CARBON SCRAMBLING UPON ELECTRON IMPACT

IN

METHYLQUINOLINES AND METHYLPYRIDINES

CARBON SCRAMBLING UPON ELECTRON IMPACT IN METHYLQUINOLINES AND METHYLPYRIDINES

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ROY CURRAN, B.Sc.

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AUTHOR: Roy Curran, B.Sc. (University of Glasgow)

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SCOPE AND CONTENTS:

The mass spectra of some monomethylquinolines and monomethylpyridines all labeled with ^{13}C in the exocyclic methyl group have been examined. Such studies were undertaken to provide more information about the possible intermediacy of ring-expanded species in the major fragmentation pathways of these compounds.

In the case of the monomethylquinolines ^{13}C labeling studies confirm the rearrangement of the M-1 ion to a ring-expanded species before loss of HCN. The results of the ^{13}C labeling in the monomethylpyridines suggest that rearrangement of the majority of the molecular ions to a ring-expanded species does not occur in the process M→M-HCN.

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HISTORICAL INTRODUCTION

Development of Mass Spectrometers

Possibly the first paper in mass spectrometry was published by E. Goldstein (1) in 1886. He reported the discovery of a luminous ray emerging in straight lines from the holes of a perforated metal disc employed as a cathode in a discharge tube. A decade later, Wien (2) confirmed a suggestion by Perrin (1895) that these positive rays could be deflected in magnetic and electric fields and consisted of positively charged particles.

Based upon these foundations, mass spectrometry developed as a distinct field during the period 1911-1925 mainly as a result of the works of the three founding fathers, Thomson, Aston, and Dempster. In 1912 J.J. Thomson (3), using the so-called parabola spectrograph of his own design, was able to demonstrate the existence of two isotopes of neon.

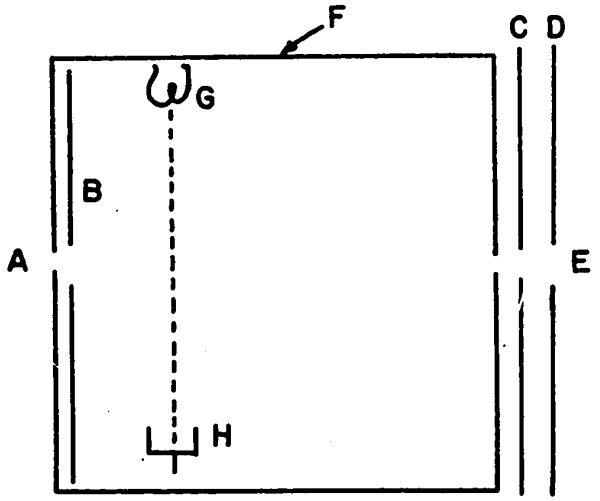
From about 1915-1920 on, mass spectrometry developed along two main lines, one concerned with the precise determination of masses and the other concerned with measuring the relative abundances of ionic species. The mass spectrograph which Aston (4) used in many of his studies of stable isotopes was readily adapted to measurements of isotopic mass, but because of the photographic recording, was not suited to accurate determination of the relative abundances of these isotopes. Working concurrently with Aston, Dempster (5) developed the first mass spectrometer where the magnetic field acts as a lens producing direction

focusing and the ions are focused on an electrometer detector which measures the ion current. Dempster's mass spectrometer could not be used for precise mass measurements but it was better suited than Aston's for measuring the relative abundance of the ionic species and was suitable for studying electron impact processes in gases.

Since then, many important advances in the art of electronics and the development of heated sample inlet systems has made possible the construction of reliable, accurate, and easy to handle mass spectrometers. For a more detailed account of the history and instrumentation of mass spectrometers, the reader is referred to books by Kiser (6) and Roboz (7).

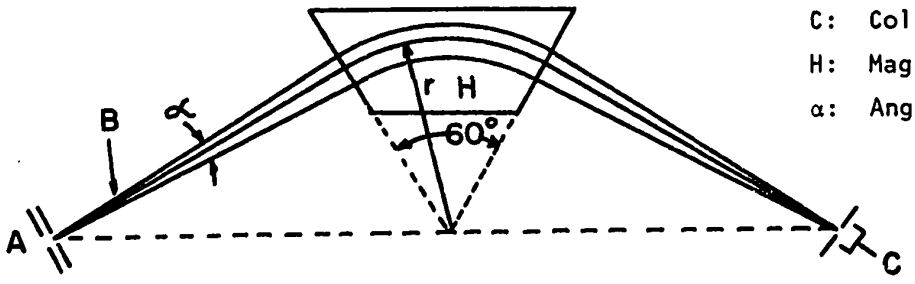
Single focusing mass spectrometers are often of the sector type introduced in 1940 by Nier (8) and use the same principle as that of Dempster's original design. Nier's sector magnetic analyzer is shown schematically in Figure 1b. The vapour is allowed to pass through a slit A into the ion chamber (Figure 1a) where it is bombarded by a beam of electrons accelerated from a filament G, usually from an energy of about 8 to 70eV. One of the processes induced by the electron bombardment is ionization of the molecules of the vapour by removal of one electron. A positively charged molecule ion is formed.

The energy of an electron beam required to remove an electron from an organic molecule is of the order of 8-12eV. However, if the energy of the bombarding electrons is much greater (e.g. 70eV), then the additional energy of the electrons may be dissipated in breaking bonds in the molecular ion producing a number of smaller fragment ions.



A: Entrance slit
B: Repeller plate
C: Lens electrode
D: Accelerating electrode
E: Exit slit
F: Chamber
G: Filament
H: Electron target

(a)



A: Source slit
B: Ion beam
C: Collector
H: Magnetic field
α: Angle of divergence

(b)

Fig. 1(a) Ion source and 1(b) 60^{o} sector magnetic analyzer

The voltage difference between the repeller plate B and the first accelerator plate C establishes a weak field which directs the ions into the acceleration area where the potential difference between plate C and D accelerates the positive ions through the exit slit E, towards the analyser portion of the mass spectrometer. The ion source is held at a positive potential, V, giving the ions a potential energy eV. After the ions are accelerated through a potential drop, V, the ions of mass m have a kinetic energy equal to their potential energy before acceleration:

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

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

$$Hev = \frac{mv^2}{r} \qquad 2)$$

By elimination of v from the above, one obtains

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

Equation 3) shows that ions of a given mass to charge ratio can be brought into focus by variation of either V or H.

In the case of magnetic scanning, V is kept constant and the magnetic field H is increased slowly leading to the recording of the ions. The same is achieved if H is kept constant and the electric field V is decreased. However since the mass to charge ratio varies as the square of the magnetic field, a large mass range can be covered in a single sweep of the magnet, whereas, with electrical scanning, resolution

and intensity decrease at high mass since contributions of initial thermal or kinetic energy become significant at low accelerating potential. On the other hand, electric scanning is easier to achieve electronically and the influence of the magnetic field on the source is kept constant.

The direction focusing of a magnetic field of 180^{o} is only a special case of the focusing action of any wedge-shaped magnetic field. Commonly used is 60^{o} or 90^{o} deflection with the former shown in Figure 1b. The ion beam enters and leaves the field at right angles to the boundary, so the deflection angle is equal to the wedge angle. The geometry is symmetrical in that the source and the detector are equidistant from the magnet.

The ion resolving slit, also known as the collector slit, is located at the focal point in magnetic deflection instruments and behind this slit is positioned a collector. Detection and measurement of the positive ions sorted by the analyser can be accomplished by electrical and photographic means. The types of ion detectors are described in detail by Roboz (7).

For a single focusing instrument only a low resolution is obtained. If there is a spread in the kinetic or thermal energies of the ions before or during acceleration, there will be a spread in the magnitude of v resulting in a spread of r for given values of m/e. The ion beam will therefore be refocused over a wider area, which limits the resolution of the system.

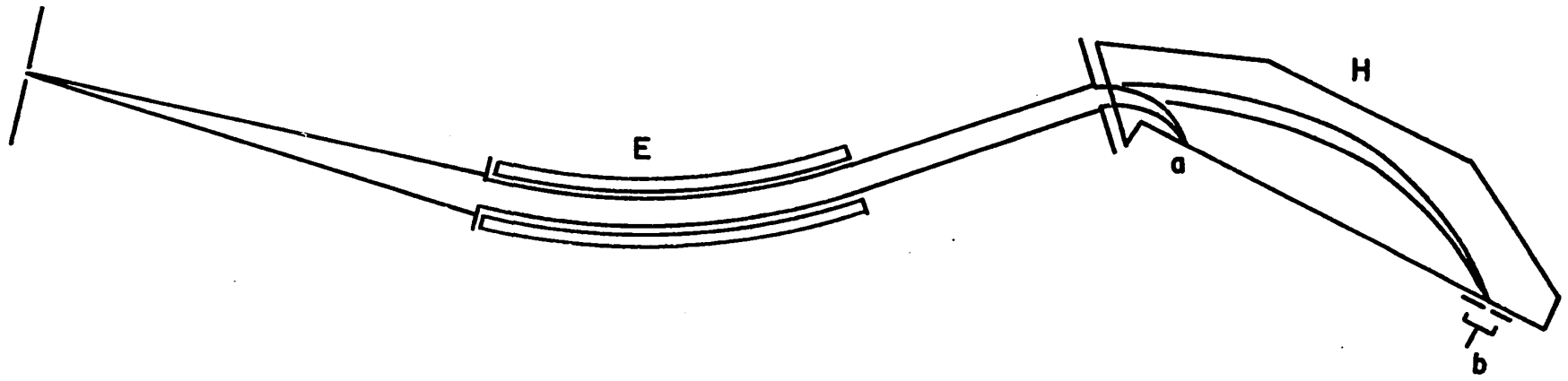
Considerable increase in resolving power is achieved by elimination of this energy spread by the use of a radial electrostatic field.

When an ion traverses a radial electric field, the field, acting as an energy separator, filters out a particular energy with the aid of a suitably located slit. The portion of the beam that passes this slit could next be introduced into a sector magnetic field which would then receive a monoenergetic beam. This is the principle used in double-focusing mass spectrometers. This radial electric field is set up such that when positive ions of various masses and energies are injected normal to the electric field, the ions, which describe an exactly circular trajectory, will have an energy content so that the centrifugal force exactly balances the acting electrostatic force:

$$\frac{mv^2}{r_e} = eE \qquad \text{or} \qquad r_e = \frac{mv^2}{eE} \qquad 4)$$

where v is the velocity of the injected ion of mass m, E is the field strength and r_e is the radius. It is seen from this equation that such a system is an energy filter and only ions with a predetermined energy can describe a circular path r_e. The geometry of a mass spectrometer employing both an electrostatic and magnetic field designed by Mattauch and Herzog (9) is shown schematically in Figure 2. Beynon (10) is credited with being the pioneer in high resolution mass spectrometry of organic compounds.

The term "resolution" is used in different ways. Most popular is, perhaps, the "% valley" definition (11) where the intensity between two peaks of equal height is expressed as a fraction of the maximum intensity. The height of the "valley" between two peaks of equal intensity is therefore an indication of the separation of the peak on



a: Photographic plate
b: Collector
E: Electrostatic field
H: Magnetic field

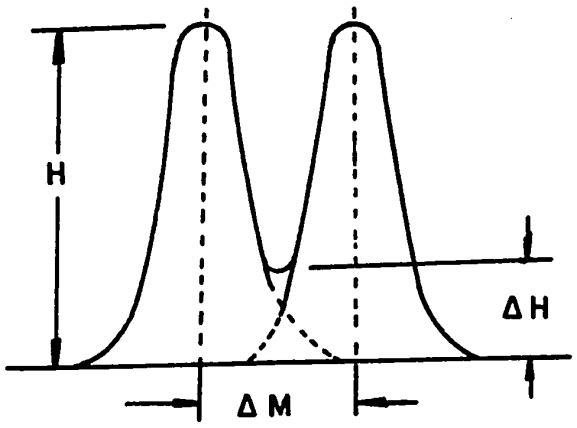
Fig. 2 Double focusing design of Mattauch and Herzog

the record. The emphasis here is on the ability to distinguish two distinct peaks, i.e. a qualitative analysis and the resolution is considered as $\frac{M}{\Delta M}$, such that the two ion beams, M and M + ΔM, exhibit a valley between them not greater than a certain percentage, i.e. $\frac{\Delta H}{H}$ = 10% as shown in Figure 3a.

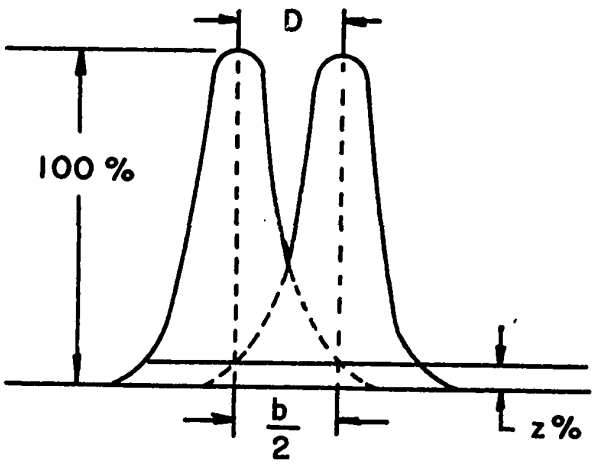
For quantitative analysis, the determined peak intensities must be accurate measures of the intensity of the ion beam producing the peak. In other words, contributions from adjacent peaks must be minimal. Using the "peak height contribution" or "cross-talk" definition of resolution, the intensity with which one peak contributes to the intensity of the other at its highest value is given as a fraction of the peak height (Figure 3b). Unit resolution is considered to mean that one peak will add less than Z% to the height of an adjacent peak of equal height with Z% usually less than 5%. Thus resolution is measured by the following equation:

$$R = \frac{2 \times \text{Distance between peaks}}{\text{Base of peak}} \times \frac{M}{\Delta M}$$

Instruments of high resolving power require a method for determining the exact mass of an unknown fragment. One such method involves the "peak matching" technique originally described by Nier (12) et al., in which two peaks, one known and the other unknown, are alternately displayed several times a second on an oscilloscope. This is accomplished by varying the electrostatic sector voltage at a constant magnetic field. The potential difference which can be measured with great accuracy may be expressed in terms of difference in mass, and the



(a)



(b)

Fig. 3(a) "Percent Valley" definition of resolution
3(b) "Cross Talk" definition of resolution

mass of the unknown may thus be calculated.

A second method that can be used with the Mattauch type of double focusing spectrometer is less time consuming and equally accurate. All masses are focused in one plane in which a photographic plate is placed. The different ions are recorded as parallel lines with the distance between the lines varying linearly with the square root of the mass of the ions. Normally a standard compound is introduced with the unknown to allow some exposures on the plate to contain ions of known mass. By means of a comparator the distances between standard masses and the unknown masses can be determined with great accuracy. The line densities (peak intensities) are measured approximately with a densitometer. All such information can be read onto a magnetic tape which can then be processed by the computer to give ion compositions and masses.

The vast amount of data thus accrued can be presented in a concise and clear form by the use of "element maps", introduced by Biemann (13,14). Further methods of data presentation are discussed in the book of Budzikiewicz, Djerassi and Williams (15).

Theory and Interpretation of Mass Spectra

When electrons of sufficient energy collide with neutral molecules and produce an inelastic collision, a number of changes may occur, the processes of ionization and dissociative ionization being the most important, as they lead to ion formation. Thus if the energy of the electron beam equals, or is slightly greater than the ionization potential of the molecule, a molecular ion will be produced. Electron energies above the ionization potential, i.e. dissociative ionization,

will tend to give rise to fragment ions.

An attempt has been made to offer a theoretical basis for the interpretation of mass spectra. This so called quasi-equilibrium theory of mass spectrometry, developed by Eyring and his co-workers (16), assumes that ions are formed by a vertical Franck-Condon type of ionization. The molecular ion is formed with a range of excitation energies and this energy is rapidly degraded into vibrational energy of the ground electronic state of the ion. Consequently it can be assumed that the excess energy can distribute itself over the whole molecular ion in a random fashion. Fragmentation of the molecular ion occurs when sufficient vibrational energy is concentrated in a particular bond, and this fragmentation is then described in terms of first order rate theory. The fragment ions so formed can themselves decompose in the same manner. Primary emphasis in the development of this model since its original introduction has been on the correct description of the first order rate constants (17). A second use of the theory, the calculation of mass spectra produced by 70eV electrons, has received considerably less attention because of the difficulty in calculating the internal energy distribution function. The results are only in semiquantitative agreement with experiments, partly due to the complexity of the theory and the many assumptions involved in its use. For example Kiser (18) has used the theory to calculate the mass spectrum of thiacyclobutane with fair success. Ten years later, the calculation of Gilbert and Stace (19) on the same compound gave calculated spectra showing only reasonable agreement with the experimental values.

For most organic compounds an empirical approach is used for interpretation of their spectra. Silverstein and Bassler (20) list nine basic rules for fragmentation. These rules are arrived at by combining experimental evidence with chemical rationalization using such concepts as resonance, hyperconjugation, polarizability, and inductive and steric effects - i.e. by the rational application of everyday concepts of organic chemistry. This approach implies, however, that the positive charge is located at a specific site and would seem to contradict the quasi-equilibrium theory. Djerassi (21) et al., believe that the concept of charge localization upon electron impact provides an admirable rationalization of the mass spectral fragmentation in a given molecule. They assume that initial ionization may occur at any site within a molecule, but that the positive charge rapidly localizes at certain favoured sites. Subsequent fragmentation is therefore directed by the site of the electron deficiency. Mandelbaum and Biemann (22) prefer the dynamic distribution concept, which distributes the charge throughout the molecule, statistically maximized at the site of the lowest ionization potential. Kinstle and Oliver (23) conclude from recent investigations that it is difficult to predict the extent of charge mobility in a particular molecule, but that in some instances a dynamic distribution of charge appears to operate. Subsequent papers by Wagner (24), Lengyel (25), and Vetter (26), seem to agree with Mandelbaum and Biemann. Howe and Williams (27) state that the equilibrium hypothesis appears capable of explaining existing data, and therefore charge is not necessarily localized in the classical sense, except

perhaps in a small fraction of ions of relatively low internal energy.

However, many fragmentation patterns are still explained using charge localization. Rules derived by Silverstein and Bassler (20), Biemann (28), and McLafferty (29), are largely formulated from experience but there is no assurance that such fragmentations do occur or that such ions do exist with the predicted structures. Since it is impossible to collect and examine these ions in the classical sense, other techniques have been devised to obtain information about the proposed ion structures. A short review of some recent work of these techniques is given below.

During the last few years a realization has developed among many research workers that the basic tenets of the quasi-equilibrium theory (16,17) of mass spectra have much to offer in the interpretation of the mass spectra of organic molecules. Among the methods currently used in ion structure determinations are: thermochemical measurements, metastable ion characteristics, isotopic labeling and substituent effects (30). Before discussing some aspects of the above methods a summary of the theories of mass spectrometry is required.

Ionization by electron impact produces a molecular ion having a range of internal energies extending from zero at the ionization potential (I.P.) to an upper limit of $E_{th} + E_{el} - I.P.$, where E_{th} is an upper limit for the thermal energy of the molecule and E_{el} is the electron beam energy. The energy distribution is therefore a function not only of the transition probability to a given energy level, but also of I.P., E_{el}, and the operating temperature. Since the pressure is

usually low, collisions between molecules can be disregarded and as a result there is no thermodynamic equilibrium and Boltzmann energy distribution. Consequently Arrhenius-type equations cannot be used. The intensity or abundance of the molecular ion is due to those ions with insufficient energy to decompose to daughter ions in the source. Fragment ions are formed when the energy in the source is above the appearance potential.

As stated before, the excited molecular ion undergoes several vibrational changes prior to decomposition. These changes result in a distribution of the excitation energy in a random fashion, and decomposition of the molecular ion occurs only when sufficient energy has concentrated in a particular bond.

A simplified version of the rate constant developed by Rosenstock et al. (17) has -

$$k(E) = \nu\left(\frac{E - E_o}{E}\right)^{s-1} \qquad 5)$$

where k(E) represents the rate constant at total internal energy E with activation energy E_o, ν is a frequency factor and s is the number of effective oscillators. This simplified equation has been used by many authors (31) for qualitative explanations of spectral features obtained from the general features of k(E) vs E curves.

(1) Energetic considerations: The heats of formation of organic ions calculated from appearance potentials have been used for several years to provide evidence for or against a particular ion structure.

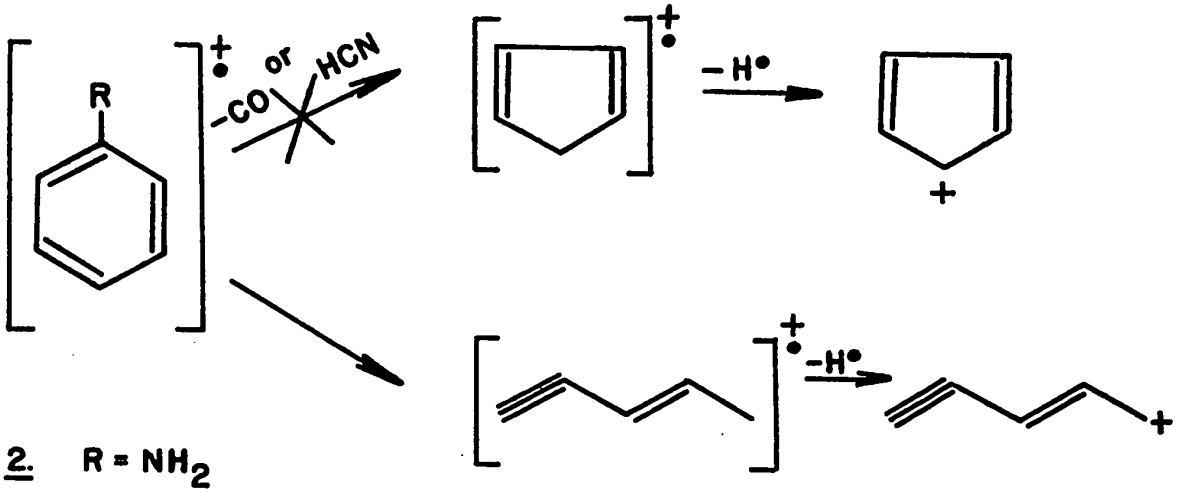
For the reaction $M + e \longrightarrow X^+ + Y + 2e$, one can express the

appearance potential $A(X^+)$ as follows:

$$A(X^+) = \Delta H_f(X^+) + \Delta H_f(Y) - \Delta H_f(M) + E \qquad 6)$$

where the ΔH_f's are standard heats of formation and the term E accounts for the fact that X^+ and/or Y may be formed with excess energy at the threshold. Problems arise, however, in the measurement of ionization and appearance potentials and the methods of interpretation of the ionization efficiency curves are quite subjective (32). The measured appearance potential is not necessarily equal to the minimum energy required to cause formation of X^+. The excess energy required to achieve ion formation is termed the kinetic shift (33). The excess energy E, which corresponds to the energy of activation for the back reaction, is also a source of error, since the conditions under which E would be significant are not well known.

