baldwin et al. up to m/e 118, but the peaks in the two spectra differ in their relative positions by one mass unit above m/e 118. Thus, the M+1 and M^+ peaks reported by Baldwin et al. appear at M^+ and M-1, respectively, in the spectrum recorded in Fig. 10c. Since the relative intensity of the peak at highest mass was found to be independent of the sample pressure, (an ion-

molecule reaction is a second order reaction and the yield of such a reaction therefore depends on the sample pressure) and since an intense M-1 ion is expected on the basis of results from the tetrahydroquinolines, it would appear that the earlier workers have made an error in counting their spectrum.

The M-1 peak in the spectrum of N-methyl-1,2,3,4-tetrahydroisoquinoline may be represented by ion 106 in Scheme 28 although some loss of H from C-3 yielding ion 107 is also possible. The spectrum of the N-α-d_3 derivative (Fig. 10d) shows that little, if any, of the hydrogen lost originates from the N-methyl group. A metastable peak observed for the transformation M-1→M-16 suggests that the relatively weak M-16 peak arises through loss of methyl from M-1. The shifts are difficult to follow in the spectrum of the labelled derivative, but the presence of a relatively large contribution at M-16 suggests that the N-methyl group is not involved to a large extent in this fragmentation. An intense peak at m/e 104 (which is useful in differentiating among the spectra of the 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydroisoquinolines) in the spectrum of the unlabelled compound remains at m/e 104 in the labelled derivative, and it may, therefore, arise through a reverse Diels-Alder fragmentation (M^+→47, Scheme 28) as was suggested by



Scheme 28

Baldwin et al. (90).

The mass spectra of 2- and 4-methyl-1,2,3,4-tetrahydroquinolines (Fig. 11a and c) are nearly identical. The expected α-cleavage with expulsion of the methyl group results in the base peak in the spectrum of the 2-isomer, while α-cleavage with loss of the smaller hydrogen is a much less important process. The M-15 ion, represented as ion 91, may then lose two hydrogens or CH_3 to give peaks at M-17, ion 49, and M-30, ion 97, respectively, as shown in Scheme 26. A metastable peak observed at m/e 103.9 (calcd. 103.7) supports formation of the M-30 ion from 91. The M-15 ion in the spectrum of 4-methyl-1,2,3,4-tetrahydroquinoline may be stabilized by ring expansion to ion 92. Peaks at M-17 and M-30 in the 4- isomer may originate through loss of two hydrogens and CH_3, respectively, from the M-15 ion, and a metastable peak is observed for the latter transition. Since the M-15 to M-30 peak intensity ratio for the 2- and 4- isomers is similar, it appears that the M-15 ion from the two isomers may have a common structure. Loss of methyl from C-4 followed by hydrogen rearrangement could lead to ion 91 which may then lose 15 mass units as shown in Scheme 26.

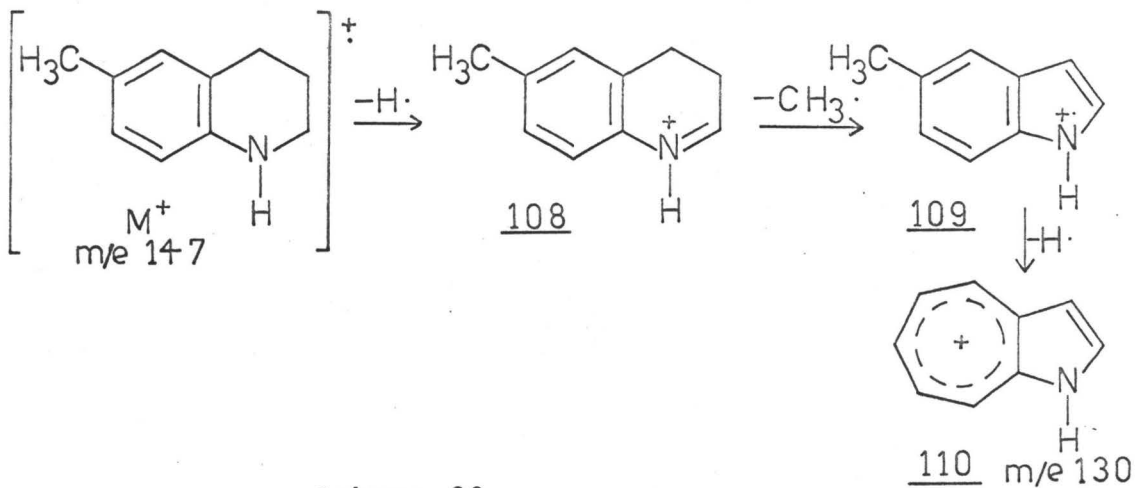
The mass spectrum of 3-methyl-1,2,3,4-tetrahydroquinoline (Fig. 11b) shows an intense M-1 peak, a less

intense M-15 peak and an intense M-29 peak relative to the spectra of the 2- and 4- isomers. Peaks at M-1 and M-29 may form in a manner analogous to the M-1 and M-15 peaks, respectively, in the spectrum of the parent compound. The intense peak at M-29, ion 94, in the spectrum of 3-methyltetrahydroquinoline provides further evidence that the M-15 peak in the parent tetrahydroquinoline arises by loss of C-3 and its hydrogens.

The presence of a metastable peak corresponding to the transformation m/e 132→117 indicates that the M-30 ion forms, in part at least, through loss of methyl from M-15. The M-15 ion formed by loss of the 3-methyl group may rearrange to ion 91 by hydrogen transfer (in a manner similar to that proposed for the M-15 ion from the 4- isomer) before expulsion of the second methyl group. However, the M-30 to M-15 peak intensity ratio is considerably larger in the spectrum of the 3-methyl isomer than in the 2- and 4- isomers which indicates that an additional pathway contributes to the M-30 ion in the spectrum of the former. The additional contribution may arise through the sequence M-1→M-30 in a similar manner to the loss of CH_3 from M-1 in the parent compound. This provides further evidence for the suggestion that loss of C-3 is involved in the sequence M-1→M-16 in the spectrum of the parent compound.

The spectra of the 2-,3- and 4-methyltetrahydroquinolines all exhibit peaks at M-1, M-16 and M-17. Metastable peaks corresponding to the transformations M-1→M-16 and M-16→M-17 are observed in the spectrum of the 3- isomer, while the 2- and 4- isomers show a metastable for the latter but not the former transformation. Thus, the sequence M-1→M-16→M-17 as well as the sequence M-15→M-16→M-17 may contribute to the M-17 ion in the spectra of the three compounds.

The spectrum of 6-methyl-1,2,3,4-tetrahydroquinoline (Fig. 11d) is similar to that of the parent tetrahydroquinoline since the substitution is not in the saturated ring and accordingly has little effect on the fragmentation. A difference from the parent compound is the presence of a peak at M-17 in the spectrum of the 6-methyl compound. The presence of an appropriate metastable peak suggests that the M-17 peak arises mainly through loss of H from the M-16 species, and its origin may be represented by the sequence M^+→<u>108</u>→<u>109</u>→<u>110</u> as shown in Scheme 29.



Scheme 29

In Table XI the most intense metastable ions observed in the spectra of the methyl-1,2,3,4-tetrahydroquinolines are listed. They have been useful in elucidating the fragmentation mechanisms of these compounds.

Table XI

Metastable Ions Observed in Spectra of Methyl-1,2,3,4-Tetrahydroquinolines

Transformation	Calcd.	Obs.	Obs. in the spectra of
M→M-1	145.0	145.0	1-,3-,6-
M-16→M-17	129.0	129.0	1-,2-,3-,4-,6-
M→M-15	118.5	118.7	2-,3-,4-
M-1→M-16	117.5	117.8	1-,3-,6-
M-15→M-30	103.7	103.9	1-,2-,3-,4-,6-
M-15→M-32	100.2	100.2	2-,4-
M-1→M-29	95.4	95.5	1-
M→M-29	94.7	95.0	3-
M-15→M-42	83.6	83.7	2-,4-
M-17→M-44	81.7	81.8	1-,2-,3-,4-,6-

In summary, it is seen that important differences exist among the spectra of many of the various methyl-1,2,3,4-tetrahydroquinolines. However, the spectra of

the 2- and 4- isomers are similar and one would expect the spectra of the 5-,6-,7- and 8- isomers to be nearly identical so additional information would be required in the positive identification of these isomers. The fragmentation mechanisms proposed for the parent tetrahydroquinoline are in accord with the spectra of the methyltetrahydroquinolines.