Calculations of heats of formation of organic ions have been carried out using equation 6) with some recognition of the limitations imposed by the excess energy terms (34). It has been shown that when excess energy is included, the method is capable of yielding good values for the heats of formation of radicals and ions (35), and in some cases the results from energetic considerations require the proposal of new structures. Occolowitz and White (36) concluded from their calculations that previous structures for the fragment ions from phenol 1, aniline 2, the naphthols, and coumarin are inconsistent with the energetics of formation of the ions and proposed ions of an open chain nature.



2. R = NH_2

1. R = OH

(2) Metastable ion characteristics: From the quasi-equilibrium theory it can be seen that ions with insufficient energy to decompose in the source, but with a half life in the range 10^{-5} to 10^{-6} sec, will, however, fragment before entering the analyzer region and will be recorded neither as m_1 nor m_2, but as a small difuse peak. These metastable peaks, m^*, observed in the spectrum, can be correlated with the decomposing ion m_1 and the daughter ion m_2 by the following expression (37):

$$m^* = \frac{m_2^2}{m_1} \qquad 7)$$

The mass spectra of most compounds contain such metastable peaks and the heights depend on the abundance of the decomposing metastable ions, on their half lives, and on the efficiency of collection of ionized

fragments produced at various points along the flight path. The usefulness of metastable ions for ion structure determinations is no longer limited to those compounds which produce large visible metastable ions. Since the advent of the logarithmic transfer recorder (38) and the defocusing technique (39), which produces pure metastable spectra, many people have used metastable ions in structural determinations. The use of the defocusing technique allows unique determination of the parent and daughter ions for the transition which is usually but not necessarily a one-step process (40).

The shape of most of the peaks observed is roughly Gaussian, but variations from "narrow triangular" through "Gaussian", "very diffuse and rounded", "flat-topped", to "continua", extending over several mass numbers are observed often in the same mass spectrum (41). The shape of the peaks depends, among other things, on the position at which the decomposition occurs and on the kinetic energy released during decomposition. Beynon and co-workers (42) have shown that the width of a "flat-topped" peak is directly related to the kinetic energy released during decomposition, and that the formation of neutral fragments is usually a necessity for this energy release to occur.

Shannon and McLafferty (43) have used metastable characteristics in assignment of structures to ions giving rise to common metastables. If the abundances of metastable ions formed from different precursors, relative to the precursor or the daughter ion abundances, are equal, the precursors must be identical in structure. This technique (44) has been used extensively in formulating "common" ion structures. Both Occolowitz

(45) and Yeo and Williams (46) have separately studied the problems involved in assigning ion structures from metastable ion abundance ratios. They have found both from theoretical and experimental evidence that the ratio of metastable abundances of ions is in general dependent on the internal energy and any assignment of structures to ions from such results must be interpreted with caution.

(3) Substituent effects: A quantitative interpretation of substituent effect (measured in terms of daughter:parent ion ratios) in organic mass spectrometry was advanced by Bursey and McLafferty (47). A large number of publications concerned with the interpretation of substituent effects in aromatic mass spectra, followed as a result of the initial publication (48). McLafferty's original work used the quantitative correlations of the Hammett equation (49) which relates the rates or equilibria of many reactions of meta and para substituted aromatic compounds in solution. McLafferty (47) modified the Hammett equation to permit correlation of ion abundances Z/Z_o with σ, the substituent constant, and ρ, a reaction constant such that

$$\log \ Z/Z_o = \rho\sigma \qquad 7)$$

where $Z = \frac{\text{intensity of daughter ion}}{\text{intensity of molecular ion}}$, i.e. $\frac{A^+}{M^+}$ and $Z_o = \frac{A_o^+}{M_o^+}$ for the unsubstituted aromatic compound. For example, Bursey and McLafferty have shown (47) that log Z/Z_o values (calculated from daughter/parent ratios) for the formation of the benzoyl ion from substituted benzophenones correlate well with Hammett σ values, indicating that the structure of the substituted ring was intact up to the transition state.

The fact that ortho and meta substituted phenetoles gave the same ratio of Z/Z_o for the formation of and subsequent decomposition of the $(M-C_2H_4)^+$ ion implied a rearrangement to a common molecular ion before fragmentation.

A recent critical review (30) on the subject of substituent effects on ion decomposition has drawn attention to several relevant points overlooked in the original work:

These are:-

(i) An electron donating substituent will increase the fraction of molecular ions with insufficient energy to decompose resulting in a decrease in $\frac{A^+}{M^+}$ (30,52).

(ii) Contrary to earlier indications $\frac{A^+}{M^+}$ ratios are dependent on the rates of competing fragmentation of the molecular ion, i.e. the observed $\frac{A^+}{M^+}$ is not necessarily the same as the $\frac{A^+}{M^+}$ in the source.

(iii) The effect of the substituent on the kinetic shift has been neglected.

A paper by Chin and Harrison (48) has collated the factors which determine the effect of substituents on ion abundances and has critically examined them.

(4) Isotope labeling: Probably the single most useful technique in mechanistic studies in mass spectrometry has been the use of isotopically labeled molecules. In this method a stable isotope, such as deuterium is specifically introduced by a known reaction. In addition to the use of deuterium there has been increasing use of ^{13}C, ^{15}N, and ^{18}O as labels, providing interesting and surprising results. If it is

assumed that the positions of the labeled atoms in a molecular ion correspond to that in the neutral molecule from which the ion is formed, then a knowledge of the fate of the label in subsequent fragmentations often allows the proposal of reasonable ion structures and fragmentation mechanisms.

Scrambling of hydrogen atoms in aromatic (53), substituted aromatics (54), and heterocyclic compounds (55) have been the subject of much recent investigation. Scrambling of the hydrogen atoms may involve one ring, those of two fused rings, or those of two directly bonded rings (56).

A primary isotope effect favouring loss of hydrogen preferentially over deuterium which was overlooked in earlier publications (57), has now been calculated for several aromatic systems (58). In an elegant paper Howe and McLafferty (54) illustrate the use of the quasi-equilibrium theory to measure the isotope effect in the toluene system, as a function of internal energy over a wide energy range. Williams and co-workers (59) have recently used the deuterium isotope effect in the investigation of the loss of CO from phenol. This reaction requires a hydrogen transfer, and a primary deuterium isotope effect in the rate of loss of CO does occur. By examining the metastable abundance ratios of $\frac{M^*(M^+-X)}{M^*(M^+-CO)}$ for p-halophenols and deuterated p-halophenols, the isotope effect on CO loss from the molecular ion was investigated. Thus a primary deuterium isotope effect may be observed in a reaction that does not involve the loss of hydrogen-containing fragments.

Recent measurements of the spectra of aromatic (60) and hetero-

aromatic systems (61,62), using ^{13}C indicate that partial or complete carbon scrambling also occurs prior to fragmentation of the molecular ion.

Many of the mass spectral reactions of organic ions have been interpreted in the above sections with the aid of the quasi-equilibrium theory. Unfortunately the quasi-equilibrium theory only allows semi-quantitative predictions due to the fact that it incorporates too many unknown, or little-known, parameters which are difficult to calculate. Several authors (67) have recently attempted to apply molecular orbital theories to organic mass spectrometry to explain the major fragmentation paths of complex molecules.

Mass Spectra of Aromatic and Heteroaromatic Compounds

A complete list of the publications concerning the mass spectra of aromatic and heterocyclic compounds is beyond the scope of this work. For a comprehensive study of the mass spectra of heterocyclic compounds the reader is referred to a recent book by Porter and Baldas (63) and to a detailed review on the same subject by Spiteller (64).

Scrambling of hydrogen and carbon in aromatic (60), substituted aromatic (61), and heteroaromatic (62) compounds produced by electron impact has been shown to be extensive. A list of publications pertinent to this phenomenon is presented in Table 1. This list is by no means complete but consists of those references related to the discussion.

Aromatic and heteroaromatic rings are usually stable. Consequently, in the absence of large aliphatic substituents, the spectra of aromatic and heteroaromatic molecules often show intense molecular

TABLE I

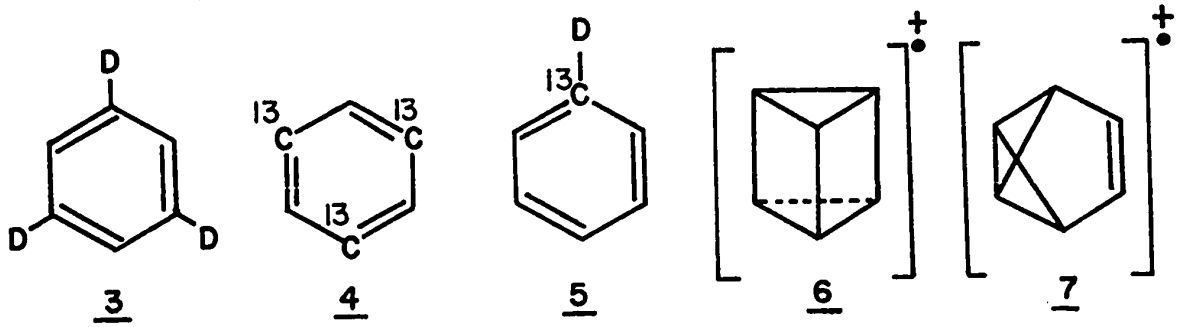
Mass Spectra of Aromatic Hydrocarbons and Heteroaromatic Compounds

Compound	Reference
aromatic hydrocarbons	
benzene	53, 60, 65, 66
toluene	54, 58a, 68, 69, 70, 71
alkylbenzenes	58a, 72, 73
C_7H_8	54, 71, 74
C_8H_{10}	75
naphthalenes	76
substituted aromatic hydrocarbons	
substituted benzene	76, 77, 79, 80, 81, 82
substituted naphthalenes	56, 83
five-membered heteroaromatic compounds with one heteroatom	
furans	84, 85, 86, 87
benzofurans	88
thiophenes	85, 87, 89, 90
benzothiophenes	56, 91, 92
pyrroles	61, 93
indoles	61, 94, 95

TABLE I (cont'd)

Compound	Reference
five-membered heteroaromatics with more than one heteroatom	
oxazoles	96, 97
isoxazoles	98,
thiazoles	56, 99
benzothiazoles	56, 100
isothiazoles	101
imidazoles	102
benzimidazoles	103
pyrazoles	104, 105
six-membered heteroaromatic compounds with one heteroatom	
pyridines	55, 58c, 106, 107, 109
quinolines	55, 62, 107, 110, 111
six-membered heteroaromatics with more than one heteroatom	
pyridazines	112
pyrimidines	113, 114
quinazolines	115
pyrazines	116
triazine	117

ions. In the case of unsubstituted aromatics, the only other ions of significance are caused by expulsion of a small neutral molecule. Peaks arising from doubly-charged ions account for a significant fraction of the total ionization in the mass spectra of many aromatic compounds. Benzene itself loses C_2H_2 (acetylene) from the molecular ion and Jennings (53) has shown that complete hydrogen equivalence exists in the molecular ion of 3 before acetylene loss. Analysis of the mass spectra of 4 (60) and 5 (66) has demonstrated that both hydrogen and carbon scrambling occurs in the benzene molecular ion prior to the loss of acetylene from molecular ions of low internal energy.

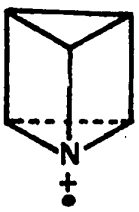


3 4 5 6 7

Such scrambling may be envisaged as occuring via prismane 6 and benzvalene 7 intermediates by analogy with known photochemical transformations (118). In the case of monosubstituted benzenes where decomposition involves loss of a fragment containing hydrogen, deuterium labeling studies have shown that hydrogen randomization occurs in the molecular ion before loss of a neutral fragment. Thus deuterium labeled phenylisocyanide (119) and benzonitrile (78) undergo complete randomization of hydrogen in their molecular ions before the metastable loss

of HCN and DCN.

In unsubstituted heteroaromatic compounds the main primary degradation is usually the loss of the heteroatom in the form of a small molecule. Nitrogen containing heteroaromatics lose the nitrogen atom as HCN. Thus, the mass spectrum of pyridine exhibits the loss of the elements of HCN from the molecular ion. Williams and Ronayne (106) have studied the fragmentation of pyridine-2-d and pyridine-2,6-d_2 and have shown that involvement of the α-, β-, and γ-hydrogen atoms occurs in the loss of HCN from the molecular ion. This randomization, which is analogous to that which occurs with the hydrogen atoms of benzene (53, 66) and thiophene (89), may involve the intermediacy of azaprismane 8 and azabenzvalene 9.



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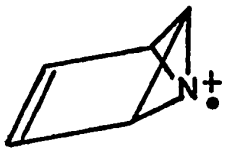

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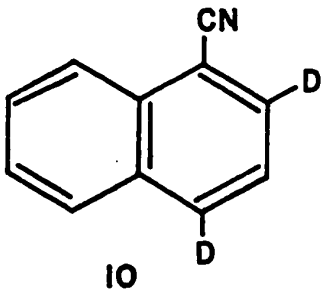
At the present time ^{13}C labeling experiments have not been reported to confirm that skeletal rearrangements occur.

In the case of thiophene (85,89), however, only partial hydrogen scrambling is observed prior to CHS^+ formation. Mass spectra of deuteriothiophenes show that about 60% of the CHS^+ ion yield is derived from

molecular ions that have not undergone prior rearrangement. The proportion of CHS^+ ions formed from molecular ions that have undergone prior rearrangement increases as the ionizing voltage is lowered as predicted by the quasi-equilibrium theory. In contrast the hydrogens of thiophene are completely scrambled prior to the elimination of C_2H_2. Siegel (90) examined the mass spectrum of thiophene-2,5-$^{13}C_2$ and found that in the formation of CHS^+ ions approximately 70% of the CHS^+ ions are formed from an unrearranged species and that this percentage decreases as the ionizing voltage is lowered. However a significant amount of scrambling occurs before expulsion of acetylene.

Unlike thiophene, furan (85,87) undergoes no hydrogen randomization prior to fragmentation. Deuterium labeling results indicate that either hydrogen randomization does not occur in furan prior to fragmentation, or is slow compared to the rate of fragmentation.

Deuterium labeling of some bicyclic aromatic systems has revealed complete or partial randomization of aromatic hydrogens on electron impact. Williams and co-workers (56) examined 1-cyanonaphthalene-2,4-d_2 10 and its isomer 2-cyanonaphthalene-2,3-d_2 and found that the molecular ions undergo HCN:DCN loss in a ratio 5:2 suggesting complete scrambling of the aromatic hydrogens over both rings prior to metastable decomposition. A similar result was obtained for benzothiophene-2,3-d_2 11 before acetylene loss (56) and Cooks (92) established that carbon scrambling occurs prior to formation of many of the decomposition products of benzothiophene-2-^{13}C 12.



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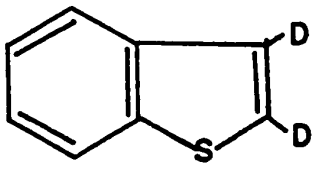

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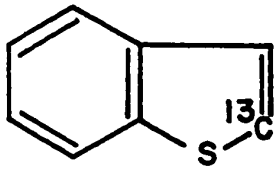

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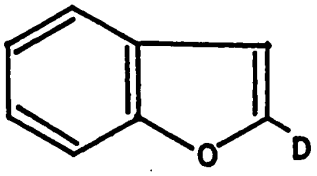

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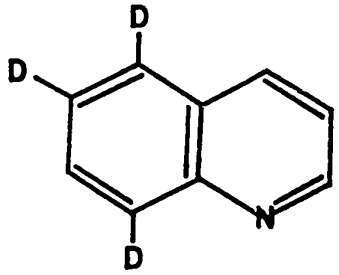

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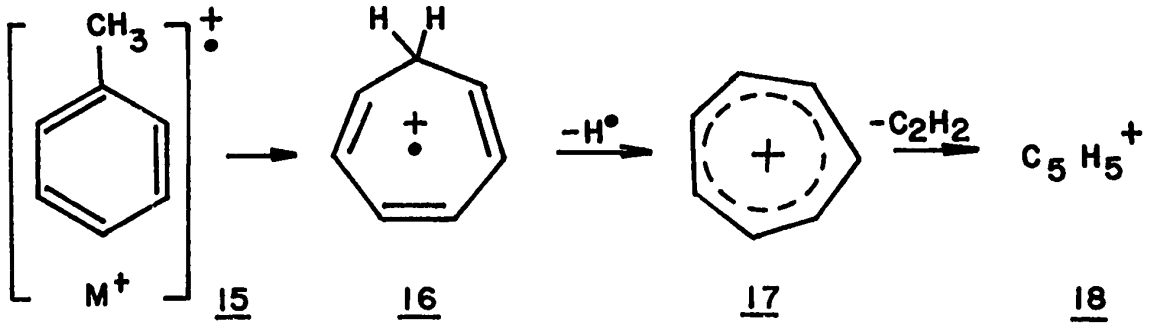
Surprisingly the mass spectra of benzofuran-2-d 13 and benzofuran-5-d (88) indicate partial scrambling prior to loss of CHO from the molecular ion, in contrast with furan itself. Williams and coworkers (55) examined deuterated quinolines (e.g. 14) and concluded that the hydrogen atom expelled in HCN from quinoline, in parent ions decomposing in the first field-free region, is derived with equal probability from all nuclear positions.

The presence of an alkyl group in aromatic or heteroaromatic molecules alters the fragmentation pattern and the cleavage of a bond β to the aromatic nucleus becomes a favoured process.

Alkylbenzenes

The classical work of Meyerson and co-workers on the fragmentation of alkylbenzenes, started in 1957 (120), has resulted in a veritable flood of publications on this and closely related topics. The formation of the abundant $C_7H_7^+$ ion from the spectra of alkylbenzenes has attracted a great deal of research interest. Extensive studies with compounds labeled with deuterium and ^{13}C (68) have led to the conclusion that the $C_7H_7^+$ ion formed from toluene, several other C_7H_8 isomers, ethylbenzene, and several other benzyl derivatives does not retain the benzyl structure but can best be represented as the symmetric tropylium ion formed by ring expansion.

The results of Meyerson's work led him to conclude that all of the C_7H_8 isomers first rearrange to a common $C_7H_8^{+\bullet}$ structure which resembles the cycloheptatriene isomer but is of even higher symmetry.



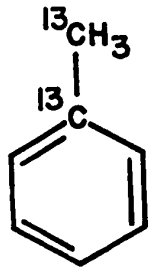
Scheme 1

Meyer and Harrison (58a) however suggest that there is an initial irreversible isomerization of the molecular ion to the cycloheptatriene isomer 16 as shown in Scheme 1 by transfer of an α-hydrogen to the adjacent ring carbon atom, followed by insertion of the methylene group

at random between any two ring carbons. The hydrogen atoms of 16 may lose their positional identity prior to the $C_7H_7^+$ formation 17 by a series of 1,2-hydrogen shifts.

Jennings (121) concluded from appearance-potential measurements on $R\text{-}C_7H_6^+$ ions in the mass spectra of substituted benzyl compounds that for $R=CH_3$, F, and OH, the ions are most probably substituted tropylium ions, whereas for $R=CH_3O$, the ion is best represented as $CH_3O\text{-}C_6H_4\text{-}CH_2^+$.

Recent evidence by Howe and McLafferty (54) has shown that hydrogen in the molecular ions of deuterated toluene and cycloheptatriene appears to be completely scrambled in the formation of low-energy ions arising from unimolecular transitions, but that the degree of scrambling decreases as the internal energy increases. It would thus appear that Harrison's (58a) postulate of an initial isomerization of the C_7H_8 molecular ion to that of cycloheptatriene is correct. Labeling of toluene with ^{13}C, as in 19 and 20, provided further evidence for formation of the tropylium ion.



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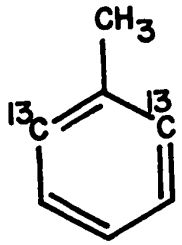


20

Rinehart and co-workers' (69) study of toluene-α,1-$^{13}C_2$, 19 provides evidence for the formation of the tropylium ion by a random insertion of the α-carbon between any carbon-carbon bond in the benzene ring. The observed abundances for the loss of $^{13}C_2H_2$, $^{13}C_1C_1H_2$, and C_2H_2 giving respectively C_5H_5, $^{13}CC_4H_5$, and $^{13}C_2C_3H_5$ agree with the theoretical abundances calculated from a tropylium ion formed by random insertion of the α-carbon between the adjacent ring carbons. By studying the formation of acetylene loss from toluene-2,6-$^{13}C_2$ 20 Siegel (70) was able to show that a small percentage of the acetylene lost contained both labeled carbon atoms. Since random insertion of the methyl carbon between adjacent carbon atoms of the ring does not permit formation of a $C_7H_7^+$ ion with the two ^{13}C atoms adjacent to one another, a further pathway has to be envisaged which will allow total scrambling of all the carbon atoms.

The above evidence indicates that in the molecular ion of C_7H_8 isomers with sufficient internal energy to decompose by expulsion of H· and subsequently C_2H_2, a complete scrambling of the hydrogen and carbon atoms has taken place in the molecular ion prior to fragmentation. There is no direct evidence from conventional mass spectral studies for the structure of the non-decomposing molecular ion of C_7H_8 isomers. Hoffmann and Bursey (71) have used ion cyclotron resonance spectroscopy to explore the molecular ion structure through ion-molecule reactions. By allowing an ion molecule reaction between toluene and an ionized alkyl nitrate Bursey was able to show that toluene undergoes an electrophilic addition reaction and also that the same nitrated species is formed by attack of

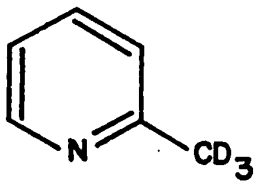
the molecular ion, $C_7H_8^{+\cdot}$, upon the neutral alkyl nitrate. On the other hand, the molecular ions of cycloheptatriene and norbornadiene are unreactive towards the neutral alkyl nitrate and the neutral C_7H_8 species are also inert to attack by alkyl nitrate ions. Thus it would appear that either scrambling of the hydrogen and carbon atoms in toluene does not occur via an irreversible isomerization of the molecular ion to cycloheptatriene isomer, or that two distinct energy structures exist for the decomposing and non-decomposing molecular ion of toluene.

Alkylpyridines

In contrast to other alkylpyridines the spectra of the methylpyridines (122) are rather similar. The main degradation reaction corresponds to the loss of HCN but a significant M-1 ion is present. 2-Methylpyridine has a greater tendency for the elimination of a methyl group than the other isomers. The M-1 ion is most intense for the 3-isomer, however, reflecting the higher electron-density at the 3-position of the pyridine ring that stabilizes the resultant carbonium ion relative to the carbonium ion species of the 2- and 4-isomers. Formation of the same carbonium ion species in the ethylpyridines (122) by loss of a methyl group again shows that the M-15 ion is most intense for the 3-isomer. Spiteller (123) has used these observations as evidence against the formation of a ring expanded azatropylium ion prior to cleavage of the side chain. Jennings et al. (121) noted that the monomethylpyridines gave weak M-1 peaks in their spectra as compared to the M-1 peak in say toluene. The failure to observe a metastable peak for the loss of HCN from the M-H ion, contrasted with the abundant metastable

observed for the loss of C_2H_2 from the M-H ion of toluene. These results were taken as evidence against the formulation of an azatropylium ion in the fragmentation of methylpyridine. In the study of the 2- and 3-methylpyridines and also 2,6-dimethylpyridine, several metastable transitions arising from the decomposition of the molecular ion are observed, suggesting that an azatropylium ion is not formed.

Deuterium labeling of 2-methylpyridine 21 and 4-methylpyridine 22 suggest that at all beam energies, complete (or almost complete) hydrogen scrambling occurs in the molecular ion before expulsion of HCN (55).



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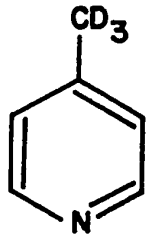

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The problem of an isotope effect prevented a definite conclusion about the amount of hydrogen scrambling in the M-1 and M-2 daughter ions of the labeled methylpyridines but while randomization may be complete in the 4-isomer, it is only partial in the 2-isomer. The loss of CD_3 in the 2-isomer occurs without hydrogen scrambling at high beam energies, but loss of CH_3, CH_2D and CHD_2 become much more prevalent as the internal energy of the decomposing molecular is lowered. Similar behaviour is observed in the spectrum of the 4-isomer, although the loss of CD_3 is

somewhat less specific. However it is clear that most of the M-15 ions from methylpyridines are formed from parent ions of high internal energy and that fragmentation occurs before hydrogen scrambling.

Further studies by Nibbering and co-workers (58c) on the mass spectral fragmentation of 4-methylpyridine and several deuterated analogues revealed a non-specific loss of the hydrogen atoms. By utilising the calculations of Meyer (58a) for an isotope effect, Nibbering found that the molecular ion of 4-methylpyridine loses α, β, and methyl hydrogens in the ratio 1.43:1:1.13. The same trend of hydrogen loss was observed in the elimination of HCN from the molecular ion. These results cannot be explained in terms of the mechanism proposed for toluene (58a) because a ratio 1:1:1 would be required. If a ring-expanded ion is invoked, then a series of rate constants is required for the shifts of hydrogen from the non-equivalent positions of the nitrogen ring. To accommodate the results for H· and HCN elimination and the lack of scrambling prior to the loss of CH_3, it would seem that either reversible isomerization occurs between 6- and 7-membered rings, or that hydrogen scrambling occurs over the whole molecule without destruction of the methylpyridine skeleton.

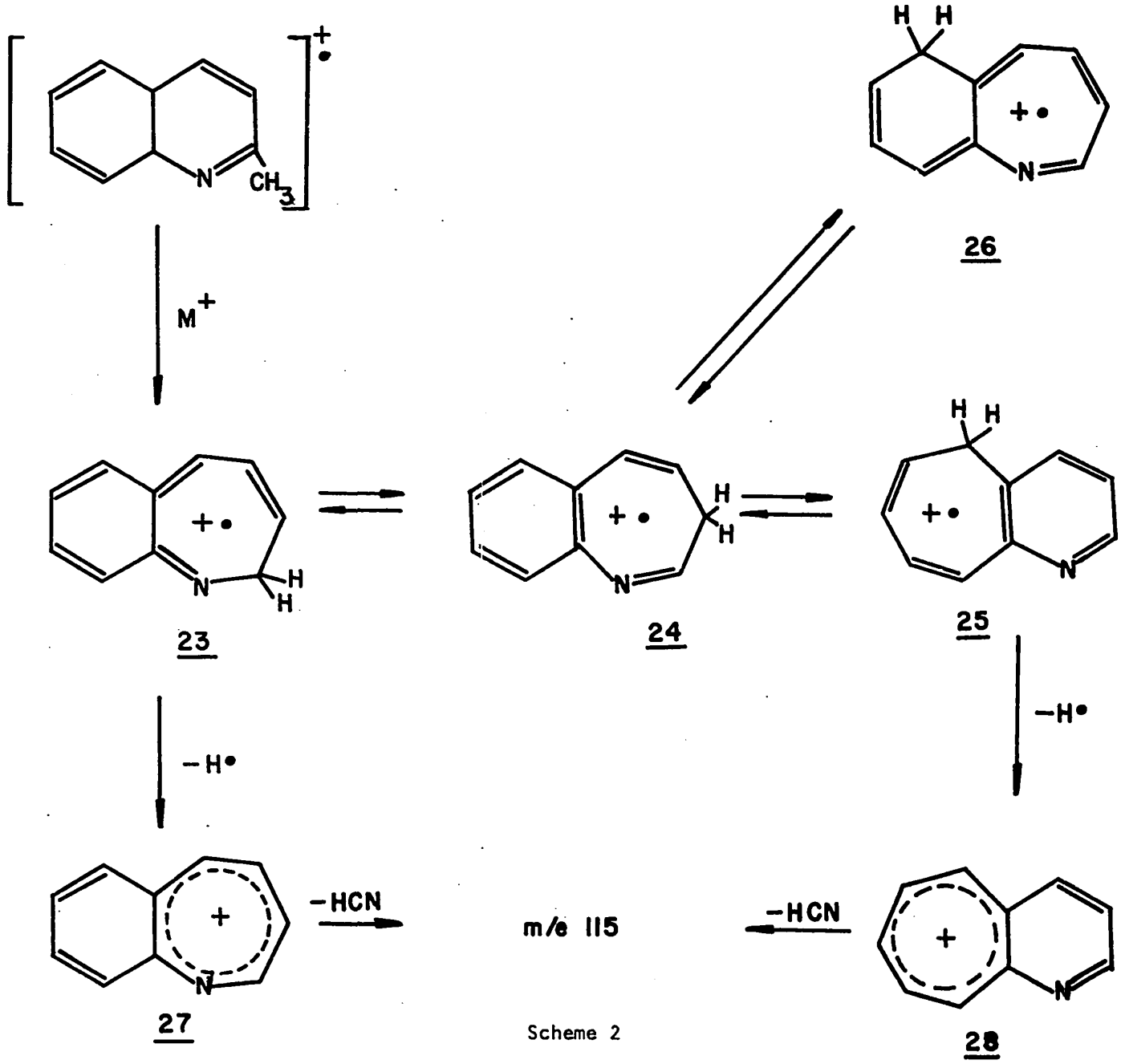
Alkylquinolines

The degradation reactions of quinolines are very similar to those of the corresponding pyridines. All the monomethylquinolines show the same fragmentation sequence; i.e. expulsion of H· followed by loss of HCN. If the α-carbon is substituted, the fragmentation pattern shows a close relationship to that of corresponding α-substituted pyridines.

A relationship is seen in the M-1 species similar to that observed for the alkylpyridines. Again the M-1 species is most intense with the 3-methyl isomer as compared with the 2- and 4-isomers.

Sample et al. (107) studied the mass spectral fragmentation patterns of all seven monomethylquinolines and from the subsequent fragmentation, the ratio of intensity M-(H+HCN)/M-H is practically constant for the three isomers methylated in the heterocyclic ring. The M-1 peaks for the quinolines having the methyl substituent in the benzene ring are more intense than those with the methyl substituent in the pyridine ring, but again the above ratio is constant, though smaller than in the previous case.

Subsequent work by Draper and MacLean (62,110) using deuterated monomethylquinolines confirmed the results of Sample and indicated that scrambling of all nine hydrogens occurs prior to formation of the M-1 ion. Their results show that the percentage label retention in the M-H ion is more consistent with random loss of H· from the whole molecule and they proposed a possible fragmentation mechanism as shown in Scheme 2. Exact determination of the degree of scrambling was precluded because of the existence of a primary isotope effect. The compound is ionized and transfer of methyl hydrogen occurs to the ring containing the original methyl substituent, followed by insertion of the methylene group at random between any two ring carbons of the pyridine ring to form a benzazacycloheptatriene ion 23. Randomization of the hydrogens can be explained by 1,2-hydrogen shifts to ions of type 24. Rearrangement to ions of type 25 or 26 permits randomization and loss of hydrogen in the



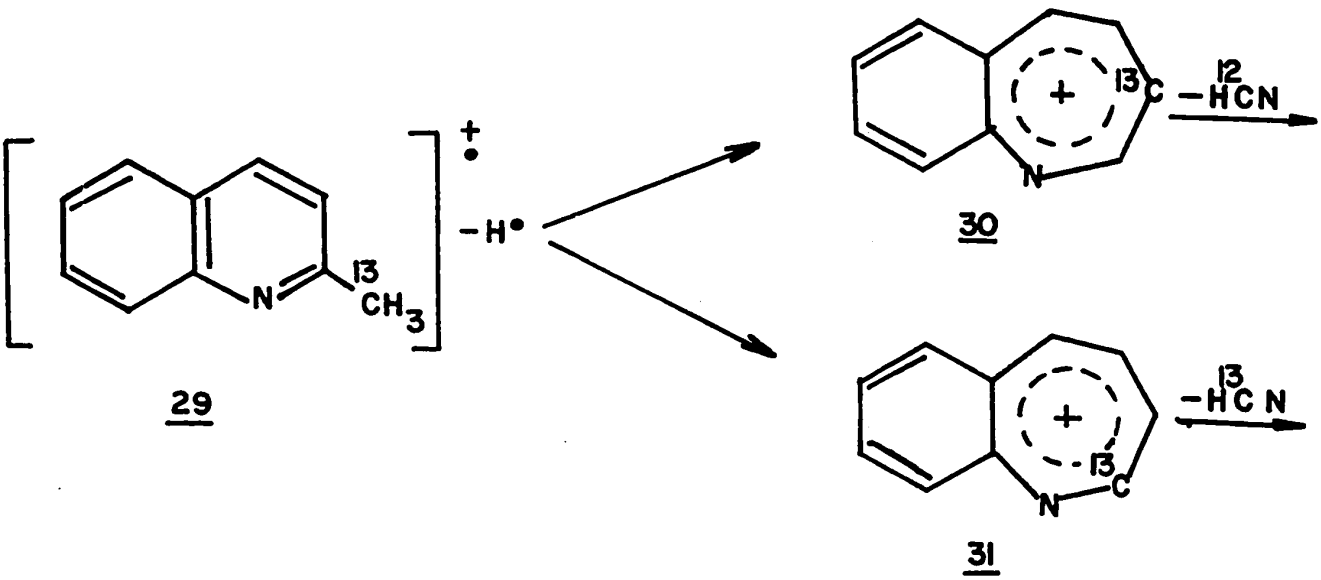
Scheme 2

benzene ring. Subsequent loss of H· from the methylene position, as is found in methylethylbenzenes (58a), from any of the expanded molecular ions, yields a benzazatropylium ion 27 or a pyridotropylium ion 28.

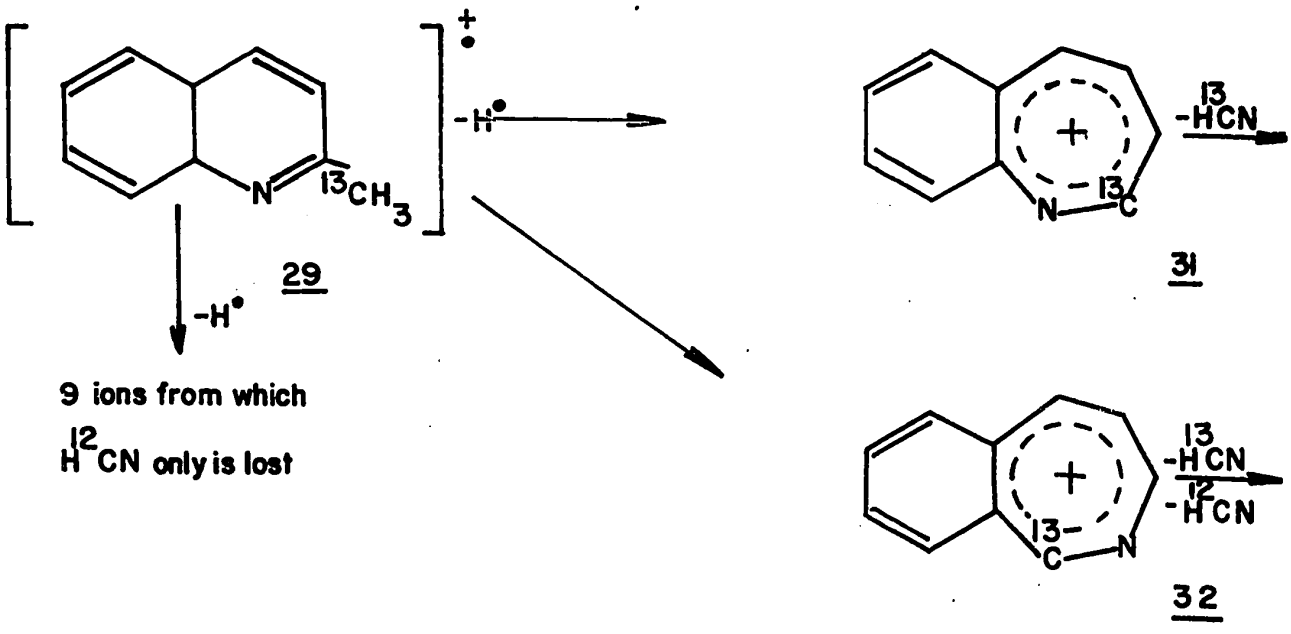
Hydrogen rearrangement is also observed prior to loss of HCN from the M-1 ion. A comparison of the percentage label retention in the M-(H+HCN) ion of the -8-α-d derivative shows excellent agreement with the percentage retention calculated for random loss from the molecule in the M-(H+HCN) process. A somewhat smaller percentage was found for the 4-methylquinoline-2-d compound. Thus randomization of the hydrogens occurs over both rings.

Draper and MacLean (62) also examined the spectrum of 2-methylquinoline-2-α-^{13}C 29 in order to examine possible mechanisms for ring expansion. The ring expansion may occur by insertion of the exocyclic methyl carbon into adjacent carbon-carbon or carbon-nitrogen bonds in the molecule. This simple 1,2-insertion was used by Marx and Djerassi (61) to account for the results in a study of ^{13}C labeled 1-methylisoquinoline. A second mechanism involves ring expansion by a random insertion of the methyl carbon into any carbon-carbon or carbon-nitrogen bond. Such an explanation was used by Rinehart et al. (69) in their investigation of the formation of a tropylium ion from toluene doubly labeled with ^{13}C.

Simple 1,2 insertion of the labeled methyl carbon of the 2-isomer is shown in Scheme 3. Ring expansion results in two possible M-H ions, namely 30 and 31. Thus such a mechanism would result in 50% retention of the ^{13}C label. However the observed result shows that 85% of the label



Scheme 3



Scheme 4

is retained eliminating the possibility of a simple 1,2 insertion being the main mechanistic pathway, unless there is a preferential insertion of the methyl group into a carbon-carbon bond rather than a carbon-nitrogen bond.

More random processes involve insertion into the ring containing the methyl group or insertion into any bond in the molecule. Scheme 4 shows the only two ions that can eliminate $H^{13}CN$. Ion 31 should eliminate $H^{13}CN$ only while ion 32 has a 50% chance of eliminating $H^{13}CN$. Therefore, if ring expansion is kept to one ring then 1½/6 or 25% loss of ^{13}C from 29 would be predicted, while a random insertion of ^{13}C over both rings predicts a 1½/11 or 14% loss of ^{13}C. The observed result of 15% loss of ^{13}C is in good agreement with the latter proposal.

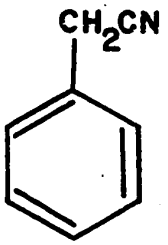
Thus it would appear that the labeling results of the monomethylquinolines may be best explained by the formation of ring expanded species before loss of hydrogen and that insertion of the methyl group to form such a species would occur via a random process.

At the present time ^{13}C labeling studies have not been reported on methylnaphthalenes and therefore no direct comparison can be made with another bicyclic system. However it should be pointed out that a strong similarity in the spectra of methylnaphthalenes and C_{12} polyacetylenes led Aplin and Safe (76) to suggest that open chain species are involved in the fragmentation of naphthalenes. Occolowitz and White (36) proposed from energy considerations that the $C_5H_6^{+\cdot}$ and $C_5H_5^{+}$ ions formed from substituted benzenes should be represented as linear structures and not as cyclic species as is often the case.

Other Aromatic and Heteroaromatic Compounds

Isotopic labeling studies have been used in an attempt to elucidate the fragmentation pathways of many aromatic and heteroaromatic compounds. A summary of some of the more recent work, where labeling has been used to prove or disprove carbon and/or hydrogen scrambling is discussed in this section.

A study of the mass spectra of benzylcyanide 33 (58b) and its α-d_2, -2,6-d_2, and -4-d analogues shows that these spectra resemble that of toluene and suggests a cyanotropylium structure for the M-1 ion. Further studies using deuterium, ^{13}C and ^{15}N labeling show that the molecular ions, decomposing in the second field-free region, i.e. those having a low internal energy, lose HCN with participation of both side-chain carbon atoms after a complete randomization of all hydrogens. However the molecular ions decomposing in the source, i.e. those having a high internal energy, lose a molecule of HCN containing the original cyano group, after almost complete randomization of all hydrogen atoms. The molecular ions of ortho-, meta- and para-cyanobenzylcyanides 34 (126) of low and high internal energy also lose HCN, involving to some extent a carbon atom, different from that of the side chain cyano group, after scrambling of hydrogens. This would indicate that the original structure of the side-chain cyano group has been partly lost before or during the elimination of HCN. Since the eliminated HCN contains predominantly the side-chain cyano group, it would seem that a ring expansion of the molecular ion of (o,m,p)-cyanobenzylcyanides to a seven membered ring before or during the loss of HCN is not a realistic mechanism.



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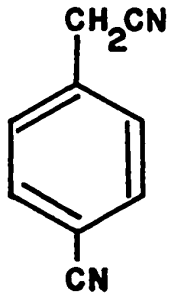

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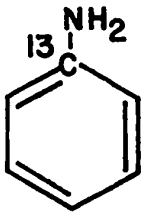
Thus the possibility arises that hydrogen randomization may occur without a carbon skeleton rearrangement.

Molenaar-Langeveld et al. (126) have attempted to explain the observed results for benzylcyanide and (o,m,p)-cyanobenzylcyanides as shown in Scheme 5 without the intervention of a tropylium ion. Many cases have been found indicating that benzyl ions do intervene in fragmentation of substituted benzenes.

Rinehart and co-workers (82) examined the mass spectral fragmentation of aniline-1-^{13}C 43 for the purpose of investigating the intermediacy of an azatropylium ion 44.