5,6,7,8-Tetrahydroquinoline

The mass spectra of 5,6,7,8-tetrahydroquinoline and its 5-d_1, 6,6-d_2 and 8,8-d_2 derivatives are recorded in Fig. 12a-d, respectively. The spectrum of 5,6,7,8-tetrahydroquinoline is readily differentiated from that of the 1,2,3,4-isomer by the presence of an intense peak at M-28 (m/e 105) in the former isomer.

Loss of hydrogen from the molecular ion results in the base peak in the mass spectrum of 5,6,7,8-tetrahydroquinoline, and the labelling studies indicate that the hydrogen loss is not specific from any one position in the molecule. A significant contribution from C-6 is observed (Fig. 12c) and a similar contribution from C-7 might be expected. A large proportion of the hydrogen lost may originate from the pyridine ring possibly by ring expansion involving C-5 or C-8 followed by random loss of hydrogen from the pyridine ring and C-5 or C-8. The fragment ion

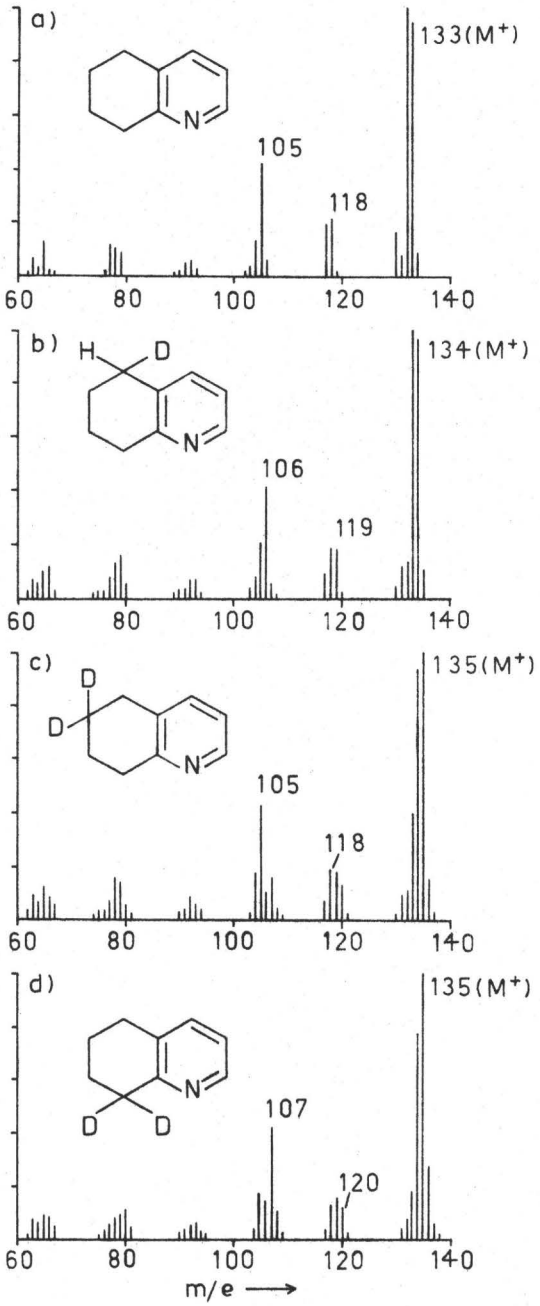
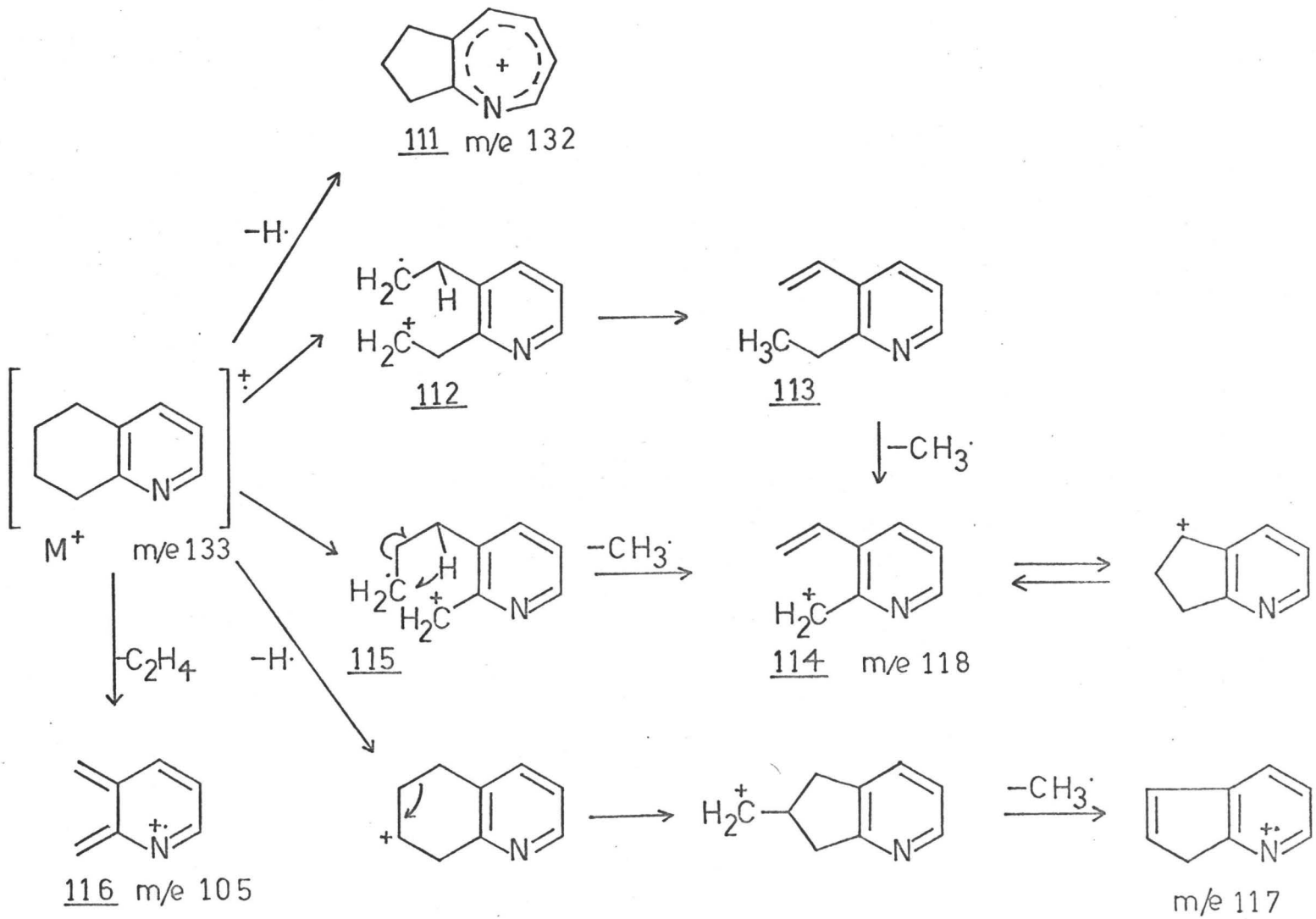


Figure 12. Mass spectra of a) 5,6,7,8-tetrahydroquinoline, b) 5,6,7,8-tetrahydroquinoline-5-d_1, c) 5,6,7,8-tetrahydroquinoline-6,6-d_2 and d) 5,6,7,8-tetrahydroquinoline-8,8-d_2.

resulting from ring expansion to C-5 may be represented by ion 111 in Scheme 30.

Peaks at M-15 and M-16 are also of significant intensity in the spectrum of 5,6,7,8-tetrahydroquinoline. The labelling results do not, however, shed much light on the origin of these peaks since their shifts are difficult to follow. In all the labelled compounds, partial shifts to M-16 and M-17 are observed, while a significant shift to M-18 is also observed in the spectrum of the 6,6-d_2 derivative. The results, therefore, indicate that considerable scrambling of hydrogen occurs or that a series of competing reactions may contribute to the M-15 and M-16 ions.

Tentative mechanisms to account for the formation of ions at M-15 and M-16 are outlined in Scheme 30. For formation of the M-15 ion, a C-6-C-7 bond fission is postulated followed by hydrogen transfer and expulsion of a methyl radical ($M^+ \rightarrow$ 112 $\rightarrow$ 113 $\rightarrow$ 114). As depicted in Scheme 30, C-7 and its hydrogens are lost along with a hydrogen from C-5. It is equally probable, however, that C-6 and its associated hydrogens along with a hydrogen from C-8 would be lost. Alternatively, the familiar β-cleavage with hydrogen transfer and loss of methyl ($M^+ \rightarrow$ 115 $\rightarrow$ 114) also leads to the same species. Initial cleavage of the C-7-C-8 bond is shown in Scheme 30, but


111 m/e 132
-H·
112
113
-CH3·
M+ m/e 133
-CH3·
115
114 m/e 118
-C2H4
-H·
116 m/e 105
-CH3·
m/e 117

Scheme 30

cleavage of the C-5-C-6 bond is equally probable.

In the formation of the M-16 ion, a loss of H from C-7 may be followed by ring contraction and elimination of methyl. (The presence of a metastable peak at m/e 103.9 (calcd. 103.7) in the spectrum of the unlabelled compound suggests that the M-16 peak does indeed arise through the sequence M-1→M-16 rather than M-15→M-16.) As shown in Scheme 30, C-6 and its hydrogens are lost along with a hydrogen from C-5 or C-8. Similarly, loss of H from C-6 may be followed by loss of C-7 and its associated hydrogens along with a single hydrogen from C-5 or C-8. These mechanisms account for the fact that some deuterium is lost in all the labelled compounds studied, and that deuterium loss is not specific for the M-15 or M-16 ions. It is noteworthy that peaks at M-15 and M-16 are also found in the spectrum of tetrahydronaphthalene (106) but their origin has not been discussed.

The peak at M-28 (m/e 105), ion 116, presumably arises by a retro Diels-Alder fragmentation since deuterium is retained in the 5-d_1 and 8,8-d_2 derivatives while it is lost in the 6,6-d_2 isomer. A similar loss of ethylene is also found in the spectrum of tetrahydronaphthalene (106).

EXPERIMENTAL

Apparatus, Methods and Materials

Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6A mass spectrometer at an ionizing potential of 80 eV and an ionizing current of 50 μA. Samples were introduced through an all glass inlet system maintained at 200°. Spectra are plotted in terms of relative abundance, with the most intense peak (base peak) taken as 100%. Only peaks equal to or greater than 2% of the base peak are recorded.

Exact mass measurements were determined on a C.E.C. 21-110 B double focusing mass spectrometer using perfluorokerosene as an internal standard.

All samples for mass spectrometry (with the exception of alkylquinolines labelled with deuterium in the 2-α-position) were purified by gas chromatography on a 6-foot column of 20% apiezon M on celite. The column temperature was maintained at 180° to 230° depending on the volatility of the material. Gas chromatography of alkylquinolines labelled in the 2-α-position caused back exchange, therefore these compounds were purified by chromatography over alumina. It was also necessary to

pump a small amount of CH_3OD through the mass spectrometer before introduction of these samples.

N.M.R. spectra were determined in $CDCl_3$ solution on a Varian A-60 spectrometer. Chemical shifts are expressed in parts per million (δ) from tetramethylsilane used as an internal standard.

Picrate derivatives were prepared by adding a hot methanolic solution of the quinoline to a slight excess of picric acid in hot methanol and they were recrystallized from methanol unless otherwise stated. Melting points were determined on a Kofler Micro Hot Stage apparatus and are uncorrected.

CH_3OD (99 atom % D), CD_3I (99 atom % D), $C^{13}H_3I$ (57 atom % C^{13}), CD_3CH_2Br (98 atom % D) and $NaBD_4$ (98 atom % D) were obtained from Merck, Sharp and Dohme of Canada Ltd. $LiAlD_4$ was obtained from Ventron Corporation, Metal Hydrides Division, Beverly, Massachusetts.

4-,6-,7- and 8-methylquinolines, 4,6-dimethylquinoline, 1,2,3,4-tetrahydroquinoline and 2- and 6- methyl-1,2,3,4-tetrahydroquinolines were obtained commercially. 5-Methylquinoline, 2,7-, 2,8-, 3,5-, 3,6-, 3,7-, 3,8-, 4,8- and 5,6-dimethylquinolines were obtained from Dr. W. A. Ayer of the University of Alberta. 5,7-, 5,8-, 6,7-, 6,8- and 7,8-dimethylquinolines were prepared by J. K. Tandan of these laboratories by procedures described by Manske, Marion

and Leger (107). The melting points of the picrate derivatives were similar to those reported (107).

Preparation of Quinolines

2-Methylquinoline

2-Methylquinoline was prepared in 31% yield from aniline and acetaldehyde in HCl (the Doebner and v. Miller synthesis). The conditions used were those described by Mills et al. (108). The picrate melted at 193.5 - 195.5°(lit. 195°(107)).

2-Methylquinoline-2-α-d_3

Quinoline N-oxide (109) was converted to N-ethoxyquinolinium iodide by treating it with excess ethyl iodide. The N-ethoxyquinolinium iodide was purified by recrystallization from methanol-ether, and was then treated with CD_3MgI using the conditions described by Červinka et al. (110) to give the labelled 2-methylquinoline. The composition of the product determined by low voltage mass spectrometry was: d_0 0.5%, d_1 1%, d_2 4%, d_3 94.5%. An n.m.r. singlet at 2.78δ(3H) in the undeuterated compound was absent in the labelled compound.

2-Methylquinoline-2-α-C^{13}

The procedure used was that described above, except that $C^{13}H_3MgI$ was substituted for CD_3MgI. The composition of the product determined by low voltage mass spectrometry was: C^{12} 45%, C^{13} 55% (corrected for naturally occurring C^{13}).

3-Methylquinoline

3-Methylquinoline was prepared in low yield from aniline, α-methylacrolein and H_2SO_4 using the conditions described by Manske et al. (107). The picrate melted at 187-90° (lit. 190° (107)).

4-Methylquinoline-2-d_1

To a stirred suspension of 100 mg $LiAlD_4$ in anhydrous tetrahydrofuran was added 215 mg lepidine in tetrahydrofuran. The reaction was heated under reflux for 24 h and excess $LiAlD_4$ destroyed with water. This process was repeated twice and the product isolated and purified by chromatography over alumina for n.m.r. analysis. The composition of the product determined by low voltage mass spectrometry was: d_0 8%, d_1 90%, d_2 2%. The n.m.r. spectrum of the undeuterated sample showed a pair of doublets at 7.36δ(1H) and 9.04δ(1H) (J = 4.5 c.p.s.) assigned to the C-3 and C-2 hydrogens, respectively, while the labelled

compound showed a singlet at 7.39δ.

8-Methylquinoline-8-α-d_1

A solution of 300 mg 8-bromomethylquinoline (prepared by the method of Prijs et al. (111)) in 1.5 ml CH_3CO_2D (112) was added dropwise to a stirred mixture of 130 mg zinc metal (granular), 0.8 ml D_2O and 1.0 ml CH_3CO_2D. The reaction mixture was stirred overnight at room temperature and then refluxed for 1 h. The reaction was cooled, dilute HCl added and the mixture washed with ether. The acid layer was basified with NH_3, extracted with ether and the ether layer dried over Na_2SO_4. Evaporation of the solvent gave 130 mg 8-methylquinoline-8-α-d_1, whose composition determined by low voltage mass spectrometry was: d_0 5.5%, d_1 94.5%.

8-Methylquinoline-8-α-d_3

8-Quinolinecarboxylic acid, m.p. 186-187.5°(lit.187-189° (113)), was prepared by Skraup reaction on anthranilic acid and converted to its ethyl ester by the method of Campbell et al. (113). The ester was reduced to 8-hydroxymethylquinoline-8-α-d_2 in 41% yield by adding an ether solution of the ester (0.6g) to a suspension of $LiAlD_4$ (70 mg) in anhydrous ether at 0° as described by Kaslow et al. (114). The deuterated alcohol, which melted at 72-73.5° (lit. 77-78°

(114)), was separated from unreacted starting material by chromatography over alumina (the unreacted ester was eluted with benzene while chloroform was required to elute the alcohol from the column). Reduction of the ester in excess $LiAlD_4$ gave a nearly quantitative yield of alcohol but extensive scrambling (probably in the 2- position) resulted.

HCl gas was bubbled into a benzene solution of the alcohol, and the resulting hydrochloride filtered off. The hydrochloride was then converted to 8-chloromethylquinoline-8-α-d_2 hydrochloride by treatment with thionyl chloride (using the conditions described by Kaslow et al. (115)). The labelled chloromethylquinoline hydrochloride was treated with dilute NH_4OH, and the free base (m.p. 52-54? lit. 53.5-54.5°(115)) was isolated by extracting the basic solution with ether. 8-Chloromethylquinoline-8-α-d_2 (0.24g) was stirred with zinc (140 mg), deuteroacetic acid (2.5 ml) and D_2O (1 ml) for 6 h at room temperature, and then the mixture was refluxed for 1 h. 8-Methylquinoline-8-α-d_3 was isolated from the reaction mixture in 67% yield in a manner similar to that described for the isolation of 8-methylquinoline-8-α-d_1. The composition of the product determined by low voltage mass spectrometry was: d_2 6.5%, d_3 86%, d_4 7.5%. A singlet at 2.76δ(3H) in the n.m.r. spectrum of the unlabelled analogue was absent in

the spectrum of the labelled compound.