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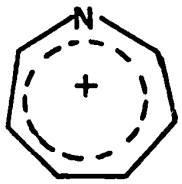

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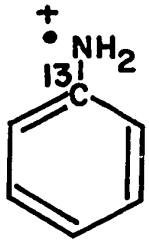

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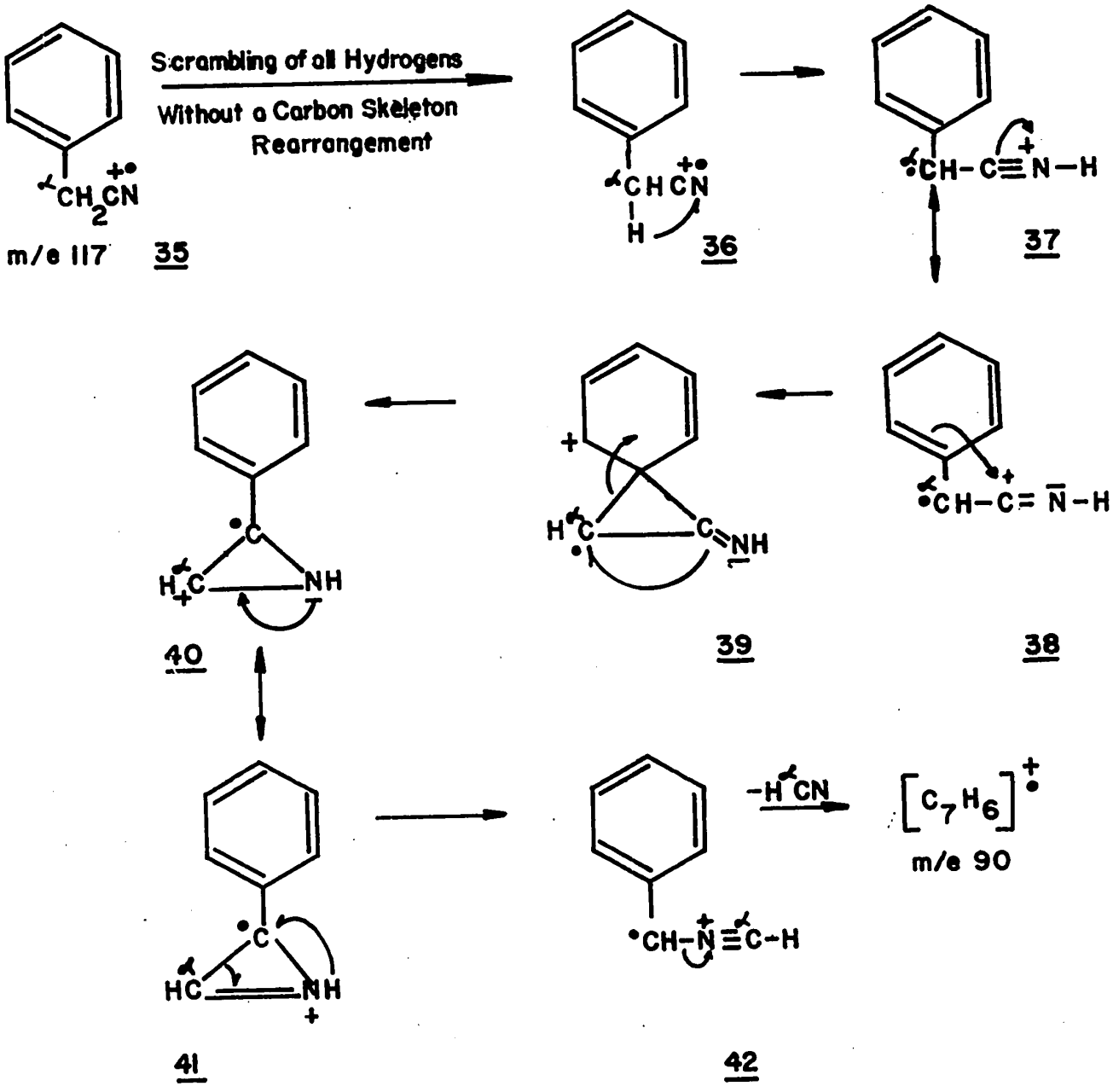

Scrambling of all Hydrogens
Without a Carbon Skeleton Rearrangement
m/e 117
35
36
37
38
39
40
41
42
-H CN
[C7H6]+
m/e 90

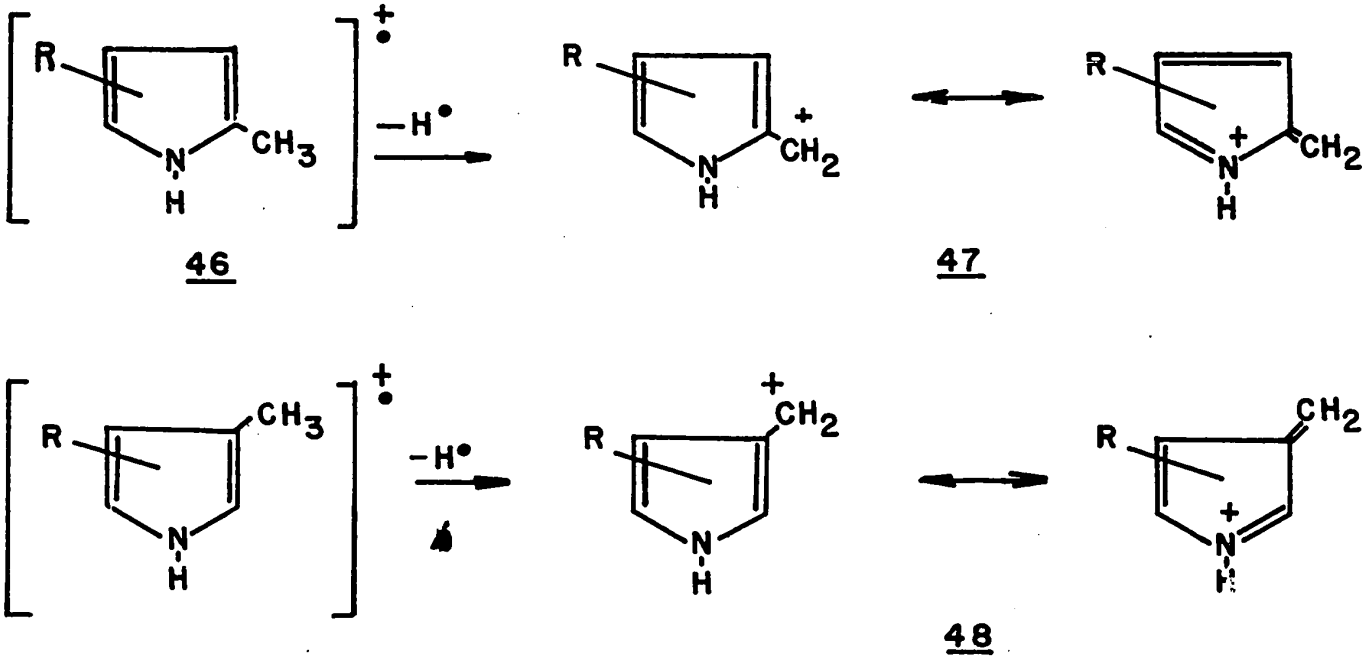
Scheme 5

If ring expansion does occur, then even a simple 1,2 insertion of the nitrogen between adjacent carbons would permit at least 50% retention of the label in the loss of HCN. From the unrearranged species 45 loss of HCN would proceed with total loss of ^{13}C label. The results indicate that more than 90% of the label is lost as $H^{13}CN$, i.e. from an unrearranged species. A similar study by Robertson and Djerassi (77) confirmed that in the reactions involving loss of HCN from the odd electron species $C_6H_7N^{+\cdot}$, prior rearrangement to a ring-expanded species occurs only to a small extent. However the loss of HCN from the even electron species $C_6H_6N^+$ involves a considerable amount of rearrangement before expulsion of HCN.

Budzikiewicz et al. (129) interpreted the higher M-1 peaks relative to the M-15 peaks in the spectra of the dimethylpyrroles 46 as evidence for the stable ions, 47 and 48, in Scheme 6 as opposed to a ring expanded pyridinium ion.

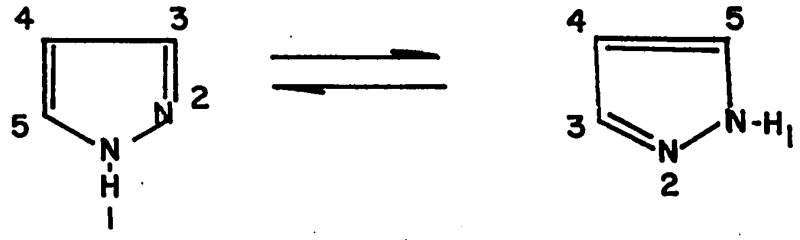
In the case of some unsubstituted heteroaromatics where ring expansion is not possible, the scrambling of hydrogens is only observed from ions of low internal energy. For example, decomposition of the M-1 ion of pyrazole (104) 49 shows a randomization of all the hydrogens before loss of HCN only in those ions of low internal energy. The loss of hydrogen and HCN from the molecular ions of high internal energy however, shows a high specificity from the 3(5) position.

The question of ring expansion in the fragmentation of nitrogen heteroaromatics prompted Marx and Djerassi (61) to study 1-methylisoquinoline, 2-methylindole and N-methylpyrrole labeled with ^{13}C. The mass

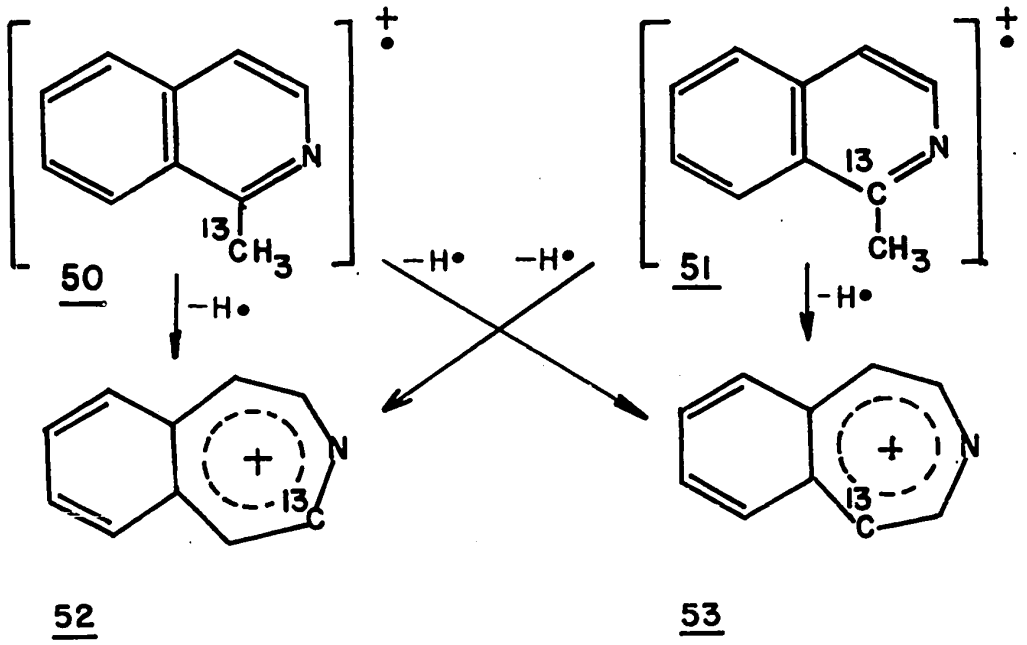


46 47 48

Scheme 6



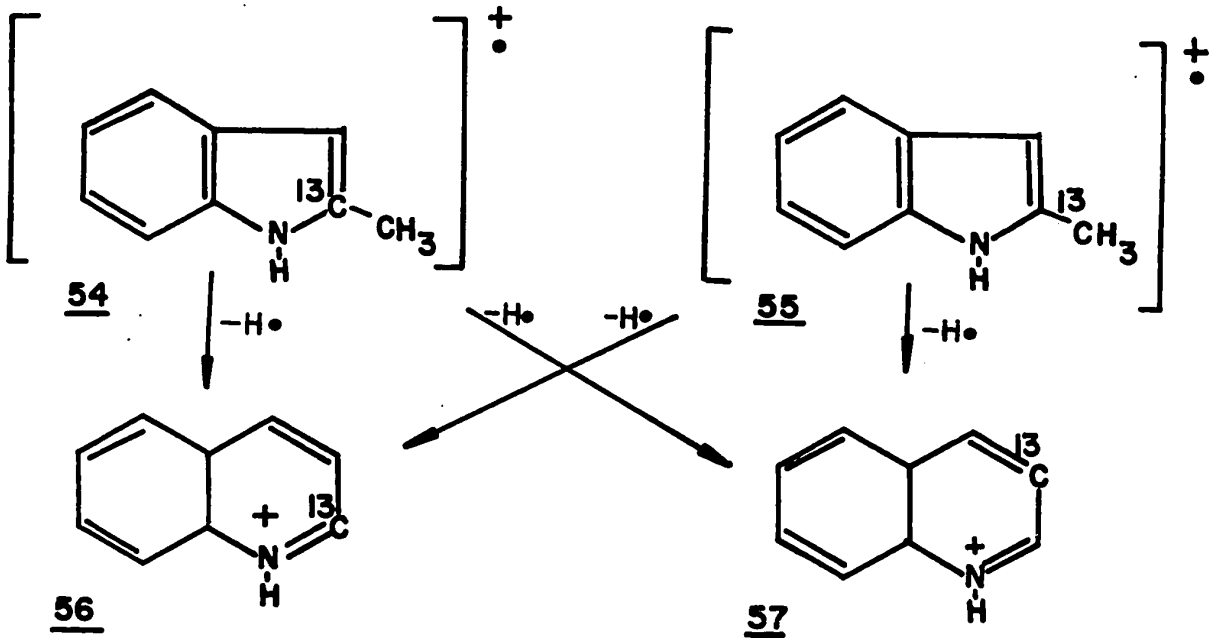
49



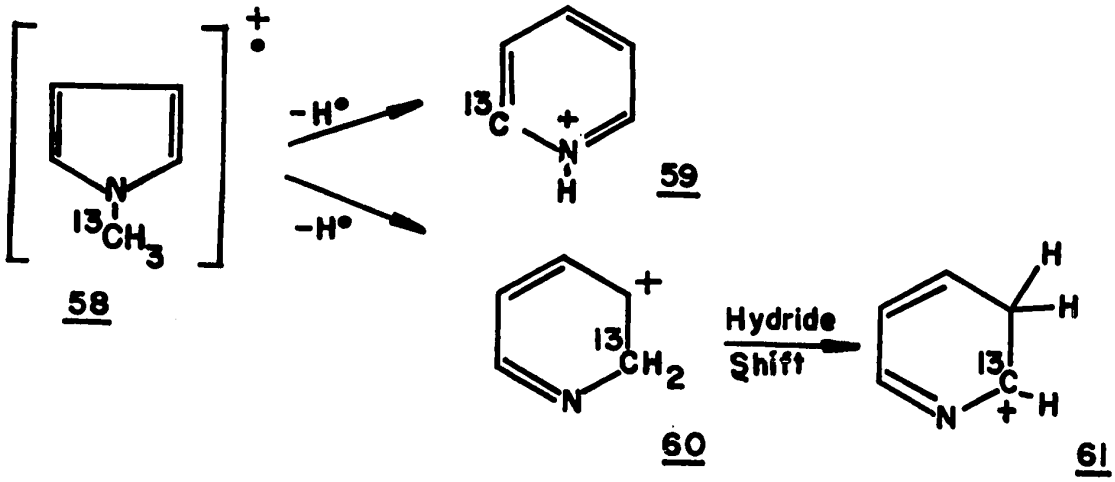
Scheme 7

spectra of 1-methylisoquinoline-1-α-^{13}C 50, Scheme 7 and 1-methylisoquinoline-1-^{13}C 51 were obtained and it was noted that loss of H· from either compound would result in two possible ring-expanded ions 52 and 53. Ion 52 can be formed from 50 by insertion of the exocyclic methyl carbon between a carbon-nitrogen bond or from 51 by insertion of the methyl carbon between a carbon-carbon bond. The opposite process in 50 and 51 would produce 53. Loss of H^{13}CN is only possible from ion 52. Twenty six percent loss of the ^{13}C label as H^{13}CN from 51 was observed while 14% was lost from 50. With the assumption that since 52 is symmetrical with respect to nitrogen, the maximum contribution to the fragmentation process will be twice the observed label loss, Djerassi was able to account for 80% of the label by proposing a ring-expanded intermediate as indicated in Scheme 7. The difference between 50 and 51 was explained by a preference for insertion of the exocyclic methyl carbon between a carbon-carbon bond over a similar insertion between a carbon-nitrogen bond.

By using deuterated indoles Powers (94) was able to show that the loss of HCN from the molecular ion involves both the amino hydrogen and the C-2 hydrogen but not the C-3 hydrogen. In the case of methylindoles, Djerassi used a similar argument for 54 and 55 to account for retention of 86% of the ^{13}C label by ring-expanded quinolinium ions 56 and 57, as shown in Scheme 8. As in the methylisoquinolines a marked preference was observed for ring expansion via insertion of the exocyclic carbon between a carbon-carbon bond.



Scheme 8



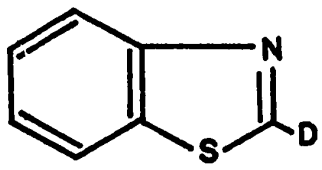
Scheme 9

The percentage retention of ^{13}C label in the spectrum of N-methylpyrrole-1-α-^{13}C 58, Scheme 9, cannot be explained by the intermediacy of the symmetrical ion 59. Clearly a species such as 59 would retain 50% of the label while the observed figure was 65%. A possible alternative to 59 was proposed to account for this result. An unsymmetrical ion 60 can lose HCN directly with retention of the label or undergo a hydride shift to form 61 from which either labeled or unlabeled HCN may be lost.

Finally the mass spectral fragmentation of N-methylindole-1-α-^{13}C again indicated that a ring expansion to a quinolinium ion is involved. The authors feel that the loss of HCN in the above compounds can partly be explained by postulating ring expanded intermediates.

Labeling studies have also been used to elucidate fragmentation of aromatics containing such heteroatoms as oxygen and sulphur. Cooks et al. showed that loss of HCN from thiazole 62 specifically involves loss of the C-2 hydrogen, but the corresponding HCN expulsion from benzothiazole does not involve specific loss of hydrogen from C-2 (as was found from the spectrum of 63) (56).

62



63

The use of deuterium and carbon-13 labeling has shown the existence of carbon and/or hydrogen scrambling, and where possible, the probable intermediacy of ring-expanded species in aromatic and heteroaromatic compounds. Thus in those processes where the internal energy of the decomposing ion(s) is high, the rate of randomization will be much slower than the rate of fragmentation. In the degradation of ions of lower internal energy, the rate of randomization has been shown to be at least comparable with the rate of fragmentation.

It should be noted that in several instances, hydrogen scrambling has been observed in cyclic aliphatic compounds. For example, examination of the mass spectral data of O-deuterated cyclohexanols and methylcyclohexanols indicate that hydrogen attached to oxygen undergoes partial scrambling with the 2,3,5 and 6 position ring hydrogens prior to or during the formation of the major primary fragment ion (130).

DISCUSSION OF RESULTS

The phenomenon of carbon and hydrogen scrambling upon electron impact in several aromatic and heteroaromatic compounds has been the subject of a great deal of investigation in recent years (55,56,58,62). In the fragmentation of alkyl aromatic and heteroaromatic compounds, the question of ring expansion to tropylium or heterotropylium ions has been of particular interest.

To gain further insight into this problem methylquinolines and pyridines all labeled with ^{13}C in the exocyclic methyl group have been prepared and their mass spectra have been examined.

In the discussion that follows, an account of the preparation of the labeled compounds will be given first, followed by an analysis of their mass spectra.

The unlabeled 2-, 4-, and 5-methylquinolines examined in this study are all well known compounds, each of which has been prepared in a number of different ways and all are available commercially. Conventional methods of synthesis are not always adaptable to the synthesis of labeled compounds. Carbon-13 is expensive and synthetic routes are limited by the availability of ^{13}C compounds. Therefore it is necessary in the synthesis of labeled compounds to seek out methods in which the label is introduced at a late stage in the synthesis, or if this is not possible, to develop a reaction sequence in which each step proceeds in high yield.

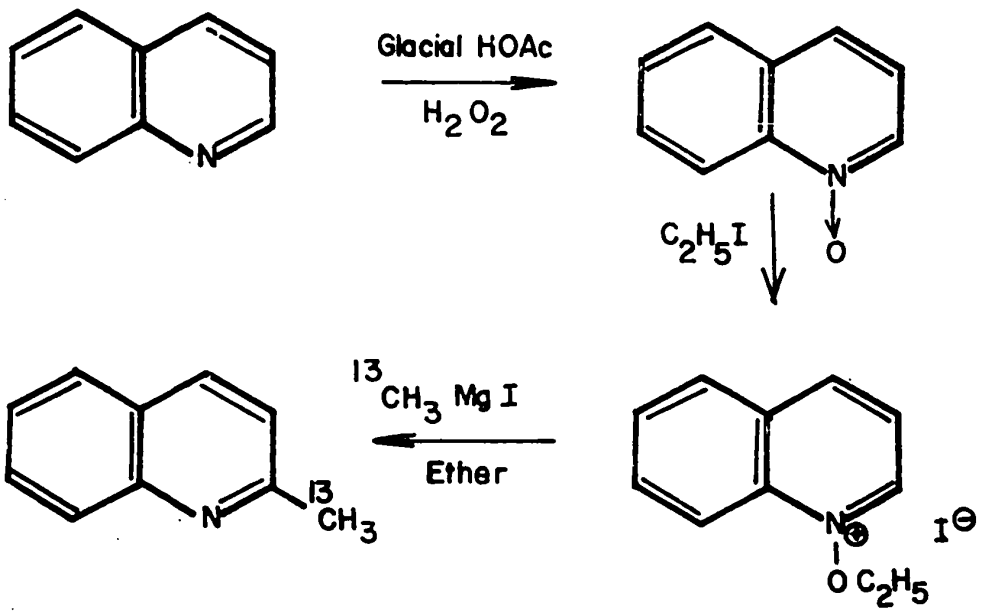
In the case of the methylquinolines relatively direct methods were found but for the methylpyridines a longer route was necessary.

Synthesis of the Labeled Compounds

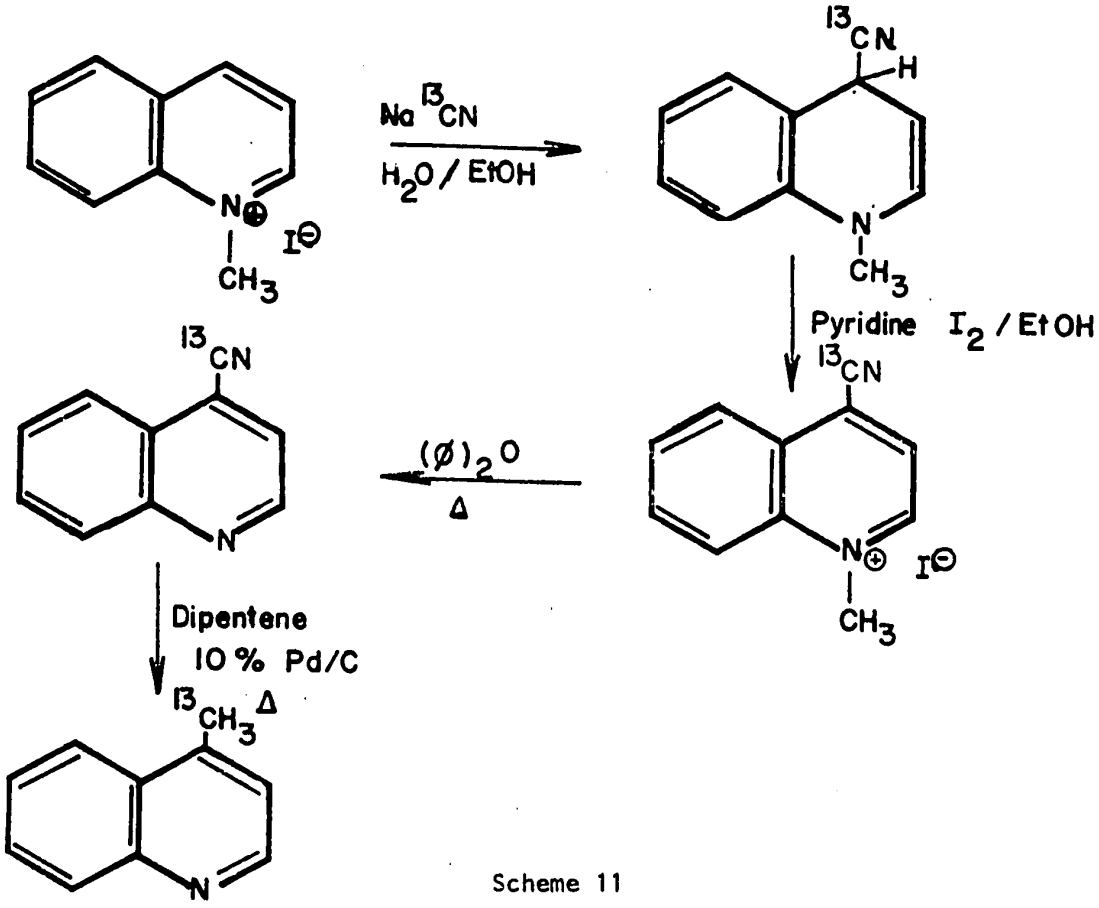
Methylquinolines

2-Methylquinoline-2-α-^{13}C had previously been prepared in this laboratory by P.M. Draper (138) in good yield and so the same method, namely treatment of N-ethoxyquinolinium iodide with $^{13}CH_3MgI$ using the conditions described by Červinka et al. (143), was used to prepare labeled 2-methylquinoline for this study (Scheme 10).

Several methods were examined before a successful synthesis of 4-methylquinoline labeled with ^{13}C in the exocyclic methyl group was found. Attempts to introduce the ^{13}C to the hetero ring by Grignard (131), Wittig (132), and alkyllithium reactions on 4-aza-1-tetralone and N-benzoyl 4-aza-1-tetralone did not produce the desired product. In the case of the Wittig reaction using the method described by Corey (132b), it has been shown that cleavage of the heterocyclic ring occurs under the influence of strong nucleophiles (133). A useful reaction for introduction of a one carbon unit to the 4-position of quinoline is the Kaufmann reaction (134), in which cyanide ion adds to quinoline methiodide to give an unstable dihydro compound that without purification was oxidized to 4-cyanoquinoline methiodide. Pyrolysis of the salt gives 4-cyanoquinoline. Thus a route was available for introduction of the carbon unit at C-4 as - ^{13}CN. Hydrolysis of the cyano group to the acid and subsequent reduction to the methyl group seemed tedious and an alternative method for conversion of the cyano group to a methyl group

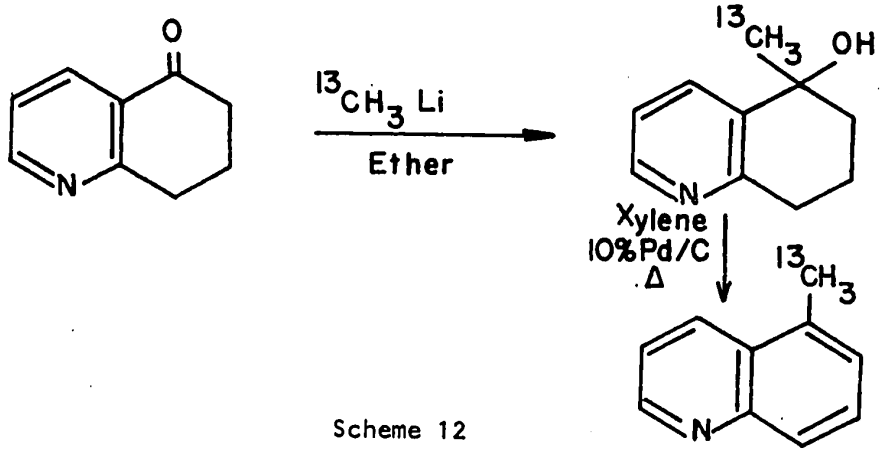


Scheme 10



Scheme 11

was sought. Kindler et al. (135) have recently shown that the cyano group of aryl and heteroaryl cyano compounds is reduced to the corresponding alkyl group and ammonia without reduction of the aromatic system. The source of hydrogen in this reaction is Δ^1-p-menthene or limonene. 4-Methylquinoline labeled with ^{13}C in the methyl group was prepared in 80% yield from 4-cyanoquinoline by this method. This would appear to be a very useful method for the preparation of alkyl aromatics labeled with ^{13}C in the side chain provided the corresponding cyano compound can be prepared. These reactions are outlined in Scheme 11. 5-Methylquinoline labeled with ^{13}C in the methyl group was prepared by addition of $^{13}CH_3Li$ to 5-aza-1-tetralone to give the corresponding methyl carbinol. Dehydration and oxidation of the carbinol were carried out simultaneously giving the desired compound as shown in Scheme 12.



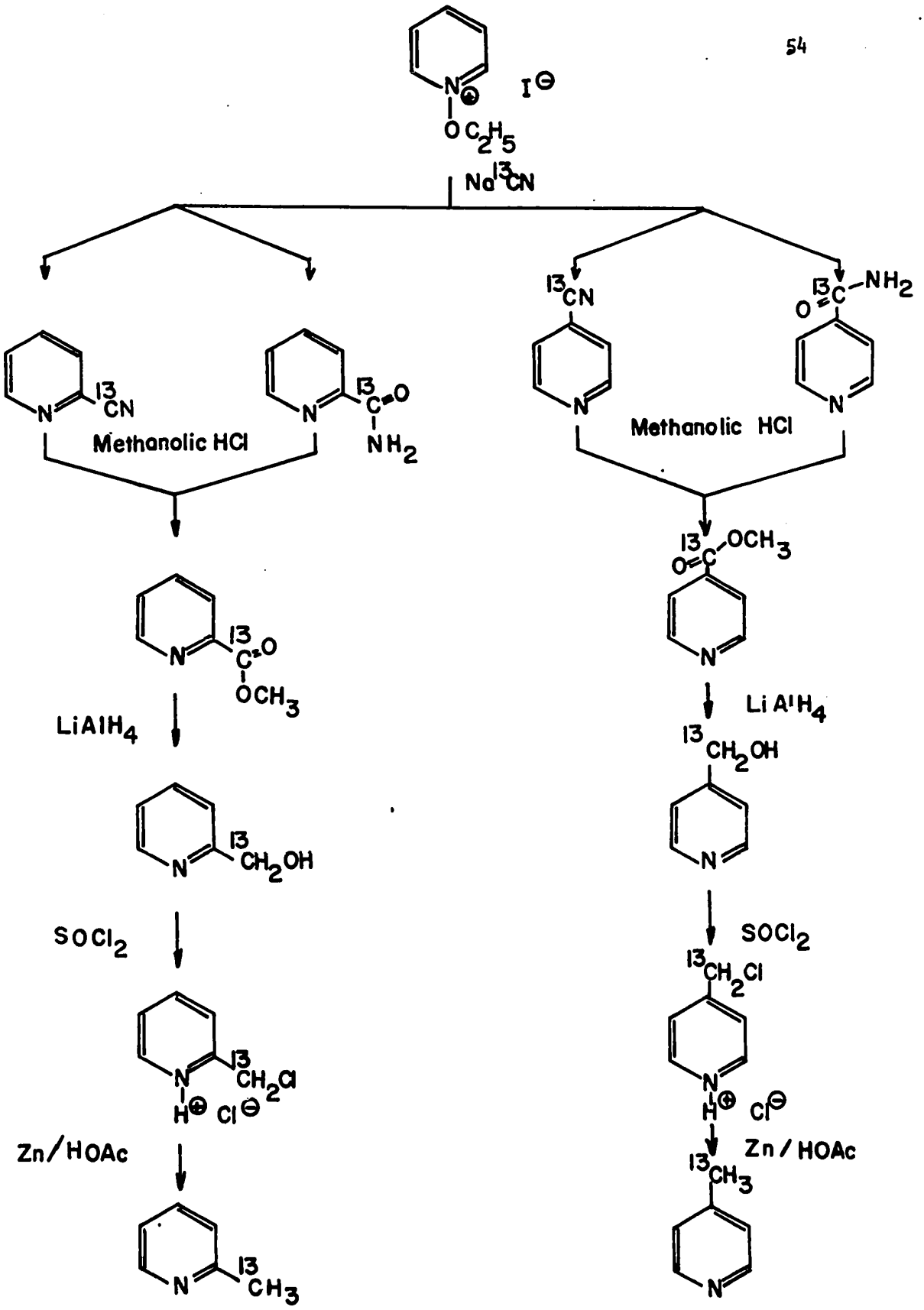
Scheme 12

Methylpyridines

There is a considerable literature dealing with the alkylation of pyridines with the Grignard reagent (136) but because of poor yields, this reaction has not been a practical method of synthesis. The method of

Červinka (137) proved to be inadequate for that reason. The addition of cyanide ion to N-alkoxy pyridinium salts is known to yield the cyano-substituted pyridines under very mild conditions. Subsequent hydrogenolysis of the cyano derivatives of pyridine by the method of Kindler (135) would be expected to produce the corresponding methylpyridines. However, attempts to prepare the methylpyridines by this method were unsuccessful. In many cases little or no starting cyano compounds or products were recovered. The conditions of the reaction require a steady flow of nitrogen and a temperature of 180°C. Such conditions may have resulted in the loss of the volatile cyanopyridines and picolines. The introduction of the ^{13}C label as $-^{13}CN$ proceeds in good yield, however, and it was decided to prepare the desired picolines by hydrolysis of the cyano group to the corresponding esters of picolinic and isonicotinic acids, followed by reduction to the alkyl group. Although this route introduces the ^{13}C label at an early stage in the synthesis, the subsequent reactions are well documented and give good yields. The reaction sequence is outlined in Scheme 13.

The method of introduction of the cyanide ion to N-alkoxy quaternary salts of pyridines, quinolines, and isoquinolines permits the preparation of heterocycles labeled with ^{13}C in the cyano group. Subsequent reduction of this group either by the direct method of Kindler (135) or by the indirect method mentioned above results in alkyl heterocycles labeled with ^{13}C in the methyl group originating from the cyano group.


I⊖
OC2H5
Na13CN
13CN
13C=O
NH2
Methanolic HCl
Methanolic HCl
13C=O
OCH3
LiAlH4
LiAlH4
13CH2OH
SOCl2
SOCl2
13CH2Cl
H⊕ Cl⊖
Zn/HOAc
Zn/HOAc
13CH3

Scheme 13

Mass Spectra of Monomethylquinolines

Studies of the mass spectra of deuterated monomethylquinolines (62,107) have shown that scrambling of the hydrogens in the molecular ion occurs before formation of the M-1 ion. This ion was represented as a benzazatropylium or pyridyltropylium ion though ring expansion is not mandatory to account for randomization of the hydrogens (58c).

Although the mechanism for ring expansion cannot be deduced from deuterium labeling results there are several possible ways in which ring expansion can occur in alkylated bicyclic systems some of which are listed below.

(a) A 1,2 insertion of the exocyclic methyl carbon into adjacent bonds of the ring.

(b) A random insertion into any bond of the ring containing the methyl group.

(c) A random insertion into any bond in the aromatic system.

or (d) A more complex mechanism.

The mass spectra of several aromatic and heteroaromatic compounds labeled with ^{13}C have been examined in an attempt to determine if ring expansion occurs and by what mechanism(s).

Marx and Djerassi (61) suggested that ring expansion occurs in 1-methylisoquinoline and the methylindoles by mechanism (a) while Draper and MacLean (62) concluded from the examination of the mass spectrum of 2-methylquinoline-2-α-^{13}C that a random insertion mechanism was involved. However, the results could also be explained by a 1,2 insertion process with a large preference for a carbon-carbon insertion over a carbon-

nitrogen insertion. Siegel (70) concluded from the observed loss of $^{13}C_2H_2$ from the M-1 ion of toluene-2,6-$^{13}C_2$ that the M-1 ion is formed by a mechanism in which all the carbon atoms have lost positional identity with respect to each other.

It was felt that, in the case of the monomethylquinolines, the possible ring expansion mechanisms might be differentiated by examination of 4-, and 5-methylquinoline labeled with ^{13}C in the exocyclic methyl group. Any loss of ^{13}C as $H^{13}CN$ from the M-1 ion in the 4- and 5-isomers would militate against a 1,2 insertion. Loss of $H^{13}CN$ from the 5-isomer would indicate whether a methyl carbon on the benzene ring may participate in the loss of HCN from the M-1 ion.

The mass spectra of 2-, 4-, and 5-methylquinoline and 2-, 4-, and 5-methylquinoline labeled with ^{13}C in the exocyclic methyl carbon are shown in Figure 4 (a-f). The region m/e 113 - m/e 118 was examined under high resolution conditions and the composition of all relevant ions determined as described in the experimental section. High resolution measurements (1 in 25,000) were necessary because of the presence of several isobaric components at each nominal mass in the region of interest. The major fragmentation pathway of the molecular ion is loss of H· followed by loss of HCN. The other fragmentation pathways of the molecular ion are shown in Scheme 14. Some of these fragmentations are supported by metastable ions observed in the spectra of the monomethylquinolines (138). In the unlabeled spectra many nominal masses near m/e 115 are composed of C_9H_n -$C_8H_{n-2}N$ doublets and the ^{13}C labeled spectra are complicated by the appearance of up to three isobaric ions at each

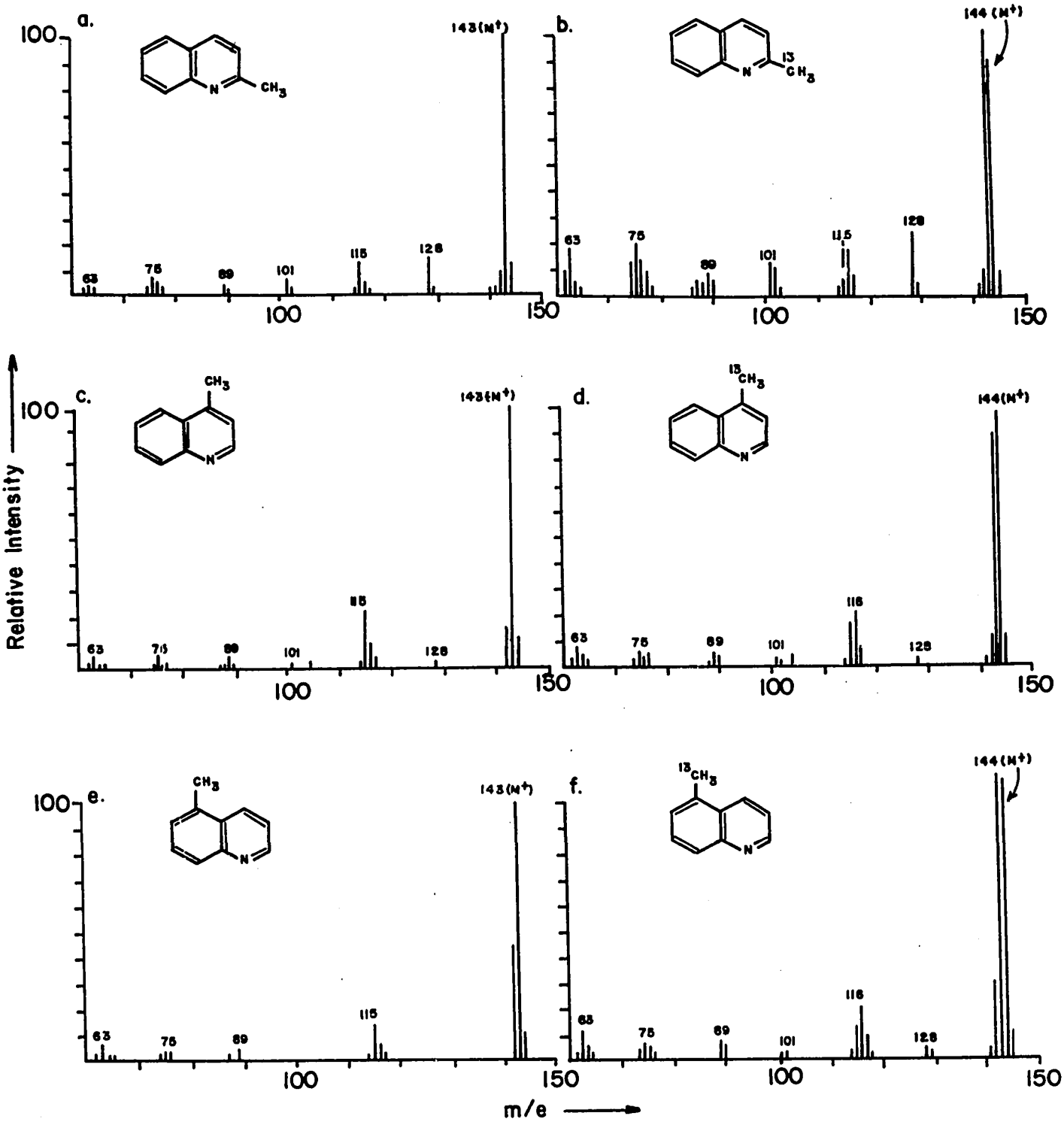
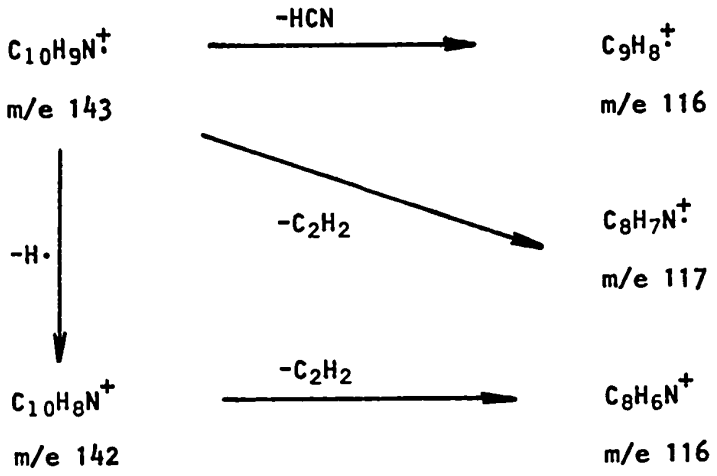


Fig. 4 Mass spectra of 2-methylquinoline, 2-methylquinoline-2-α-^{13}C, 4-methylquinoline, 4-methylquinoline-4-α-^{13}C, 5-methylquinoline, and 5-methylquinoline-5-α-^{13}C



Scheme 14

nominal mass, e.g. at m/e 116 the ions present are $C_9H_8^{+\cdot}$, $^{13}C_1C_8H_7^+$, and $C_8H_6N^+$, while at m/e 117 the ions present are $^{13}C_1C_8H_8^{+\cdot}$, $C_8H_7N^{+\cdot}$, and $^{13}C_1C_7H_6N^+$. Exact mass measurements of the ions in the region m/e 113-118 in the spectra of 4-methylquinoline unlabeled and labeled are given in Tables II and III respectively. The mass spectral peaks of the labeled and unlabeled compounds are set out in Tables IV, V, and VI. A detailed account of the calculation of their abundances is given in Appendix I.