Quinoline-2-d_1

To a stirred suspension of 60 mg $LiAlD_4$ in anhydrous ether was added 0.4g quinoline in ether. The reaction was stirred at room temperature for about 12 h. Excess $LiAlD_4$ was then destroyed with water and the process was repeated an additional three times. The composition of the product determined by low voltage mass spectrometry was: d_0 22%, d_1 76%, d_2 2%. The n.m.r. spectrum of unlabelled quinoline showed a quartet at 8.93δ(1H), while the spectrum of the labelled compound indicated that it was about 80% monodeuterated at C-2. Gas chromatography of the product showed that a small amount of an impurity (possibly 1,2-dihydroquinoline (116)) was present.

2,3-Dimethylquinoline

Condensation of isatin and methyl-ethyl-ketone in the presence of base as described by Plant and Rosser (117) gave 2,3-dimethylquinoline-4-carboxylic acid. 2,3-Dimethylquinoline was obtained by distillation of the acid under vacuum, and was separated from the side product (2-ethylquinoline) by fractional recrystallization of their picrates. 2,3-Dimethylquinoline melted at 65-67° (lit. 70° (107)) after recrystallization from petroleum ether, and the picrate

melted at 229-32° (lit. 235° (107)).

2,4-Dimethylquinoline

2,4-Dimethylquinoline was prepared in 53% yield from aniline and 2,4-pentanedione by the method of Combes (118). The picrate melted at 194-196° (lit. 196° (107)).

2,4-Dimethylquinoline-2-α-d_3

2,4-Dimethylquinoline-2-α-d_3 was prepared in a manner similar to that described for 2-methylquinoline-2-α-d_3; 4-methylquinoline-N-oxide was converted to 4-methyl-N-ethoxyquinolinium iodide (m.p. 119-121°) which was in turn reacted with CD_3MgI. The composition of the product determined by low voltage mass spectrometry was: d_2 6% , d_3 92%, d_4 2%. The n.m.r. spectrum of the labelled compound showed a singlet at 2.56δ(3H) while the spectrum of the unlabelled analogue showed singlets at 2.54 (3H) and 2.62δ(3H) assigned to the C-4 and C-2 methyl hydrogens, respectively.

2,6-Dimethylquinoline

2,6-Dimethylquinoline was prepared in 41% yield by a procedure similar to that described for the preparation of 2-methylquinoline (108) except that ρ-toluidine was substituted for aniline. The product melted at 58-59°

(lit. 60° (107)) after recrystallization from petroleum ether (30-60°), and the picrate melted at 189-90° (lit. 191°(107)).

2,6-Dimethylquinoline-2-α-d_3

The procedure used was similar to that described for the preparation of 2-methylquinoline-2-α-d_3; 6-methylquinoline-N-oxide was converted to 6-methyl-N-ethoxyquinolinium iodide (m.p. 105-107°) which was in turn reacted with CD_3MgI. The composition of the product determined by low voltage mass spectrometry was: d_2 2.5%, d_3 97.5%. The n.m.r. spectrum of the labelled compound showed a singlet at 2.43δ(3H) while the spectrum of the undeuterated compound showed singlets at 2.42 (3H) and 2.67δ(3H) assigned to methyl hydrogens at C-6 and C-2, respectively.

3,4-Dimethylquinoline

3,4-Dimethylquinoline was prepared in 26% yield by a Skraup reaction on aniline and 2-methyl-3-keto-butanol. The conditions used were those described by Manske, Marion and Leger (107). The product melted at 79-80.5°(lit. 74° (107)) and the picrate melted at 219-221°(lit. 221°(107)).

4,8-Dimethylquinoline-8-α-d_3

Methyl-vinyl-ketone (18 ml) was added gradually to a stirred solution (at 0°) of 10.2g anthranilic acid in 30 ml. conc HCl. After 0.5 h, 8g $ZnCl_2$ was added and the mixture boiled gently for 4 h. The mixture was cooled, poured on crushed ice and washed twice with chloroform. The mixture was adjusted to ph 4 and extracted five times with chloroform. The residue from the chloroform extracts was recrystallized from methanol yielding 6.3g (45%) 4-methylquinoline-8-carboxylic acid which melted at 167-181° (lit. 183° (119)).

The acid was converted to the corresponding methyl ester (m.p. 35-42°) in 83% yield by treating a methanolic solution of the acid with excess diazomethane at 0°. The ester (1.03g) was reduced with $LiAlD_4$ (120 mg) in ether at 0° yielding 4-methyl-8-hydroxymethylquinoline-8-α-d_2 (0.43g). A sample of the alcohol recrystallized from ethanol-petroleum ether melted at 112.5-114° and the most intense peaks in the mass spectrum (with relative intensities in parentheses) were as follows: m/e 175 (100), 174 (70), 173 (59), 170 (14), 145 (72), 144 (27), 143 (37). The spectrum of the undeuterated analogue showed intense peaks at m/e 173 (83), 172 (100), 170 (13), 144 (72) and 143 (35).

The deuterated alcohol was converted to its hydrochloride which was in turn converted to 4-methyl-8-chloromethylquinoline-8-α-d_2 (m.p. 43°) using the same conditions as those used for the preparation of the labelled 8-chloromethylquinoline. Treatment of the labelled chloromethylquinoline with zinc, deuteroacetic acid and D_2O at room temperature for 6 h afforded the desired 4,8-dimethylquinoline-8-α-d_3 (heating the reaction mixture resulted in extensive scrambling). The product was recrystallized from petroleum ether and melted at 52-54° (lit. 58°(107)), while the picrate of the undeuterated compound prepared by the same sequence of reactions melted at 223-226° (lit. 229° (107)). The composition of the product determined by low voltage mass spectrometry was: d_2 5%, d_3 81%, d_4 13%, d_5 1%. The n.m.r. spectrum showed a singlet at 2.62δ(3H) while the spectrum of the unlabelled compound gave singlets at 2.58 (3H) and 2.82δ(3H) assigned to methyl protons at C-4 and C-8, respectively.

5,8-Dimethylquinoline-5-α-d_3

H_2SO_4 (7.5 ml) was added dropwise to a mixture of 5.1 g 3-amino-4-methylbenzoic acid (Aldrich), 3 ml nitrobenzene and 10.5 ml glycerol. The mixture was heated under gentle reflux for 5 h, cooled and poured on crushed

ice. It was then basified with ammonia and extracted with ether to remove unreacted nitrobenzene. The aqueous layer was boiled with charcoal, filtered and acetic acid added to the hot filtrate. 8-Methylquinoline-5-carboxylic acid crystallized from the cooled solution. Yield 3.0 g (48%). The acid melted at 273-277° with decomposition (rapid heating). The acid was converted to the corresponding methyl ester with excess diazomethane, and the ester reduced to 8-methyl-5-hydroxymethylquinoline-5-α-d_2 (m.p. 116-118°)with $LiAlD_4$ in the usual manner. Intense peaks in the mass spectrum of the deuterated alcohol were observed at m/e 175 (75), 158 (100) and 145 (23). The deuterated alcohol was converted to 8-methyl-5-chloromethylquinoline-5-α-d_2 (m.p. 86-87°) which was in turn reduced to 5,8-dimethylquinoline-5-α-d_3 with zinc and deuteroacetic acid. The composition of the product determined by low voltage mass spectrometry was: d_2 7%, d_3 90%, d_4 3%. The n.m.r. spectrum gave a singlet at 2.78δ(3H) while the spectrum of the unlabelled compound showed singlets at 2.56 (3H) and 2.78δ(3H) assigned to methyl hydrogens at C-5 and C-8, respectively. The picrate of the undeuterated compound prepared by the same series of reactions melted at 182-184° (lit. 186° (107)).

5,8-Dimethylquinoline-8-α-d_3

5-Methylquinoline-8-carboxylic acid [m.p. 173-175°) (lit. 174°(120)] was prepared in 66% yield from 2-amino-4-methylbenzoic acid (Aldrich) under Skraup conditions similar to those described by Campbell et al. (113) for the preparation of 8-quinolinecarboxylic acid. The acid was converted to the corresponding methyl ester, and the ester reduced to 5-methyl-8-hydroxymethylquinoline-8-α-d_2 (m.p. 71-72.5°)with $LiAlD_4$ in the usual manner. The deuterated alcohol was converted to 5-methyl-8-chloromethylquinoline-8-α-d_2 (m.p. 65-68°) which was in turn reduced to 5,8-dimethylquinoline-8-α-d_3 with zinc and deuteroacetic acid under the usual reaction conditions. The composition of the product determined by low voltage mass spectrometry was: d_2 4.5%, d_3 74.5%, d_4 21%. The n.m.r. spectrum showed a singlet at 2.56δ(3H) while the unlabelled compound showed singlets at 2.56 (3H) and 2.78δ(3H) assigned to the methyl hydrogens at C-5 and C-8, respectively.