Examination of the abundance ratio (ii) in Tables IV, V, and VI, shows that a finite amount of the ^{13}C is lost as $H^{13}CN$ from the M-1 ion of the labeled compound. The results from 2-methylquinoline-2-α-^{13}C 29 indicate that 14.6 ±1.0% of the ^{13}C is lost as $H^{13}CN$ from the M-1 ion. Scheme 15 shows two possible ions that may arise through ring expansion

TABLE II

Exact Masses of the Ions in the Region m/e 113 - 118 of 4-Methylquinoline (Unlabeled)

Observed Mass	Calculated Mass	Ion Composition
113.0385	113.0391	C_9H_5
114.0341	114.0344	C_8H_4N
114.0460	114.0469	C_9H_6
115.0422	115.0422	C_8H_5N
115.0549	115.0548	C_9H_7
116.0494	116.0500	C_8H_6N
116.0580	116.0581	$^{13}C_1C_8H_7$
116.0621	116.0626	C_9H_8
117.0571	117.0578	C_8H_7N
117.0655	117.0660	$^{13}C_1C_8H_8$
118.0611	118.0612	$^{13}C_1C_7H_7N$

TABLE III

Exact Masses of the Ions in the Region m/e 113 - 118 of 4-Methylquinoline-4-α-^{13}C

Observed Mass	Calculated Mass	Ion Composition
113.0393	113.0391	C_9H_5
114.0347	114.0344	C_8H_4N
114.0430	114.0425	$^{13}C_1C_8H_5$
114.0470	114.0469	C_9H_6
115.0375	115.0377	$^{13}C_1C_7H_4N$
115.0421	115.0422	C_8H_5N
115.0503	115.0503	$^{13}C_1C_8H_6$
115.0543	115.0548	C_9H_7
116.0499	116.0500	C_8H_6N
116.0580	116.0581	$^{13}C_1C_8H_7$
116.0620	116.0626	C_9H_8
117.0539	117.0534	$^{13}C_1C_7H_6N$
117.0581	117.0578	C_8H_7N
117.0663	117.0660	$^{13}C_1C_8H_8$
118.0614	118.0612	$^{13}C_1C_7H_7N$
118.0694	118.0693	$^{13}C_2C_7H_8$

TABLE IV

Mass Spectral Peaks for 2-Methylquinoline

m/e	Composition	Relative abundance[a,b] 2-Methylquinoline (unlabeled)	Relative abundance[a,b] 2-Methylquinoline-2-α-^{13}C [c]	Abundance Ratios
115	$^{13}C_1C_7H_4N$		0.014 ±0.001 [d]	(i) $\frac{C_9H_8}{C_9H_8 + {}^{13}C_1C_8H_8} = 0.155 \pm 0.108$
	$^{13}C_1C_8H_6$		0.034 ±0.001	
	C_9H_7	0.589 ±0.003	0.085 ±0.007	
116	C_8H_6N	0.125 ±0.004	0.062 ±0.008	(ii) $\frac{C_9H_7}{C_9H_7 + {}^{13}C_1C_8H_7} = 0.146 \pm 0.010$
	$^{13}C_1C_8H_7$		0.495 ±0.007	
	C_9H_8	0.058 +0.002	0.009 ±0.006	
117	$^{13}C_1C_7H_6N$		0.061 ±0.004	(iii) $\frac{C_8H_7N}{C_8H_7N + {}^{13}C_1C_7H_7N} = 0.666 \pm 0.089$
	C_8H_7N	0.110 ±0.002	0.072 ±0.007	
	$^{13}C_1C_8H_8$		0.050 ±0.004	(iv) $\frac{C_8H_6N}{C_8H_6N + {}^{13}C_1C_7H_6N} = 0.503 \pm 0.074$
118	$^{13}C_1C_7H_7N$		0.036 ±0.002	

[a] $\Sigma_{113-118} = 1.000$. [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Error calculated from standard deviations of intensity measurements.

TABLE V

Mass Spectral Peaks for 4-Methylquinoline

m/e	Composition	Relative abundance[a,b] 4-Methylquinoline (unlabeled)	Relative abundance[a,b] 4-Methylquinoline-4-α-^{13}C [c]	Abundance Ratios
115	$^{13}C_1C_7H_4N$		0.008 ±0.001 [d]	(i) $\frac{C_9H_8}{C_9H_8 + {}^{13}C_1C_8H_8}$ = 0.213 ±0.048
	$^{13}C_1C_8H_6$		0.029 ±0.001	
	C_9H_7	0.663 ±0.003	0.062 ±0.007	
116	C_8H_6N	0.069 ±0.002	0.034 ±0.002	(ii) $\frac{C_9H_7}{C_9H_7 + {}^{13}C_1C_8H_7}$ = 0.096 ±0.011
	$^{13}C_1C_8H_7$		0.594 ±0.007	
	C_9H_8	0.069 ±0.002	0.019 ±0.003	
117	$^{13}C_1C_7H_6N$		0.027 ±0.001	(iii) $\frac{C_8H_7N}{C_8H_7N + {}^{13}C_1C_7H_7N}$ = 0.594 ±0.051
	C_8H_7N	0.096 ±0.002	0.061 ±0.004	
	$^{13}C_1C_8H_8$		0.070 ±0.002	(iv) $\frac{C_8H_6N}{C_8H_6N + {}^{13}C_1C_7H_6N}$ = 0.561 ±0.040
118	$^{13}C_1C_7H_7N$		0.041 ±0.004	

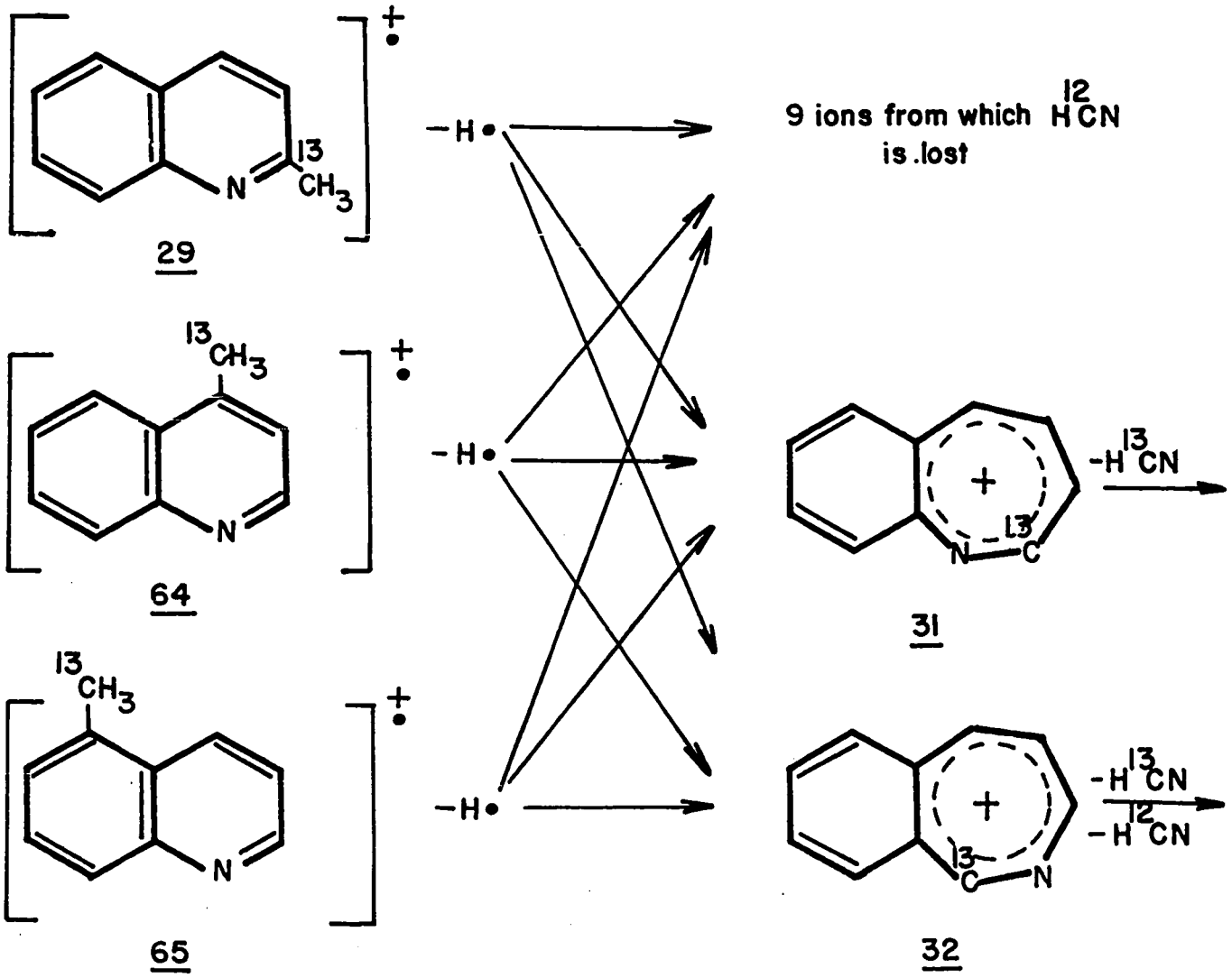
[a] $\Sigma_{113-118} = 1.000$. [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Error calculated from standard deviations of intensity measurements.

TABLE VI

Mass Spectral Peaks for 5-Methylquinoline

m/e	Composition	Relative abundance[a,b] 5-Methylquinoline (unlabeled)	Relative abundance[a,b] 5-Methylquinoline-5-α-^{13}C [c]	Abundance Ratios
115	$^{13}C_1C_7H_4N$		0.008 ±0.005 [d]	(i)
	$^{13}C_1C_8H_6$		0.079 ±0.002	
	C_9H_7	0.553 ±0.002	0.054 ±0.005	
116	C_8H_6N	0.131 ±0.001	0.077 ±0.006	(ii) $\frac{C_9H_7}{C_9H_7 + {}^{13}C_1C_8H_7} = 0.101 \pm 0.009$
	$^{13}C_1C_8H_7$		0.482 ±0.003	
	C_9H_8	0.034 ±0.001		
				(iii) $\frac{C_8H_7N}{C_8H_7N + {}^{13}C_1C_7H_7N} = 0.529 \pm 0.048$
117	$^{13}C_1C_7H_6N$		0.065 ±0.004	
	C_8H_7N	0.121 ±0.001	0.555 ±0.004	
	$^{13}C_1C_8H_8$		0.024 ±0.003	(iv) $\frac{C_8H_6N}{C_8H_6N + {}^{13}C_1C_7H_6N} = 0.543 \pm 0.037$
118	$^{13}C_1C_7H_7N$		0.049 ±0.005	

[a] $\Sigma_{113-118} = 1.000$ [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Error calculated from standard deviations of intensity measurement.


9 ions from which H12CN is lost
-H•
-H•
-H•
-H13CN
-H13CN
-H12CN
29
64
65
31
32

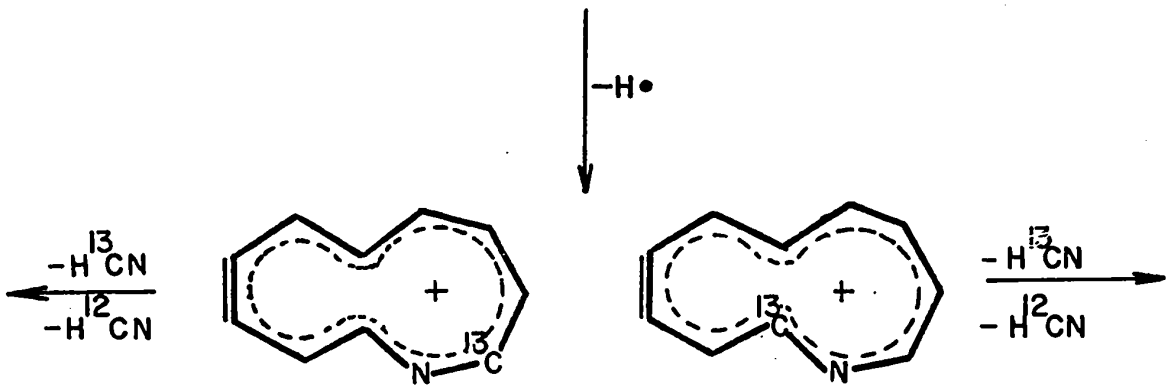
Scheme 15

by a random insertion of the methyl carbon into any bond in the molecule. If ring expansion occurs by a random insertion of the exocyclic methyl carbon into any of the carbon-carbon or carbon-nitrogen bonds of the molecule, then 11 possible ions may be formed of which only two, 31 and 32 can eliminate $H^{13}CN$. If one assumes that the carbon-nitrogen link in the intermediate retains its identity in the HCN fragment and that the carbon of the ring junction is not involved in the loss of HCN then one would expect 1½/11 or 14% loss of ^{13}C from the labeled methylquinolines on expulsion of HCN. The observed value of 14.6 ±1.0% for the 2-isomer is in close agreement with the expected value and with the value of 15% observed by Draper and MacLean (62).

The fact that a significant amount of ^{13}C is lost as $H^{13}CN$ from the M-1 ion in compounds 64 and 65 means that scrambling of carbon must be occurring before loss of HCN. The slightly lower values obtained from 4-methylquinoline-4-α-^{13}C 64 and 5-methylquinoline-5-α-^{13}C 65, namely 9.6 ±1.1% and 10.1 ±0.9% respectively, can be explained in several ways. If one assumes that more than one mechanism may be involved in the fragmentation pathway M→M-(H + HCN), then approximately 65-70% of the M-(H + HCN) ions can be accounted for by ring expansion in a random insertion process.

An alternative explanation to account for the observed results involves the formation of an eleven-membered ring as shown in Scheme 16.

$M^{+}_{\bullet}$ of compounds 29, 64, and 65



66 67

+ 8 ions from which $H^{12}CN$ only is lost

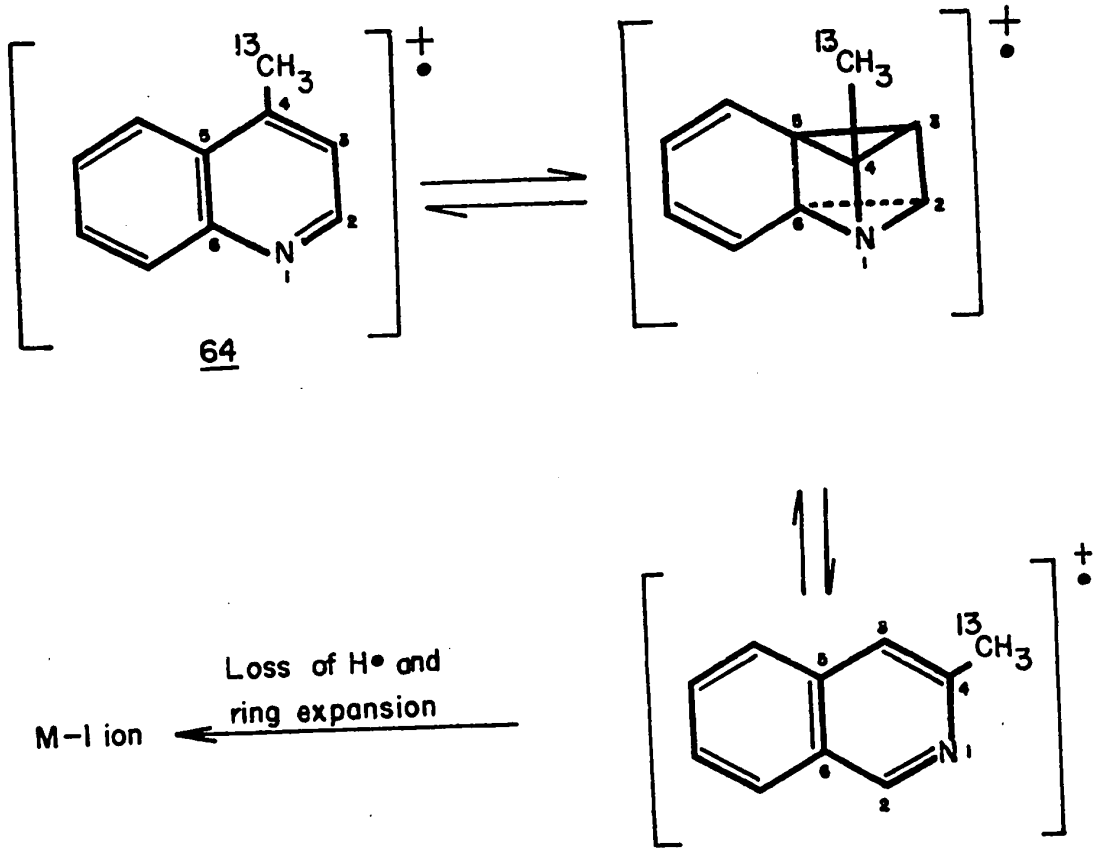
Scheme 16

Intermediates 66 and 67 might eliminate $H^{12}CN$ and $H^{13}CN$ in approximately equal proportions. Therefore if such intermediates are feasible one might expect 1/10 or 10% loss of ^{13}C on expulsion of HCN from the M-1 ion. A calculated result of 9% is obtained if one permits elimination towards the ring junction in the bicyclic systems 31 and 32. The use of ground state structures such as 29 and 31 etc. for the molecular and fragment ions of methylquinolines cannot alone represent the actual structures of the species formed on electron impact. Evidence now points to the formation of molecular ions with a range of internal energies (54) and of different skeletal structures. It is therefore not impossible that

intermediate ions such as 66 may exist.

A second alternative involves the intermediacy of fulvene or prismane type ions. Formation of such intermediates has been invoked to account for carbon scrambling and/or hydrogen scrambling in benzene (60,66) and pyridine (106). If an equilibrium exists between the quinoline nucleus and a prismane intermediate and if the rate of reformation of the quinoline nucleus is much greater than the rate of fragmentation, then it is possible for the methyl group, in effect, to migrate round the ring and for the ring atoms to lose positional identity (Scheme 17). Subsequent 1,2 or random insertion to form ring expanded species would permit the loss of $H^{13}CN$ from the M-1 ion. Possibly the closeness of the methyl group to the nitrogen in the original structure accounts for the larger percentage loss of ^{13}C as $H^{13}CN$ from the 2-isomer compared with the 4- and 5-isomers.

The processes M→M-HCN, M→M-C_2H_2, and M→M-(H+C_2H_2) were also investigated since the results were available from the same compounds studied above. The loss of $H^{13}CN$ from the molecular ion of the labeled compounds was calculated but conclusions drawn from the results are at best speculative because of the low intensity of the (M-HCN) ion. If the calculated intensities are meaningful, the loss of $H^{13}CN$ from the molecular ion in the 2- and 4-isomers and the absence of the loss of $H^{13}CN$ from the molecular ion in the labeled 5-isomer would seem to indicate that different mechanisms are involved in the pathway M→M-HCN for the various isomers.

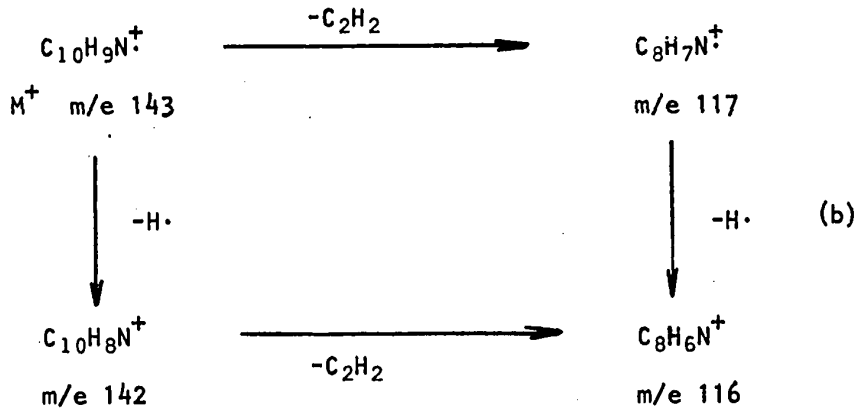


Scheme 17

In the case of 2-methylquinoline the loss of HCN from the molecular ion seems possible only if preceded by a rearrangement giving a species in which the nitrogen atom is adjacent to a methine. It does not seem possible for 2-methylquinoline labeled with ^{13}C in the exocyclic group to lose $H^{13}CN$ from the molecular ion without some interchange

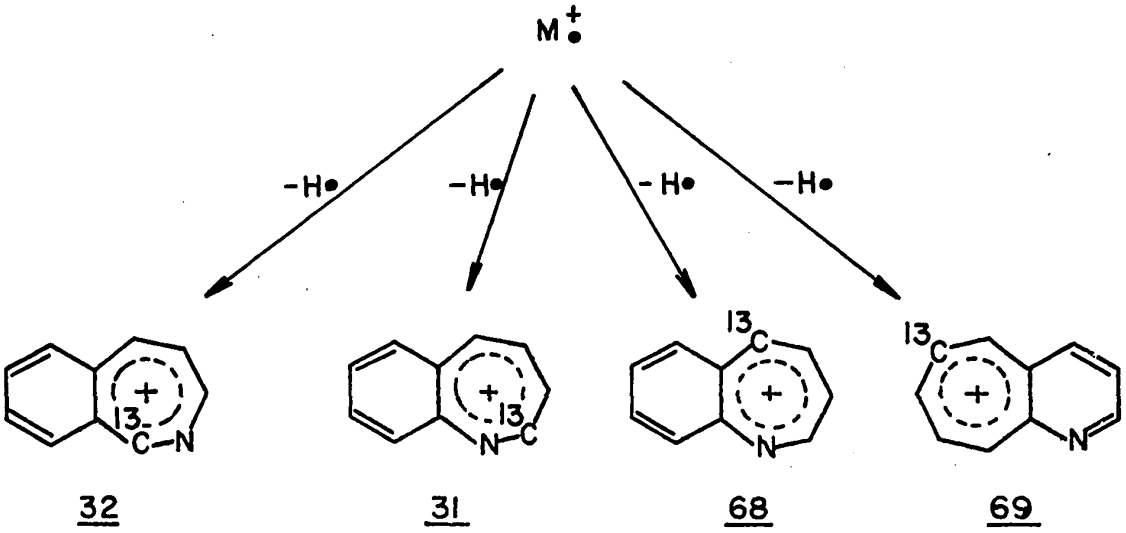
between the exocyclic carbon and a ring carbon adjacent to the nitrogen atom. The error calculated in abundance ratio (i) for the 2-isomer is greater than 66% and so the figure of 15.5% for the loss of ^{13}C as $H^{13}CN$ from the molecular ion is uncertain. Elimination of HCN from the molecular ion of the 4- and 5-isomers is possible without such a rearrangement. However the 4-isomer shows a loss of 21.3 ±4.8% of ^{13}C as $H^{13}CN$ from the molecular ion and the 5-isomer does not.

Conclusions drawn from examination of abundance ratios (iii) and (iv) Tables IV, V, and VI, are also speculative, since again the ions involved are of low intensity. The peak intensities of the $C_8H_7N^{+\cdot}$ ion ($M-C_2H_2$) and the $C_8H_6N^+$ ion ($M-(H+C_2H_2)$) are approximately 20% of the intensity of the corresponding $C_9H_7^+$ ion ($M-(H+HCN)$). In Scheme 18 the possible fragmentation pathways for the formation of the ions $C_8H_7N^{+\cdot}$ and $C_8H_6N^+$ are outlined.