2-Ethylquinoline and 2-n-propylquinoline

2-Ethylquinoline was prepared by treatment of quinaldine with n-butyllithium followed by addition of methyl iodide as described by Ziegler and Zeiser (121).

The picrate melted at 151-153° (lit. 148°(117)).

2-n-propylquinoline was prepared in a similar manner; ethyl iodide was used instead of methyl iodide. The picrate melted at 163-164.5°(lit. 162-163°(122)).

2-Ethylquinoline-2-α-d_2

2-Ethylquinoline (1.5 mmoles) in anhydrous ether was added to 1.4 ml of a 1.6 N hexane solution of n-butyllithium. One equivalent of D_2O was added with stirring after the reaction mixture had been heated for 0.75 h under nitrogen. This process was repeated an additional five times. The reaction mixture was poured into D_2O, acidified, and washed with ether. The acid layer was then basified and extracted with ether. The ether layer was dried over Na_2SO_4 and the ether evaporated. The composition of the product determined by low voltage mass spectrometry was: d_0 3%, d_1 15%, d_2 69%, d_3 12%, d_4 1%.

2-Ethylquinoline-2-β-d_3

The procedure used was similar to that described for the unlabelled 2-ethylquinoline except that CD_3I was substituted for CH_3I. The composition determined by low voltage mass spectrometry was: d_2 3%, d_3 97%.

2-n-Propylquinoline-2-γ-d_3

2-n-Propylquinoline-2-γ-d_3 was prepared by a procedure similar to that used for the unlabelled compound except that CD_3CH_2Br was used instead of CH_3CH_2I. The composition of the product determined by low voltage mass spectrometry was: d_1 2%, d_2 5%, d_3 93%.

2-Isopropylquinoline

Quinaldine (2g) was treated with 10 ml of a 1.6 N solution of n-butyllithium followed by an equivalent of methyl iodide (12l). After 1 h a second equivalent of n-butyllithium and methyl iodide was added to the reaction. The reaction was quenched by pouring into water and the product extracted with dilute HCl. The acid layer was basified, extracted with ether, and the dried ether extracts evaporated. The n.m.r. spectrum of the product had a doublet at 1.43δ(6H) and a septet at 3.39δ(1H) (J= 7.2 c.p.s.). The picrate melted at 154-155°(lit. 155-157°(123)).

2-Isopropylquinoline-2-β-d_3

The procedure used was that described above, except that CD_3I was substituted for the second equivalent of CH_3I. The composition of the product determined by low voltage mass spectrometry was: d_0 1.5%, d_1 1%, d_2 2.5%, d_3 80%, d_4 3.5%,

d_5 2.5%, d_6 9%.

2-Isopropylquinoline-2-β-d_6

The procedure used was the same as that described above except that CD_3I was substituted for CH_3I. The composition of the product determined by low voltage mass spectrometry was d_3 1%, d_4 1%, d_5 2.5%, d_6 91%, d_7 1%, d_8 3.5%.

3-Ethylquinoline and 3-n-propylquinoline

Ethyl ethylmalonanilate (2.5g), prepared from aniline and diethyl ethylmalonate (124), was heated under reflux with 12.5 g phosphorus oxychloride for 10 hours. The mixture was cooled, poured on crushed ice, basified and extracted with ether. The resulting 2,4-dichloro-3-ethylquinoline was converted to 3-ethylquinoline by heating it with 15 g of tin metal and 55 ml hydrochloric acid for 1 hour. The yield of 3-ethylquinoline was 0.46 g (27% based on ethyl ethylmalonanilate). The picrate melted at 197-198.5° (lit. 199° (125)).

3-n-Propylquinoline was prepared in a similar manner from ethyl n-propylmalonanilate. The yield was 12.5% based on ethyl n-propylmalonanilate. The picrate melted at 168-169° (literature 174-175° (126)).

4-Ethylquinoline and 4-n-propylquinoline

4-Ethylquinoline was prepared by adding 4-methylquinoline and methyl bromide to a stirred suspension of sodamide in ether (at 0°). The reaction conditions used were similar to those described by Tchitchibabine for the preparation of 4-n-propylquinoline (127) and the procedure described by Vogel (128) was used to prepare the sodamide suspension. The picrate of 4-ethylquinoline melted at 191-192° (lit. 200° (129)).

4-n-propylquinoline was prepared by adding 4-methylquinoline and ethyl bromide to the sodamide suspension (127). The picrate melted at 204-207° (lit. 205° (129), 207° (127)).

6-Ethylquinoline and 6-n-propylquinoline

6-Ethylquinoline was prepared in 66% yield from p-ethylaniline using the Skraup conditions described by Long and Schofield (130). The picrate melted at 205-206° (lit. 200-201° (130), 205-205.5° (131)).

6-n-Propylquinoline was prepared in a similar manner from p-propylaniline. The yield was 42% and the picrate melted at 173.5-174.5° (lit, 171-172° (130)). p-Propylaniline was prepared by Raney nickel reduction of p-aminopropiophenone as described by Long and

Schofield (132).

8-Ethylquinoline and 8-n-propylquinoline

8-Ethylquinoline was prepared by a Skraup reaction on o-ethylaniline as described by Glenn and Bailey (133). The nitrate salt melted at 146-149° (lit. 146° (133)).

8-n-Propylquinoline was prepared in 26% yield using the Skraup reaction on o-propylaniline. The picrate melted at 138-140° (lit. 142° (134)). o-Propylaniline was prepared by heating diisobutyllithium hydride and quinoline under nitrogen. The conditions used were those described by Neumann (135).

8-Ethylquinoline-8-β-d_3 and 8-n-propylquinoline-8-γ-d_3

An ether solution of 8-bromomethylquinoline (0.015 mole)(111) was added dropwise to an ether solution of CD_3MgI (0.03 mole). The reaction mixture was heated with stirring for about 45 minutes. The excess Grignard reagent was destroyed by adding water and the mixture extracted with ether. 8-Ethylquinoline-8-β-d_3 was separated from the crude reaction product by gas chromatography, and its composition determined by low voltage mass spectrometry was: d_1 0.5%, d_2 2%, d_3 97.5%.

8-n-Propylquinoline-8-γ-d_3 was prepared in a

similar manner; CD_3CH_2Br was substituted for CD_3I in the preparation of the Grignard solution. Low voltage mass spectrometry showed the composition of the product to be: d_1 2%, d_2 5%, d_3 93%. Yields were low in both preparations.

1,2,3,4-Tetrahydroquinoline-1-d_1

A sample of tetrahydroquinoline, purified by gas chromatography, was treated with 0.3 ml CH_3OD and the CH_3OD evaporated in a vacuum desiccator. The process was repeated three times. A small amount of CH_3OD was pumped through the mass spectrometer before introduction of the sample to minimize back exchange. The composition of the product determined by low voltage mass spectrometry was: d_0 29%, d_1 71%.

1,2,3,4-Tetrahydroquinoline-2,2-d_2

3,4-Dihydrocarbostyril (100 mg) (136) was heated under reflux with 80 mg $LiAlD_4$ in 15 ml anhydrous ether for 2 h. The excess $LiAlD_4$ was destroyed by adding wet ether, then water. The precipitate was removed by filtration and the ether solution dried over Na_2SO_4. The yield of product was 82 mg and its composition determined by low voltage mass spectrometry was: d_1 2%, d_2 98%. The n.m.r. spectrum showed a triplet at 1.96δ(2H) and a triplet at

2.84δ(2H)(J = 6.5 cps) while the spectrum of the non-deuterated isomer showed a multiplet at 1.87δ(2H), a triplet at 2.75δ(2H)(J = 6.5 cps), and a triplet at 3.25δ(2H)(J = 6 cps).

1,2,3,4-Tetrahydroquinoline-3,3-d_2

3,4-Dihydrocarbostyril (85 mg) and sodium methoxide (45 mg) were heated under reflux with 1 ml CH_3OD for 3 h. The solvent was evaporated and the process repeated. The residue was extracted with chloroform and the product reduced with $LiAlH_4$ as described above. The composition of the product determined by low voltage mass spectrometry was: d_1 10%, d_2 90%. The n.m.r. spectrum showed singlets at 2.81δ(2H) and 3.32δ(2H).

1,2,3,4-Tetrahydroquinoline-4,4-d_2

The following sequence of reactions described by Johnson et al. (137) was used to synthesize 4-ketotetrahydroquinoline which was in turn converted to the desired product. Aniline and methylacrylate were condensed to give methyl β-anilinopropionate which was converted to the N-tosyl derivative. Hydrolysis of this ester in methanolic KOH afforded N-tosyl-β-anilinopropionic acid which was converted to the corresponding acid chloride with PCl_5.

The acid chloride was cyclized to 4-ketotetrahydroquinoline tosylate in the presence of stannic chloride and the free base regenerated from the tosylate by acid hydrolysis. The 4-ketotetrahydroquinoline was reduced to 1,2,3,4-tetrahydroquinoline-4,4-d_2 by heating with excess $LiAlD_4$ in ether for 3 h (138). Gas chromatography was used to isolate the tetrahydroquinoline from the crude product (which also contained quinoline and some unreacted starting material). The composition of the product determined by low voltage mass spectrometry was: d_1 6%, d_2 90%, d_3 4%. The desired product was formed in insufficient yield for n.m.r. analysis.

N-methyl-1,2,3,4-tetrahydroquinoline

A stirred mixture of tetrahydroquinoline (1.3 g), dimethylsulfate (2.5 g) and 5 ml H_2O was cooled to 0° and 2.2 g sodium bicarbonate was added slowly. After about 15 minutes the reaction was allowed to warm to room temperature, and 1 ml conc. NH_4OH added after CO_2 evolution had ceased. The mixture was diluted and extracted with chloroform. The dried chloroform extracts gave 0.92 g (64%) N-methyl-1,2,3,4-tetrahydroquinoline on evaporation of the chloroform. The picrate melted at 119-121°, resolidified and melted again at 135-137° (lit.121°, 136-137° (139)).

N-methyl-1,2,3,4-tetrahydroquinoline-N-α-d_3

CD_3I (0.7 g) was added to an acetone solution of quinoline (0.5 g). The resulting methiodide was heated under reflux with tin (5 g) in conc. HCl (15 ml) for 20 h, and the product basified and steam distilled. The distillate was extracted with ether and the ether extracts dried over Na_2SO_4. Evaporation of the solvent gave 0.31 g N-methyltetrahydroquinoline-N-α-d_3 contaminated with a small amount of tetrahydroquinoline. The tetrahydroquinoline was removed by converting it to its non-basic N-benzoyl derivative. The composition of the product determined by low voltage mass spectrometry was: d_2 5%, d_3 95%. The n.m.r. spectrum of the unlabelled compound gave a singlet at 2.80δ(3H) which was absent in the spectrum of the deuterated compound.

N-methyl-1,2,3,4-tetrahydroisoquinoline

Isoquinoline was converted to its methiodide and reduced with tin and hydrochloric acid as described above. The yield was 61% based on isoquinoline. The picrate melted at 152-154° (lit.148-150° (140)).

N-methyl-1,2,3,4-tetrahydroisoquinoline-N-α-d_3

The procedure used was that described above, except

that CD_3I was substituted for CH_3I in the preparation of the methiodide. Determination of the composition of the product by low voltage mass spectrometry was impractical since fragmentation occurred even at 9eV. The n.m.r. spectrum of the unlabelled compound showed a singlet (3H) at 2.33δ which was absent in the spectrum of the labelled compound.

3-Methyl-1,2,3,4-tetrahydroquinoline and 4-methyl-1,2,3,4-tetrahydroquinoline

3-Methylquinoline (85 mg) was heated under gentle reflux with excess tin (1 g) and hydrochloric acid (2 ml) for 72 h. The product was basified, steam distilled and the distillate extracted with ether. Evaporation of the dried ether extracts gave 3-methyl-1,2,3,4-tetrahydroquinoline in about 60% yield. The picrate (recrystallized from toluene) melted at 153-155° (lit.155-156° (141)). 4-Methyl-1,2,3,4-tetrahydroquinoline was prepared in a similar manner from lepidine. The picrate (recrystallized from toluene) melted at 134° (lit.157° (142), 138° (143)), and the N-benzoyl derivative melted at 135-137° (lit.138° (143)).

5,6,7,8-Tetrahydroquinoline

The following sequence of reactions described by

Thesing and Müller (144) was used to prepare 5,6,7,8-tetrahydrocarbostyril which was in turn converted to 5,6,7,8-tetrahydroquinoline by the method of v. Braun (145). Cyclohexanone, formaldehyde solution and dimethylamine-hydrochloride were condensed to give 2-dimethylaminomethyl-cyclohexanone-1 hydrochloride which was converted to the free base. This compound was then condensed with acetamido-pyridinium chloride (prepared by heating pyridine and chloroacetamide) to afford the 5,6,7,8-tetrahydrocarbostyril. 5,6,7,8-Tetrahydrocarbostyril was treated with $POCl_3$ and PCl_5 (145) and the resulting 2-chloro-5,6,7,8-tetrahydroquinoline reduced to 5,6,7,8-tetrahydroquinoline with zinc and hydrochloric acid (145). The picrate of 5,6,7,8-tetrahydroquinoline melted at 155-157° (lit. 157° (145)).

5,6,7,8-Tetrahydroquinoline-5-d_1

3-Amino-2-cyclohexen-1-one was condensed with propargyl aldehyde as described by Zymalkowski et al. (146) to give 5-aza-1-tetralone. Reduction of the tetralone with $NaBD_4$ by Zymalkowski's method yielded 5-aza-1-tetralol-1-d. 110 mg of the alcohol was added to excess $LiAlH_4$ (80 mg) in anhydrous tetrahydrofuran and the mixture heated under reflux overnight. The composition of the product determined by low voltage mass spectrometry was: d_0 5%,

d_1 94%, d_2 1%. Reduction of the tetralone with $LiAlD_4$ resulted in large amounts of d_3 and d_4 species (probably by exchange in the pyridine ring as shown in the preparation of 4-methylquinoline-2-d_1).

5,6,7,8-Tetrahydroquinoline-6,6-d_2

5-Aza-1-tetralone was treated with 50 mg CH_3ONa and 1 ml CH_3OD for 1 h at room temperature. The solvent was evaporated under reduced pressure and the process repeated. The residue was extracted with ether and the ether layer dried over Na_2SO_4. The exchanged tetralone was reduced to 5,6,7,8-tetrahydroquinoline-6,6-d_2 by refluxing it with excess $LiAlH_4$ in tetrahydrofuran for 15 h. The composition of the product determined by low voltage mass spectrometry was: d_0 3%, d_1 12%, d_2 81%, d_3 4%.

5,6,7,8-Tetrahydroquinoline-8,8-d_2

5,6,7,8-Tetrahydroquinoline (20 mg), CH_3ONa and CH_3OD (1 ml) were sealed in a glass tube and heated in a steam bath for about 3 weeks. The composition of the product determined by low voltage mass spectrometry was: d_0 2%, d_1 8.5%, d_2 70%, d_3 16%, d_4 3.5%.

SUMMARY

The mass spectra of some monomethylquinolines, dimethylquinolines, monoethylquinolines and monopropylquinolines have been determined. In addition, the mass spectra of 1,2,3,4-tetrahydroquinoline, 5,6,7,8-tetrahydroquinoline and some monomethyl-1,2,3,4-tetrahydroquinolines have been examined.

Fragmentation of the monomethylquinolines proceeds mainly by loss of H and then HCN, and the spectra of several deuterated analogues suggest that all the hydrogens in the molecule become randomized before loss of H. In the light of these results, it is concluded that the molecule may undergo ring expansion before loss of H. The ring expansion may occur by insertion of the exocyclic carbon between adjacent carbon-carbon or carbon-nitrogen bonds, or it may occur by random insertion between any carbon-carbon or carbon-nitrogen bonds in the molecule. The labelling experiments in this investigation were not extensive enough to differentiate between the two possibilities.

Fragmentation of the dimethylquinolines proceeds by loss of H or CH_3, and then HCN, and the deuterium labelling results on these compounds may similarly be

interpreted in terms of loss of H or CH_3 from two possible ring expanded ions. The spectrum of 5,8-dimethylquinoline-5-α-d_3 is anomalous in that the proportion of H lost from the C-5 methyl in the transformation M→M-H is much greater than predicted from ring expansion prior to loss of H.

The fragmentation of alkylquinolines containing a two or more carbon alkyl side chain depends on the position of the side chain relative to the nitrogen atom. Thus, 2- and 8-ethylquinolines exhibit intense M-1 peaks in their spectra while the remaining isomers show intense M-15 peaks arising from β-cleavage. Similarly, the fragmentation of 2- and 8-n-propylquinoline and 2-isopropylquinoline is influenced by the interaction of the side chain with the nitrogen while 3-,4- and 6-n-propylquinoline exhibit intense peaks arising from β-cleavage.