Scheme 18

If the ion $C_8H_6N^+$ is formed by loss of C_2H_2 from the M-1 ion ($C_{10}H_8N^+$), path (a), then the value of 50-56% obtained for the loss $^{13}C_1{}^{12}C_1H_3$ from the labeled compounds is much higher than is predicted for such a loss from a completely randomized system. The theoretical value for the loss of $^{13}C_1{}^{12}C_1H_3$ depends on the model chosen. If one assumes that ring expansion occurs in the same manner as Draper and MacLean (62) suggested for the M-1 ion, then the following results are obtained. Again eleven species may be formed. Four of these intermediates are shown in Scheme 19.



Scheme 19

If elimination does not occur towards the ring junction, then intermediate 32 can lose C_2H_2 in 5 ways but cannot lose $^{13}C_1{}^{12}C_1H_2$. The remaining intermediates can lose C_2H_2 in 6 ways and can lose $^{13}C_1{}^{12}C_1H_2$ in either none, one, or two ways depending on the position of the ^{13}C atom.

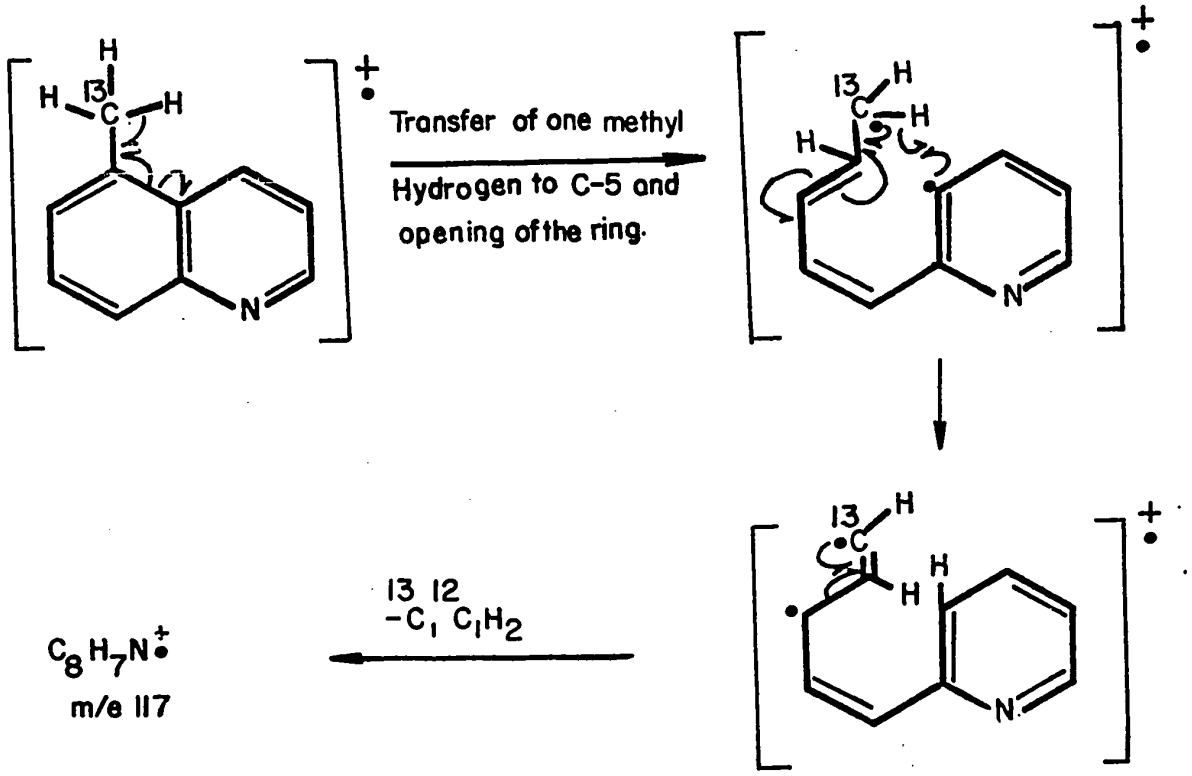
For example, because the ^{13}C atom is adjacent to the ring junction in 68, $^{13}C_1{}^{12}C_1H_2$ can only be lost in one way, while in 69 $^{13}C_1{}^{12}C_1H_2$ can be lost in two ways. Thus of a total of 65 ways of losing C_2H_2 from all eleven intermediates, $^{13}C_1{}^{12}C_1H_2$ can be lost in 12 ways giving a theoretical percentage loss of $^{13}C_1{}^{12}C_1H_2$ of 18% from the M-1 ion.

If an eleven-membered ring intermediate is used as a model, e.g. 66, then $^{13}C_1{}^{12}C_1H_2$ can be lost in 18 ways from the M-1 ion from a total of 90 possibilities, i.e. 20% loss of $^{13}C_1{}^{12}C_1H_2$ from the M-1 ion would be expected from such a model. Numerous other models, such as ring expansion occurring only in the ring containing the methyl group, give theoretical values for the loss of $^{13}C_1{}^{12}C_1H_2$ from the M-1 ion ranging from 9 to 30%.

However, as Scheme 18 indicates, C_2H_2 must be lost from the molecular ion but the loss of C_2H_3 may occur by path (a) or (b). Thus if the loss of C_2H_2 and C_2H_3 occurs by path (b), the amount of label lost will depend on whether or not randomization of the carbon in the molecular ion $C_{10}H_9N^{+\cdot}$ occurs before expulsion of C_2H_2. The fact that the observed loss of $^{13}C_1{}^{12}C_1H_3$ is approximately the same as the observed loss of $^{13}C_1{}^{12}C_1H_2$ would suggest that ion $C_8H_6N^+$ is formed by path (b).

The results indicate that a fraction of the $C_8H_7N^{+\cdot}$ and $C_8H_6N^+$ ions arise by ring opening in the molecular ion, followed by loss of the methyl carbon and the carbon to which the methyl group is attached. A possible intermediate is shown in Scheme 20.

The observed result for the loss of ^{13}C as $^{13}C_1{}^{12}C_1H_3$ is surprising in the case of the 5-isomer since one might have expected a

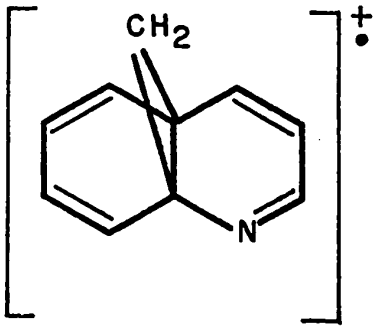


Scheme 20

result similar to that observed for the loss of $^{13}C_1{}^{12}C_1H_2$ from the M-1 ion of toluene labeled with ^{13}C (68).

In summary of this section, it appears that the loss of ^{13}C as $H^{13}CN$ in the fragmentation pathway M→M-(H+HCN) may be explained in terms of formation of a species formed by random insertion of the exocyclic methyl carbon into any bond in the molecule. It should be pointed out, however, that formation of a ring expanded intermediate cannot exactly parallel the case of toluene for two reasons. The presence of a hetero-atom in the molecule may result in a preference for insertion of the exo-cyclic carbon between a carbon-carbon bond over insertion between a carbon-nitrogen bond or vice-versa. In the bicyclic system insertion of

the methyl carbon between the two carbons of the ring junction may result in a [4,4,1] type of intermediate 70 complicating matters further.



70

Evidence for the intermediacy of ring-opened species has been found for other aromatic systems. The similarity of the spectra of some C_{12} polyacetylenes with the spectra of the dimethylnaphthalenes led Aplin and Safe (76) to suggest that the acetylenes rearrange to the stable benztropyllium cation but an equilibrium between the cyclic and open chain species cannot be excluded. Such an equilibrium between the monomethylquinolines and a linear polyacetylene type ion should therefore be considered. Recent evidence (60,65,66) has shown that hydrogen scrambling occurs in the benzene molecular ion by two processes, carbon scrambling with the bond to each substituent remaining intact, and by carbon-hydrogen bond cleavage with hydrogen migration. A recent study by Cooks and co-workers (139) indicated that scrambling of substituents other than hydrogen in the thiophene molecular ion does occur. It was suggested that in the benzene and thiophene molecular ions, randomization occurs both by scrambling of the ring atoms and by cleavage and subsequent

migration of the substituent. It was further suggested that scrambling of the ring carbons occurs only in the cyclic form of the ion and that only a ring-opened form can undergo substituent migration. Thus in the case of the monomethylquinolines an equilibrium may exist between the cyclic form of the molecular ion and a ring-opened form. Migration of the methyl substituent could then occur in the ring-opened form. Subsequent ring closure would result in the methyl group losing positional identity relative to its methylquinoline origin.

Future studies along the lines suggested below appear desirable. A study of the mass spectrum of a monomethylquinoline labeled with ^{13}C in the ring except at C-2 should determine whether scrambling of the ring carbons occurs in the process M→M-(H+HCN). Any loss of ^{13}C as $H^{13}CN$ from the M-1 ion in a ring-labeled compound can only arise by randomization of the ring carbons before or during the process M→M-(H+HCN). A study of the mass spectrum of a monomethylquinoline labeled with ^{13}C at the position of methyl substitution and in the exocyclic methyl group should provide further information regarding the loss of C_2H_2 from the molecular ion. The value for the loss of ^{13}C as $^{13}C_2H_2$ from the molecular ion would indicate how much of the process M→M-C_2H_2 occurs before randomization of the ring carbons and/or the exocyclic methyl group takes place.

Mass Spectra of Monomethylpyridines

Several groups (55,58c) have examined the mass spectra of monomethylpyridines labeled with deuterium but no reports of ^{13}C labeling have

appeared. The studies with deuterium were undertaken in an attempt to determine if hydrogen scrambling occurs upon electron impact in methylpyridines as it does in the case of toluene.

Cole et al. (55) studied 2-methyl and 4-methylpyridine labeled with deuterium in the methyl group and found that at all beam energies almost complete scrambling of the hydrogens occurs in the molecular ion before the loss of HCN. The loss of the methyl group was shown to take place from a molecular ion of higher internal energy than the molecular ions which expel H· and HCN and that little or no hydrogen scrambling is observed before the loss of CH_3 at high beam energies. The increase in hydrogen scrambling in the loss of the methyl group as the beam energy was lowered, indicated that scrambling was more complete in parent ions of low internal energy. Cole et al. concluded that the lower the internal energy of the parent ions the greater the amount of hydrogen scrambling and that in the process M→M-HCN randomization of all the hydrogens takes place before expulsion of HCN. The existence of an isotope effect in the M→M-H process prevented a definite conclusion concerning the amount of hydrogen scrambling. The authors did not attempt to suggest a mechanism to account for the scrambling results.

In another study Neeter et al. (58c) compared the mass spectrum of 4-methylpyridine with that of deuterated analogues. The observed results indicated that the molecular ion loses the α-, β-, and methyl hydrogens in the ratio 1.43:1:1.13 in the M-H ion and that a similar ratio is observed in the elimination of HCN from the molecular ion. These results led Neeter et al. (58c) to conclude that although hydrogen

scrambling does occur before the loss of H· and HCN from the molecular ion of 4-methylpyridine, it is unlikely that a ring-expanded ion is involved.

Because conclusions drawn about carbon scrambling from deuterium labeling work are suspect, the mass spectra of 2- and 4-methylpyridine labeled with ^{13}C in the exocyclic methyl group were examined in this study. This work was undertaken in order to see if ^{13}C scrambling is involved in the processes M→M-HCN and M→M-(H+HCN) and as well to gain further insight into the mechanism of the fragmentation.

The mass spectra of 2- and 4-methylpyridine and 2- and 4-methylpyridine labeled with ^{13}C in the exocyclic methyl carbon are shown in Figure 5 (a-d). The region m/e 61 - m/e 68 was examined under high resolution conditions (1 in 20,000) and the composition of the ions determined as described in the experimental section. In the unlabeled spectra of 2- and 4-methylpyridine all nominal masses near m/e 65 are C_5H_n -$C_4H_{n-2}N$ doublets and the ^{13}C labeled spectra have the added complication of two ^{13}C isobaric peaks also present at each nominal mass, e.g. at m/e 66 the ions present are $^{13}C_1C_3H_3N^+$, $C_4H_4N^+$, $^{13}C_1C_4H_5^+$, and $C_5H_6^{+\cdot}$. Exact mass measurements of the ions in the region m/e 63 - 69 in the spectra of 4-methylpyridine unlabeled and labeled are given in Tables VII and VIII respectively. The mass spectral peaks of interest of the labeled and unlabeled compounds are set out in Tables IX and X.

If the process M→M-HCN involves expulsion of HCN from an azacycloheptatriene intermediate, e.g. 73, formed by random insertion of the methyl carbon into any bond in the molecule, then six possible

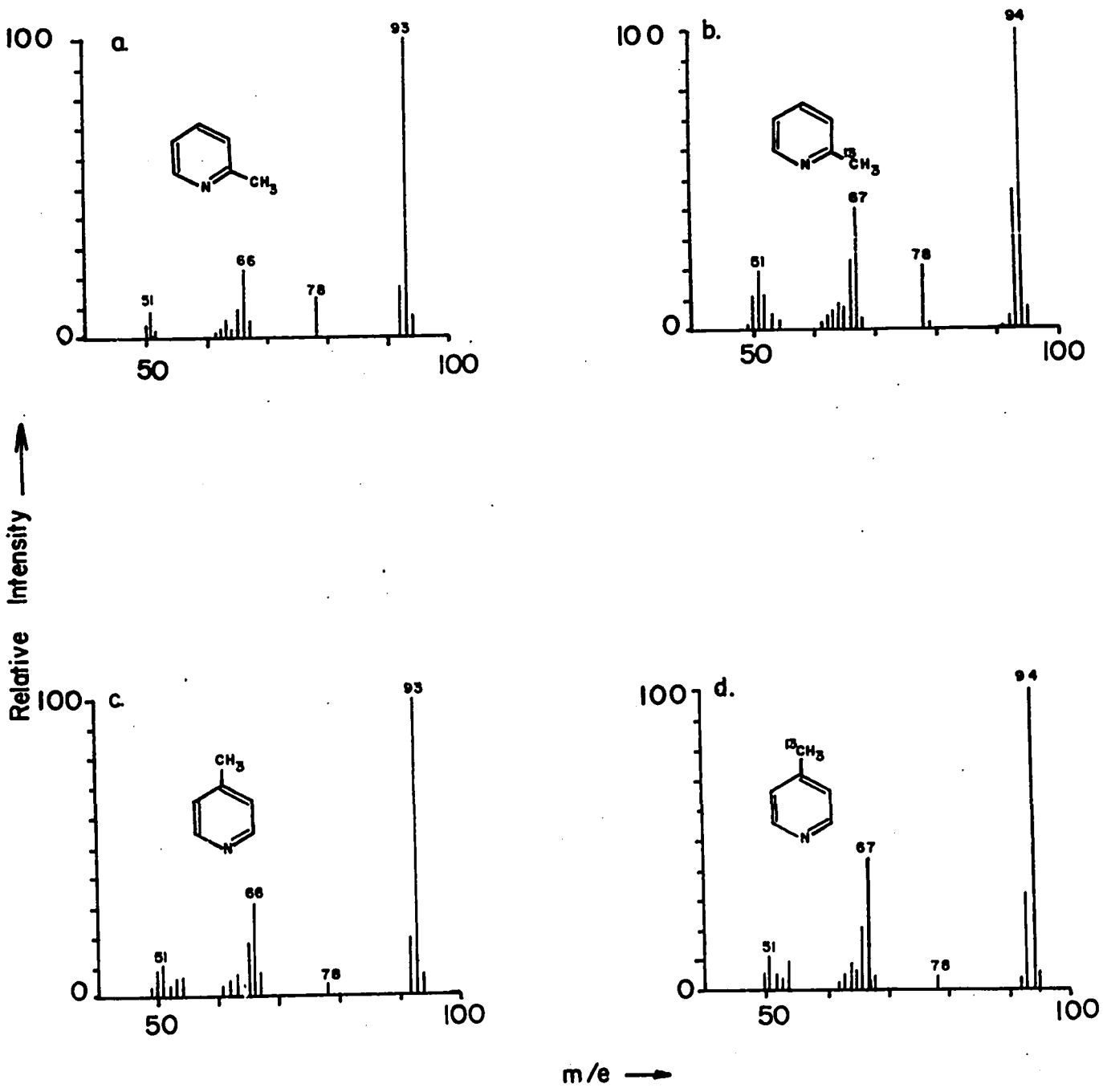


Fig. 5 Mass spectra of 2-methylpyridine, 2-methylpyridine-2-α-^{13}C, 4-methylpyridine, and 4-methylpyridine-4-α-^{13}C

TABLE VII

Exact Masses of the Ions in the Region m/e 63 - 68 of 4-Methylpyridine (Unlabeled)

Observed Mass	Calculated Mass	Ion Composition
63.0233	63.0235	C_5H_3
64.0181	64.0187	C_4H_2N
64.0315	64.0313	C_5H_4
65.0267	65.0266	C_4H_3N
65.0347	65.0347	$^{13}C_1C_4H_4$
65.0394	65.0391	C_5H_5
66.0341	66.0344	C_4H_4N
66.0423	66.0425	$^{13}C_1C_4H_5$
66.0479	66.0470	C_5H_6
67.0414	67.0422	C_4H_5N
67.0473	67.0503	$^{13}C_1C_4H_6$
68.0448	68.0455	$^{13}C_1C_3H_5N$

TABLE VIII

Exact Masses of the Ions in the Region m/e 63 - 68 of 4-Methylpyridine-4-α-^{13}C

Observed Mass	Calculated Mass	Ion Composition
63.0126	63.0101	C_4H_1N
63.0194	63.0190	$^{13}C_1C_4H_2$
63.0238	63.0235	C_5H_3
64.0137	64.0143	$^{13}C_1C_3H_1N$
64.0189	64.0187	C_4H_2N
64.0270	64.0268	$^{13}C_1C_4H_3$
64.0310	64.0313	C_5H_4
65.0230	65.0221	$^{13}C_1C_3H_2N$
65.0263	65.0266	C_4H_3N
65.0354	65.0347	$^{13}C_1C_4H_4$
65.0399	65.0391	C_5H_5
66.0297	66.0299	$^{13}C_1C_3H_3N$
66.0341	66.0344	C_4H_4N
66.0363	66.0379	$^{13}C_2C_3H_4$
66.0419	66.0425	$^{13}C_1C_4H_5$
66.0464	66.0470	C_5H_6
67.0371	67.0377	$^{13}C_1C_3H_4N$

TABLE VIII (cont'd)

Observed Mass	Calculated Mass	Ion Composition
67.0417	67.0422	C_4H_5N
67.0497	67.0503	$^{13}C_1C_4H_6$
68.0448	68.0456	$^{13}C_1C_3H_5N$
68.0531	68.0537	$^{13}C_2C_3H_6$

TABLE IX

Mass Spectral Peaks of 2-Methylpyridine

m/e	Composition	Relative abundance[a,b] 2-Methylpyridine (unlabeled)	Relative abundance[a,b] 2-Methylpyridine-2-α-^{13}C[c]	Abundance Ratios
65	$^{13}C_1C_3H_2N$		0.010 ±0.001[d]	
	C_4H_3N	0.011 ±0.001	0.005 ±0.001	(i) $\frac{C_5H_6}{C_5H_6 + {}^{13}C_1C_4H_6} = 0.017 \pm 0.008$
	$^{13}C_1C_4H_4$		0.023 ±0.001	
	C_5H_5	0.180 ±0.004	0.010 ±0.002	
66	$^{13}C_1C_3H_3N$		0.005 ±0.001	(ii) $\frac{C_5H_5}{C_5H_5 + {}^{13}C_1C_4H_5} = 0.058 \pm 0.007$
	C_4H_4N	0.014 ±0.002	0.008 ±0.002	
	$^{13}C_1C_4H_5$		0.161 ±0.003	
	C_5H_6	0.465 ±0.045	0.008 ±0.004	(iii) $\frac{C_4H_5N}{C_4H_5N + {}^{13}C_1C_4H_5N} = 0.547 \pm 0.019$
67	$^{13}C_1C_3H_4N$		0.011 ±0.002	
	C_4H_5N	0.084 ±0.002	0.037 ±0.002	
	$^{13}C_1C_4H_6$		0.463 ±0.006	(iv) $\frac{C_4H_4N}{C_4H_4N + {}^{13}C_1C_4H_4N} = 0.421 \pm 0.047$
68	$^{13}C_1C_3H_5N$		0.031 ±0.001	

[a] $\Sigma_{61-68} = 1.000$ [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Error calculated from standard deviations of intensity measurements.