Peaks at M^+, M-1, M-15 and M-16 characterize the spectrum of 1,2,3,4-tetrahydroquinoline. The M-1 peak originates mainly by loss of a hydrogen α- to the nitrogen, and a mechanism involving ring contraction is proposed to account for formation of the M-16 ion from M-1. The spectra of the monomethyl-1,2,3,4-tetrahydroquinolines are, in most cases, consistent with that of the parent tetrahydroquinoline. An intense peak at M-28 in the spectrum of 5,6,7,8-tetrahydroquinoline readily differentiates it from the spectrum of 1,2,3,4-tetrahydroquinoline.

The results of this investigation show that, in many cases, mass spectrometry may be used to differentiate among the isomers in the various groups of alkylquinolines and tetrahydroquinolines. However, the spectra of some of the isomers (particularly the mono- and dimethylquinolines) are very similar to one another and additional information (possibly the retention times on a gas chromatography column) would be required for the positive identification of these compounds.

REFERENCES

1. S. D. Sample, D. A. Lightner, O. Buchardt and C. Djerassi, J. Org. Chem., 32, 997 (1967).

2. M. Marx and C. Djerassi, J. Am. Chem. Soc., 90, 678 (1968).

3. J. J. Thomson, Rays of Positive Electricity and Their Application to Chemical Analysis, Longmans, Green and Co. Ltd., London, 1913.

4. J. J. Thomson, Phil. Mag., 21, 225 (1911).

5. A. J. Dempster, Phys. Rev., 11, 316 (1918).

6. F. W. Aston, Phil. Mag., 38, 707 (1919).

7. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co. Inc., New York, 1962, P.4.

8. M. J. O'Neal, Jr. and T. P. Wier, Jr., Anal. Chem., 23, 830 (1951).

9. R. I. Reed, J. Chem. Soc., 3432 (1958).

10. H. E. Duckworth, Mass Spectroscopy, University Press, Cambridge, 1958.

11. R. W. Kiser, Introduction to Mass Spectrometry and its Applications, Prentice-Hall Inc., Englewood Cliffs, N.J., 1965.

12. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co. Inc., New York, 1962, P.10.

13. H. E. Duckworth and S. N. Ghoshal in "Mass Spectrometry", (Edited by C. A. McDowell), McGraw-Hill Book Co.Inc., New York, 1963, Chapter 7.

14. J. H. Beynon, Mass Spectrometry and its Applications to Organic Chemistry, Elsevier Publishing Company, Amsterdam, 1960.

15. J. Mattauch and R. Herzog, Z. Physik, 89, 786 (1934).

16. J. Mattauch, Phys. Rev., 50, 617 (1936).

17. K. S. Quisenberry, T. T. Scolman and A. O. Nier, Phys. Rev., 102, 1071 (1956).

18. K. Biemann, P. Bommer and D. M. Desiderio, Tetrahedron Letters, 1725 (1964).

19. H. Budzikiewicz, C. Djerassi and D. H. Williams, Mass Spectrometry of Organic Compounds, Holden-Day Inc., San Francisco, 1967, P.39.

20. R. Ryhage, Anal. Chem., 36, 759 (1964).

21. J. Throck Watson and K. Biemann, Anal. Chem., 36, 1135 (1964).

22. J. A. Völlmin, W. Simon and R. Kaiser, Fresenius' Z. Anal. Chem., 229, 1 (1967).

23. K. Biemann and W. McMurray, Tetrahedron Letters, 647 (1965).

24. A. G. Sharkey, R. A. Friedel and S. H. Langer, Anal. Chem., 29, 770 (1957).

25. H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig and H. Eyring, Proc. Natl. Acad. Sci. U.S., 38, 667 (1952).

26. F. H. Field and J. L. Franklin, Electron Impact Phenomena, Academic Press Inc., New York, 1957, P.68-80.

27. H. Budzikiewicz, C. Djerassi and D. H. Williams, Mass Spectrometry of Organic Compounds, Holden-Day Inc., San Francisco, 1967, P.1.

28. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co., Inc., New York, 1962, Chapter 3.

29. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co., Inc., New York, 1962, Chapter 5.

30. H. Budzikiewicz, C. Djerassi and D. H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, Volume 1, Holden-Day Inc., San Francisco, 1964, Chapter 2.

31. F. H. Field and J. L. Franklin, Electron Impact Phenomena, Academic Press Inc., New York, 1957, P.204-217.

32. J. K. MacLeod and C. Djerassi, J. Am. Chem. Soc., 89, 5182 (1967).

33. K. Knöppel and W. Beyrich, Tetrahedron Letters, 291 (1968).

34. J. A. Hipple and E. U. Condon, Phys. Rev., 68, 54 (1945).

35. J. H. Beynon, R. A. Saunders and A. E. Williams, Table of Metastable Transitions for Use in Mass Spectrometry, Elsevier, Amsterdam, 1965.

36. R. E. Rhodes, M. Barber and R. L. Anderson, Anal. Chem., 38, 48 (1966).

37. K. R. Jennings, Chem. Commun., 283 (1966).

38. J. Seibl, Helv. Chim. Acta, 50, 263 (1967).

39. J. H. Beynon, R. A. Saunders and A. E. Williams, Z. Naturforsch., 20a, 180 (1965).

40. T. W. Shannon and F. W. McLafferty, J. Am. Chem. Soc., 88, 5021 (1966).

41. W. T. Pike and F. W. McLafferty, J. Am. Chem. Soc., 89, 5954 (1967).

42. F. H. Field and J. L. Franklin, Electron Impact Phenomena, Academic Press Inc., New York, 1957, Chapter 2.

43. M. Baldwin, A. Kirkien-Konasiewicz, A. G. Loudon, A. Maccoll and D. Smith, Chem. Commun., 574 (1966).

44. H. M. Grubb and S. Meyerson in "Mass Spectrometry of Organic Ions", (Edited by F. W. McLafferty), Academic Press, New York, 1963, Chapter 10.

45. M. M. Bursey and F. W. McLafferty, J. Am. Chem. Soc., 88, 529 (1966).

46. M. M. Bursey and F. W. McLafferty, J. Am. Chem. Soc., 88, 4484 (1966).

47. M. M. Bursey and F. W. McLafferty, J. Am. Chem. Soc., 89, 1 (1967).

48. F. W. McLafferty, M. M. Bursey and S. M. Kimball, J. Am. Chem. Soc., 88, 5022 (1966).

49. H. Budzikiewicz, C. Djerassi and D. H. Williams, Mass Spectrometry of Organic Compounds, Holden-Day Inc., San Francisco, 1967.

50. H. Budzikiewicz, C. Djerassi and D. H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, 2 Volumes, Holden-Day Inc., San Francisco, 1964.

51. G. Spiteller, Mass Spectrometry of Heterocyclic Compounds in Advances in Heterocyclic Chemistry (Edited by A. R. Katritzky and A. J. Boulton), Academic Press, New York, Volume 7, 1966, P.301.

52. K. R. Jennings, Z. Naturforsch., 22a, 454 (1967).

53. P. N. Rylander, S. Meyerson and H. M. Grubb, J. Am. Chem. Soc., 79, 842 (1957).

54. S. Meyerson and P. N. Rylander, J. Phys. Chem., 62, 2 (1958).

55. F. Meyer and A. G. Harrison, J. Am. Chem. Soc., 86, 4757 (1964).

56. V. Hanuš and Z. Dolejšek, Collection Czech. Chem. Commun., 28, 652 (1963).

57. F. Meyer, P. Haynes, S. McLean and A. G. Harrison, Can. J. Chem., 43, 211 (1965).

58. R. T. Alpin and S. Safe, Chem. Commun., 140 (1967).

59. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co. Inc., New York, 1962, P.302-305.

60. J. H. Bowie, R. G. Cooks, S.-O. Lawesson and G. Schroll, Australian J. Chem., 20, 1613 (1967).

61. V. P. Joynt, R. R. Arndt, A. Jordann, K. Biemann and J. L. Occolowitz, J. Chem. Soc., [B], 980 (1966).

62. J. H. Beynon and A. E. Williams, Applied Spectroscopy 13, 101 (1959). 14, 27 (1960).

63. W. D. Crow, J. H. Hodgkin and J. S. Shannon, Australian J. Chem., 18, 1433 (1965).

64. F. G. Holliman, R. A. W. Johnstone and B. J. Millard, J. Chem. Soc., [C], 2351 (1967).

65. T. Goto, A. Tatematsu and S. Matsuura, J. Org. Chem., 30, 1844 (1965).

66. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co. Inc., New York, 1962, P.184-186.

67. T. Nishiwaki, J. Chem. Soc., [B], 885 (1967).

68. M. H. Benn, T. S. Sorensen and A. M. Hogg, Chem. Commun., 574 (1967).

69. D. H. Williams and J. Ronayne, Chem. Commun., 1129 (1967).

70. K. Biemann, Mass Spectrometry: Organic Chemical Applications, McGraw-Hill Book Co. Inc., New York, 1962, P.130,134-135,152.

71. R. A. Khmel'nitskii, P. B. Terent'ev, A. A. Polyakova and A. N. Kost, Dokl. Akad. Nauk SSSR, 167, 1066 (1966).

72. K. R. Jennings and J. H. Futrell, J. Chem. Phys., 44, 4315 (1966).

73. T. F. Palmer and F. P. Lossing, J. Am. Chem. Soc., 85, 1733 (1963).

74. J. M. Rice, G. O. Dudek and M. Barber, J. Am. Chem. Soc., 87, 4569 (1965).

75. T. Nishiwaki, Tetrahedron, 22, 3117 (1966). 23, 1153 (1967).

76. Y. Rahamin, J. Sharvit, A. Mandelbaum and M. Sprecher, J. Org. Chem., 32, 3856 (1967).

77. H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman and J. M. Wilson, J. Chem. Soc., 1949 (1964).

78. A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams and C. Djerassi, J. Am Chem. Soc., 87, 805 (1965).

79. T. J. Batterham, A. C. K. Triffett and J. A. Wunderlich, J. Chem. Soc., [B], 892 (1967).

80. Catalog of Mass Spectral Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, Spectra No.625,626.

81. C. La Lau, Anal. Chim. Acta, 22, 239 (1960).

82. D. M. Clugston and D. B. MacLean, Can. J. Chem., 44, 781 (1966).

83. T. A. Bryce and J. R. Maxwell, Chem. Commun., 206 (1965).

84. S. J. Weininger and E. R. Thornton, J. Am. Chem. Soc., 89, 2050 (1967).

85. W. M. Bryant, A. L. Burlingame, H. O. House, C. G. Pitt and B. A. Tefertiller, J. Org. Chem., 31, 3120 (1966).

86. J. P. Kutney, I. Vlattas and G. Eigendorf, Tetrahedron, 23, 4587 (1967).

87. A. M. Duffield, H. Budzikiewicz, D. H. Williams and C. Djerassi, J. Am. Chem. Soc., 87, 810 (1965).

88. M. Spiteller-Friedmann and G. Spiteller, Monatsh., 96, 104 (1965).

89. A. M. Duffield, H. Budzikiewicz and C. Djerassi, J. Am. Chem. Soc., 87, 2920 (1965).

90. M. Baldwin, A. G. Loudon, A. Maccoll, L. J. Haynes and K. L. Stuart, J. Chem. Soc., [C], 154 (1967).

91. H. Budzikiewicz, C. Djerassi and D. H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, Volume 1, Holden-Day Inc., San Francisco, 1964, P.173-175.

92. J. Collin, Bull. Soc. Chim. Belges, 69, 449 (1960).

93. K. Heyns, R. Stute and H. Scharmann, Tetrahedron, 22, 2223 (1966).

94. R. I. Reed and W. K. Reid, J. Chem. Soc., 5933 (1963).

95. B. Willhalm, A. F. Thomas and F. Gautschi, Tetrahedron, 20, 1185 (1964).

96. S. D. Sample, Ph.D. Thesis, Stanford University, 1966. Dissertation Abstr., 27, 4326B (1967).

97. R. A. Olofson and J. S. Michelman, J. Org. Chem., 30, 1854 (1965).

98. E. J. Gallegos and R. W. Kiser, J. Phys. Chem., 66, 136 (1962).

99. G. Ohloff, K.-H. Schulte-Elte and B. Willhalm, Helv. Chim. Acta, 47, 602 (1964).

100. G. M. Clarke, R. Grigg and D. H. Williams, J. Chem. Soc., [B], 339 (1966).

101. I. W. Kinney, Jr. and G. L. Cook, Anal. Chem., 24, 1391 (1952).

102. V. Hanuš and V. Čermak, Collection Czech. Chem. Commun., 24, 1602 (1959).

103. Q. N. Porter, Australian J. Chem., 20, 103 (1967).

104. H. Budzikiewicz, C. Djerassi and D. H. Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day Inc., San Francisco, 1964, P. XII.

105. J. G. Burr and R. A. Meyer, J. Chem. Phys., 40, 2046 (1964).

106. Z. Kecki and H. Wincel, Nukleonika, 8, 117 (1963).

107. R. H. F. Manske, L. Marion and F. Leger, Can. J. Research, B20, 133 (1942).

108. W. H. Mills, J. E. G. Harris and H. Lambourne, J. Chem. Soc., 119, 1294 (1921).

109. E. Ochiai, J. Org. Chem., 18, 534 (1953).

110. O. Červinka, A. Fabryova and L. Matouchova, Collection Czech. Chem. Commun., 28, 535 (1963).

111. B. Prijs, R. Gall, R. Hinderling and H. Erlenmeyer, Helv. Chim. Acta, 37, 90 (1954).

112. M. J. S. Dewar and R. C. Fahey, J. Am. Chem. Soc., 85, 2245 (1963).

113. K. N. Campbell, J. F. Kerwin, R. A. LaForge and B. K. Campbell, J. Am. Chem. Soc., 68, 1844 (1946).

114. C. E. Kaslow and W. R. Clark, J. Org. Chem., 18, 55 (1953).

115. C. E. Kaslow and J. M. Schlatter, J. Am. Chem. Soc., 77, 1054 (1955).

116. F. Bohlmann, Ber., 85, 390 (1952).

117. S. G. P. Plant and R. J. Rosser, J. Chem. Soc., 1864 (1929).

118. A. Combes, Compt. Rend., 106, 142 (1888).

119. H. Arai, K. Saito and N. Murata, Kogyo Kagaku Sasshi, 63, 319 (1960). C.A., 59, 6362g (1963).

120. L. Bradford, T. J. Elliott and F. M. Rowe, J. Chem. Soc., 437 (1947).

121. K. Ziegler and H. Zeiser, Ann., 485, 174 (1931).

122. H. Gilman, J. Eisch and T. Soddy, J. Am. Chem. Soc., 79, 1245 (1957).

123. W. Koenigs, Ber., 32, 223 (1899).

124. F. D. Chattaway and J. M. D. Olmsted, J. Chem. Soc., 97, 938 (1910).

125. W. P. Utermohlen, Jr., J. Org. Chem., 8, 544 (1943).

126. R. W. Brown and G. Dougherty, J. Am. Chem. Soc., 69, 2232 (1947).

127. A. E. Tchitchibabine, Bull. Soc. Chim. France, [5], 3, 1607 (1936).

128. A. I. Vogel, A Text Book of Practical Organic Chemistry, Third Edition, Longmans, Green and Co. Ltd., London, 1964, P.197.

129. J. Kenner and F. S. Statham, Ber., 69B, 16 (1936).

130. R. Long and K. Schofield, J. Chem. Soc., 2350 (1953).

131. W. S. Emerson, R. A. Heimsch and T. M. Patrick, Jr., J. Am. Chem. Soc., 75, 2256 (1953).

132. R. Long and K. Schofield, J. Chem. Soc., 2066 (1953).

133. R. A. Glenn and J. R. Bailey, J. Am. Chem. Soc., 63, 639 (1941).

134. J. v. Braun, K. Heider and W. Wyczatkowska, Ber., 51, 1215 (1918).

135. W. P. Newmann, Ann., 618, 90 (1958).

136. L. H. Briggs and G. C. De Ath, J. Chem. Soc., 456 (1937).

137. W. S. Johnson, E. L. Woroch and B. G. Buell, J. Am. Chem. Soc., 71, 1901 (1949).

138. W. S. Johnson and B. G. Buell, J. Am. Chem. Soc., 74, 4517 (1952).

139. P. J. Scheuer, W. I. Komoto and K. Ohinata, J. Am. Chem. Soc., 75, 3029 (1953).

140. S. Hünig and W. Baron, Ber., 90, 403 (1957).

141. M. Avramoff and Y. Sprinzak, J. Am. Chem. Soc., 78, 4090 (1956).

142. A. Tchitchibabine and C. Barkovsky, Compt. Rend., 212, 914 (1941).

143. N. V. Bringi and P. V. Deshmukh, J. Org. Chem., 27, 4117 (1962).

144. J. Thesing and A. Müller, Ber., 90, 711 (1957).

145. J. von Braun and G. Lemke, Ann., 478, 176 (1930).

146. F. Zymalkowski and H. Rimek, Arch. Pharm., 294, 759 (1961).