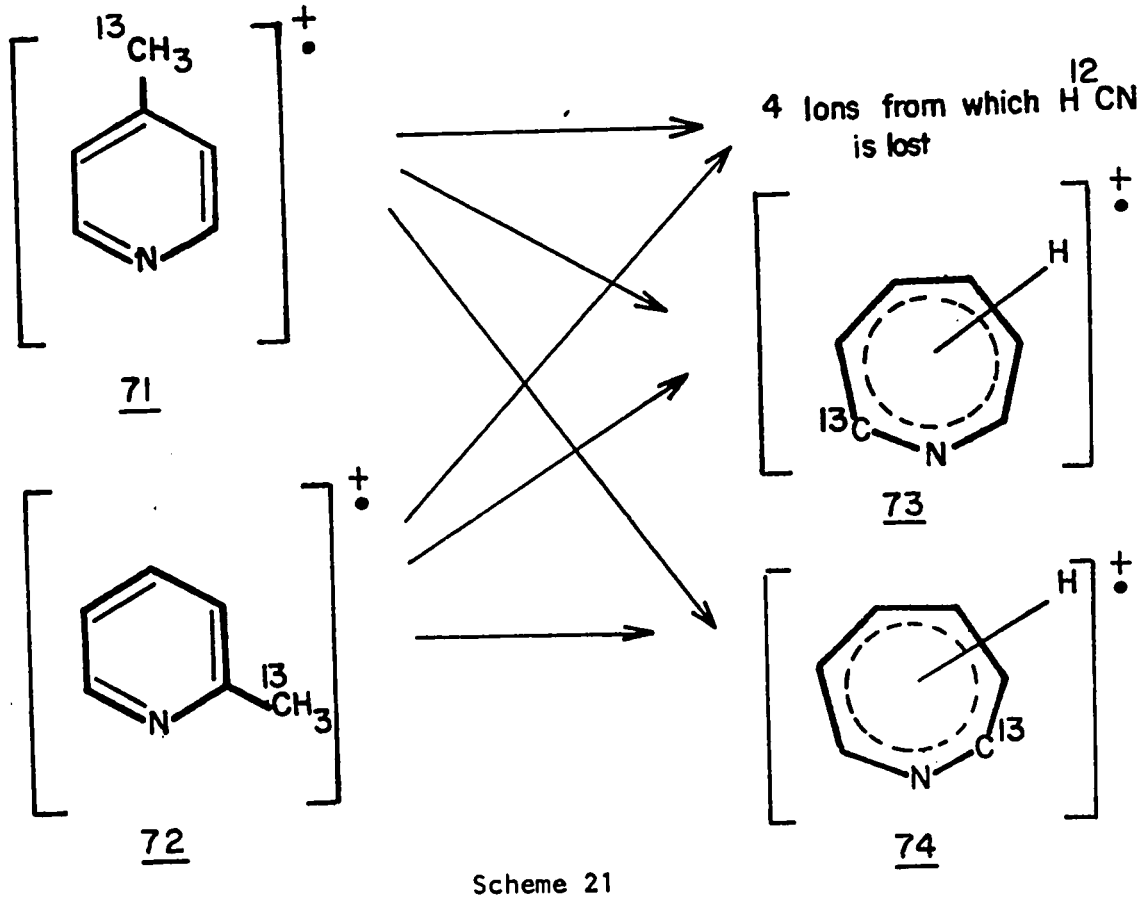
TABLE X

Mass Spectral Peaks of 4-Methylpyridine

m/e	Composition	Relative abundance[a,b] 4-Methylpyridine (unlabeled)	Relative abundance[a,b] 4-Methylpyridine-4-α-^{13}C [c]	Abundance Ratios
65	$^{13}C_1C_3H_2N$		0.012 ±0.001 [d]	
	C_4H_3N	0.018 ±0.001	0.010 ±0.001	(i) $\frac{C_5H_6}{C_5H_6 + {}^{13}C_1C_4H_6}$ = 0.040 ±0.004
	$^{13}C_1C_4H_4$		0.025 ±0.001	
	C_5H_5	0.227 ±0.004	0.011 ±0.002	
66	$^{13}C_1C_3H_3N$		0.006 ±0.001	(ii) $\frac{C_5H_5}{C_5H_5 + {}^{13}C_1C_4H_5}$ = 0.048 ±0.007
	C_4H_4N	0.012 ±0.001	0.004 ±0.001	
	$^{13}C_1C_4H_5$		0.223 ±0.004	
	C_5H_6	0.402 ±0.005	0.016 ±0.002	(iii) $\frac{C_4H_5N}{C_4H_5N + {}^{13}C_1C_3H_5N}$ = 0.488 ±0.018
67	$^{13}C_1C_3H_4N$		0.010 ±0.001	
	C_4H_5N	0.087 ±0.002	0.038 ±0.001	
	$^{13}C_1C_4H_6$		0.383 ±0.005	(iv) $\frac{C_4H_4N}{C_4H_4N + {}^{13}C_1C_3H_4N}$ = 0.307 ±0.048
68	$^{13}C_1C_3H_5N$		0.040 ±0.001	

[a] $\Sigma_{61-68} = 1.000$ [b] Corrected for naturally abundant ^{13}C. [c] Calculated for 100% isotopic enrichment. [d] Error calculated from standard deviations of intensity measurements.

intermediates can be formed (Scheme 21). Of these, only 2 ions, 73 and 74 can eliminate $H^{13}CN$.



Scheme 21

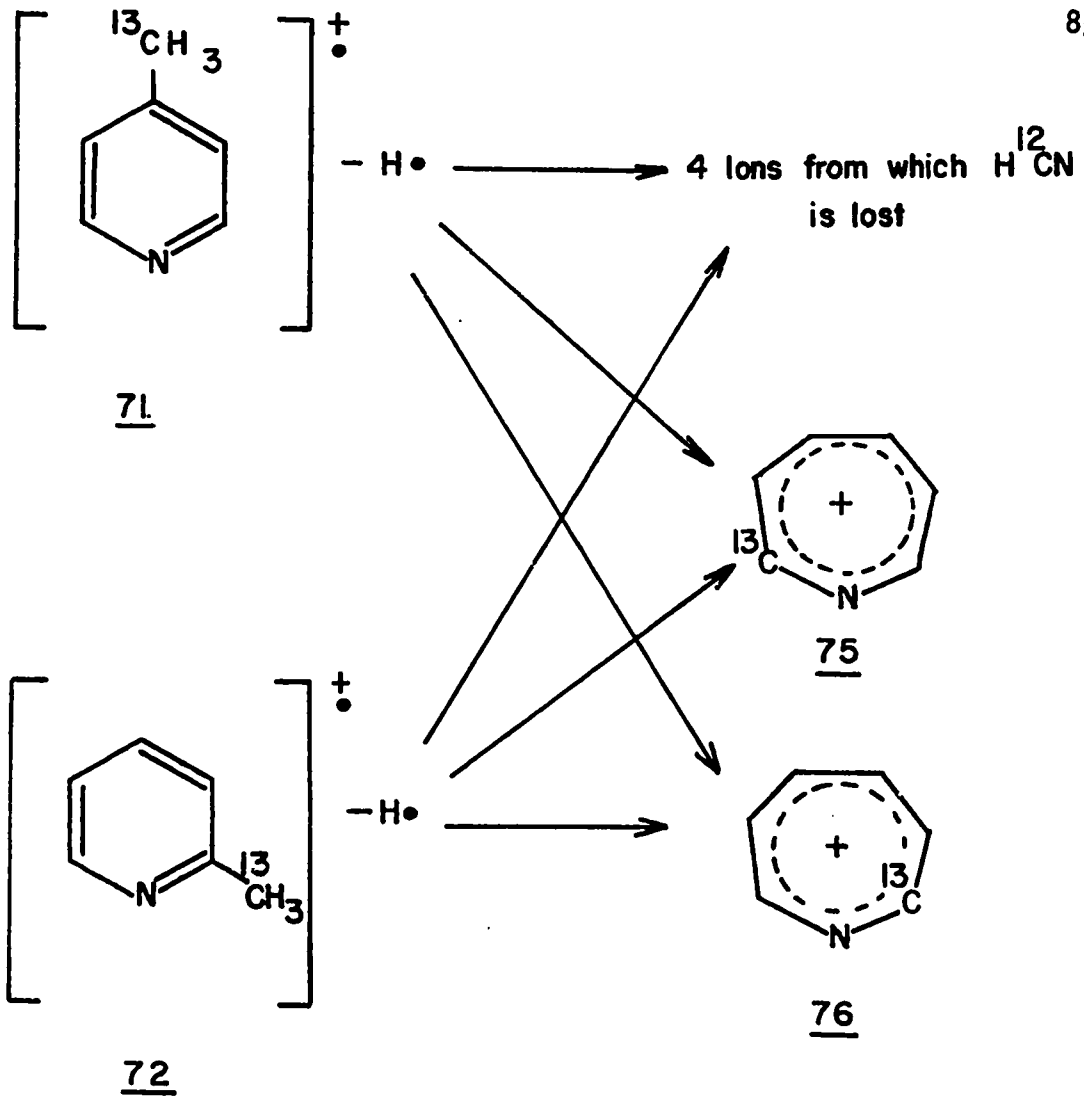
Ions 73 and 74 might eliminate $H^{13}CN$ and $H^{12}CN$ in approximately equal proportions. Therefore 1/6 or 16.6% loss of ^{13}C from 71 and 72 on expulsion of HCN is expected. If ring expansion involves a 1,2 insertion of the methyl carbon into the adjacent carbon-carbon or carbon-nitrogen bonds, then obviously 71 cannot lose $H^{13}CN$ and 72 would lose 25% of the ^{13}C as $H^{13}CN$.

Examination of abundance ratio (I), the loss of $H^{13}CN$ from the molecular ion of the labeled compounds, shows little or no loss of $H^{13}CN$. In the 2-isomer 1.7 ±0.8% loss of ^{13}C as $H^{13}CN$ has occurred. Such a value is only one tenth the calculated value for ring expansion by a random process. One has to conclude that ring expansion is not a major process in the fragmentation of 2-methylpyridine involving loss of HCN. The slightly higher value of 4.0 ±0.4% observed for the 4-isomer is only one quarter the calculated value for azacycloheptatriene ion formation by a random process and again precludes the intermediacy of an azacycloheptatriene ion as a major fragmentation pathway. Certainly if ring expansion does occur in the 4-isomer, only 25% occurs by this process. Thus it would appear that formation of a ring-expanded species by any mechanism is not a major process in the fragmentation of monomethylpyridines in the process M→M-HCN.

In a manner analogous with loss of C_2H_2 from the M-1 ion of toluene (58a) loss of HCN from the M-1 ion of methylpyridines could arise from an azatropylium ion as depicted in Scheme 22.

The expected loss of ^{13}C as $H^{13}CN$ from the M-1 intermediates is again 16.6% for ring expansion by a random process. Similarly, ring expansion by a 1,2 insertion of the methyl group into the adjacent carbon-carbon or carbon-nitrogen bond will permit only a 25% loss of ^{13}C as $H^{13}CN$ from isomer 72.

Unlike the process M→M-(H+HCN) in monomethylquinolines, the loss of HCN from the M-1 ion in monomethylpyridines is not the major fragmentation pathway but is secondary to the loss of HCN from the



Scheme 22

molecular ion. In fact the process M→M-(H+HCN) is approximately half the intensity of the M→M-HCN process in monomethylpyridines.

Examination of abundance ratio (ii) indicates that 2-methyl and 4-methylpyridine labeled with ^{13}C in the exocyclic group lose 5.8 ±0.7% and 4.8 ±0.7%, respectively, of the ^{13}C label as $H^{13}CN$ in the process M→M-(H+HCN). These values are approximately one third and one quarter, respectively, of the calculated value for loss of $H^{13}CN$ from an azatropylium ion intermediate formed by a random process. Thus, as in the

case of the M→M-HCN process, it appears that formation of ring expanded species is not the major pathway in the process M→M-(H+HCN) in the monomethylpyridines.

The fragmentations leading to loss of C_2H_2 and C_2H_3 were also examined in the pyridine series. The values obtained for the loss of ^{13}C as $^{13}C_1{}^{12}C_1H_2$ and $^{13}C_1{}^{12}C_1H_3$ from the labeled compounds, 30-55%, are not compatible with the loss of a two carbon unit from a ring expanded species. The similarity between the above values and those obtained for the same processes in the monomethylquinolines suggest that the same mechanism is involved in the loss of C_2H_2 and C_2H_3 from their respective molecular ions. It would appear that expulsion of C_2H_2 and C_2H_3 from the molecular ions of monomethylpyridines involves mainly the exocyclic carbon. This requires that cleavage of the ring occurs between the carbon attached to the methyl group and an adjacent ring carbon.

It may be that a ring-opened intermediate is involved before the loss of H·or HCN from the molecular ion. Cooks et al. (139), as stated before, suggested that a ring-opened form is implicated in randomization of substituents including hydrogen in aromatic molecular ions such as benzene and thiophene. A ring-opened form of the monomethylpyridines in which scrambling of the methyl hydrogens and the ring hydrogens takes place would account for the observed hydrogen scrambling (55,58c) in the processes M→M-H and M→M-HCN. Such a ring-opened intermediate would permit loss of HCN from the M-1 ion without involvement of the exocyclic methyl carbon.

Cole et al. (55) showed in the monomethylpyridines that scrambling of hydrogen increases as the internal energy of the molecular ion is lowered. Because of difficulties in obtaining accurate high resolution results below 20 eV with the C.E.C. 21-110B, it was not possible to determine if carbon scrambling was most favoured from molecular ions of low internal energy.

In the light of these results, it would seem that the formation of a ring-expanded species is not involved in the major fragmentation processes of monomethylpyridines. Further labeling studies with ^{13}C are required to determine if scrambling of the ring carbons occurs. Examination of the spectra of a methylpyridine labeled with ^{13}C in the ring should permit a conclusion to be made regarding scrambling of the ring carbons before expulsion of HCN from the molecular ion. The mass spectrum of 4-methylpyridine-4,4-α-$^{13}C_2$ should furnish further information regarding the mechanism involved in the expulsion of C_2H_2 and C_2H_3 from the molecular ion.

EXPERIMENTAL

Apparatus, Methods, and Materials

Mass spectra were determined on a C.E.C. 21-110B double focusing mass spectrometer at an ionizing potential of 70 eV and an ionizing current of 140 μA. Focus, repellers, and acceleration output were adjusted to give maximum beam. For low resolution one maximized on the total beam, while for high resolution one maximized on the peak of interest. Samples were introduced through a hypodermic injection port into a one litre reservoir using a standard Hamilton microsyringe. The glass inlet system was maintained at a temperature of 200°C. All spectra are plotted relative to the most abundant peak in the spectrum (base peak) which is given the value of 100%. All peaks with an intensity of 2% or more of the base peak are reported.

The high resolution mass spectra were recorded on type Q2 thin glass photographic plates manufactured by Ilford Photographic Materials, Ilford Ltd., Ilford, England, and were developed in the usual manner (140). The line distances were examined using a Gaertner Special Spectrum Linear Comparator. The most intense point of each line in the region of interest was determined using an Electronics Associates Inc. digital voltmeter and the distances were read from the comparator. The composition of the ions that produced the lines was determined by the use of a computer program developed by Dr. L. Baczynskyj and modified by Mr. T.I. Martin.

At low resolution the mass spectrum of each compound was recorded on Kodak Linagraph Direct Print paper. The intensities of the nominal masses used in the calculations were the average of at least ten scans.

At high resolution (at least 1 in 20,000) the mass regions of interest were recorded as follows:- At a particular mass the electric signal from the detector was recorded on a Varian Associates time averaging computer C-1024 (CAT). After 50 such scans the read-out from the CAT was recorded on a Moseley Autograf, model 7001 AR X-Y recorder. For greater detail of the electronic set-up the reader is referred to Appendix II. Each mass was recorded several times by this method.

Analytical and preparative gas-liquid chromatography (g.l.c.) analyses were performed on Varian 204B and 90P-3 gas chromatographs respectively with helium as the carrier gas. Reaction products were analysed by g.l.c. using a 5' x 0.125" O.D. stainless steel column packed with 5% SE-30 on chromosorb-W. Column temperatures were adjusted to allow retention times to fall in the range of 3-10 minutes.

The heterocyclic bases were purified by g.l.c. using a 10' x 0.375" O.D. stainless steel column packed with chromosorb-W which was coated with 5% potassium hydroxide and 20% carbowax 20M. The column temperature was maintained at 130-200^{o}C, depending on the volatility of the material. Collection of the purified bases was aided by a thermal gradient collector device which permitted collection of >90% of the injected material (Appendix III). The bases were further purified by vacuum distillation to remove any possible column bleed and finally sealed under vacuum.

The n.m.r. spectra were run on a Varian T-60 instrument with samples dissolved in $CDCl_3$ with TMS as internal reference. A Perkin-Elmer 337 Grating infrared spectrometer was used to record infrared spectra of samples dissolved in $CHCl_3$.

Melting points were determined on a Kofler Micro Hot Stage apparatus and are uncorrected.

$Na^{13}CN$(55.3 atom % ^{13}C, 90.0 atom % ^{13}C, and 91.9 atom % ^{13}C) and $^{13}CH_3I$(55.5 atom % ^{13}C and 62.8 atom % ^{13}C) were obtained from Merck, Sharp, and Dohme of Canada Ltd. and were used as such or after dilution. 2- and 4-Methylpyridine and 4-methylquinoline were obtained commercially.

Preparation of Quinolines

2-Methylquinoline

The 2-methylquinoline used was a laboratory sample prepared by P.M. Draper by condensation of aniline and acetaldehyde in HCl using the conditions described by Mills et al. (141).

2-Methylquinoline-2-α-^{13}C

N-Ethoxyquinolinium iodide was prepared by allowing a mixture of quinoline N-oxide (142) and an excess of ethyl iodide to stand for 20 hours at room temperature. The resulting quaternary salt was purified by recrystallisation from methanol-ether and dried over P_2O_5. The purified salt was added to a solution of $^{13}CH_3MgI$ in dry ether as described by Červinka et al. (143), to give the labeled 2-methylquinoline in 32% yield as calculated from $^{13}CH_3I$. Analysis of the labeled product by g.l.c. showed one peak with a retention time identical with an

authentic sample of 2-methylquinoline. Only one peak was observed when a mixture of labeled and unlabeled 2-methylquinoline was examined by g.l.c. The percentage of carbon-13 in the sample was obtained using the method of Biemann (144): ^{13}C 44.6 ±0.5%, ^{12}C 55.4 ±0.5%.

4-Methylquinoline-4-α-^{13}C

(a) Preparation of 4-Cyanoquinoline-4-α-^{13}C

Quinoline methiodide (4.065 g) in water (7 ml) and ether (0.5 ml) was shaken with a solution of $Na^{13}CN$ (0.50 g) in water (1.5 ml) according to the method of Ainley and King (145). Without purification, the dihydro compound, dissolved in pyridine (3.6 ml), was oxidised with iodine (2.5 g) in absolute ethanol (19 ml) to give labeled 4-cyanoquinoline methiodide in 55% yield as calculated from $Na^{13}CN$. Pyrolysis of the methiodide in diphenyl ether (4.0 ml) for 30 minutes gave labeled 4-cyanoquinoline. The crude material was sublimed at 85-90° at a pressure of 0.005 mm. Hg and gave a white crystalline powder; m.p. 102-104° (lit. 102° (134)). The yield of 4-cyanoquinoline-4-α-^{13}C was 0.705 g (45% based on $Na^{13}CN$).

The mass spectrum showed the molecular ions at m/e 154 and 155. The i.r. spectrum had medium absorption at 2225 cm^{-1} (-C≡N).

(b) Conversion of 4-Cyanoquinoline-4-α-^{13}C to 4-Methylquinoline-4-α-^{13}C

4-Cyanoquinoline-4-α-^{13}C (0.705 g) was boiled under reflux with 10% Pd/C (0.62 g) and dipentene (42 ml) as described by Kindler and Lührs (135). The mixture was heated for 4 hours, allowed to cool to room temper-

ature, and finally filtered and made acidic with 3N HCl. The aqueous layer was separated and extracted with ether, made basic with potassium hydroxide and finally extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated to dryness. Analysis of the product mixture by g.l.c. indicated two products, quinoline (20%) and 4-methylquinoline -4-α-^{13}C (80%). Purification of the labeled 4-methylquinoline by preparative gas chromatography yielded 0.50 g of the pure product (35% based on $Na^{13}CN$). Calculations showed the isotopic composition of the product was: ^{13}C 55.1 ± 0.5%, ^{12}C 44.9 ± 0.5%.

5-Methylquinoline

3-Amino-2-cyclohexene-1-one was condensed with propargyl aldehyde as described by Zymalkowski et al. (146) to give 5-aza-1-tetralone. Addition of the tetralone (0.40 g) in absolute ether (3 ml), to a solution of CH_3Li in dry ether gave a gelatinous complex. After stirring the mixture for 1 hour the complex was destroyed by the addition of water (10 ml). The aqueous layer was extracted with ether, and the ether layer washed with saturated salt solution and finally dried over Na_2SO_4. The desired alcohol was separated from the starting ketone by column chromatography over Fisher alumina A540, grade I. The ketone was eluted with benzene while the 5-aza-1-methyl-1-tetralol m.p. 109-110° was eluted with chloroform. The i.r. spectrum showed a strong sharp absorption at 3600 cm^{-1} (O-H) and no absorption around 1700 cm^{-1}. The n.m.r. spectrum confirmed the presence of a methyl group on a quaternary carbon by the presence of a peak of area 3 at 1.6 p.p.m. (singlet). The mass spectrum had a molecular ion at m/e 163.

The tertiary alcohol (0.27 g) was then refluxed for 24 hours in xylene, in which was suspended 10% Pd/C (0.25 g). The xylene layer was extracted with 3N HCl and the acid extracts washed with ether. The acid extract was made basic with solid $NaHCO_3$ and extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated to dryness. The yield of 5-methylquinoline was 0.23 g (59% based on 5-aza-1-tetralone). Analysis of the product by g.l.c. showed one peak. A mixture of the product and an authentic sample of 5-methylquinoline showed only one peak by g.l.c. The mass spectrum showed a molecular ion at m/e 143 and was identical with the mass spectrum of an authentic sample of 5-methylquinoline.

5-Methylquinoline-5-α-^{13}C

The procedure used was that described above, except that the methyllithium ($^{13}CH_3Li$) was prepared from $^{13}CH_3I$. The mass spectrum showed molecular ions at m/e 143 and 144. Calculations indicated the isotopic composition was: ^{13}C 60.6 ±4%, ^{12}C 39.4 ±0.3%.

Preparation of Pyridines

2-Methylpyridine-2-α-^{13}C and 4-methylpyridine-4-α-^{13}C

2-Methylpyridine-2-α-^{12}C and 4-methylpyridine-4-α-^{12}C were prepared by the method indicated below. The products from the initial reaction, namely 2- and 4-cyanopyridine were separated and identified by their infrared and mass spectra, by chromatographic techniques, and by comparison with authentic samples. The remaining reactions in the conversion of the cyano compounds to the methylpyridines were carried

out separately on each isomer so that the products could be identified. However, in the synthesis of the labeled compounds, the reactions were carried out on a mixture of both isomers. Separation of the final products, the labeled picolines, was carried out by preparative g.l.c.

N-Methoxypyridinium iodide was prepared according to the method of Okamoto and Tani (147). To a solution of $Na^{13}CN$ (1.0 g) dissolved in water (10 ml) and cooled to 0° was added slowly, a solution of N-methoxypyridinium iodide (5.0 g) in water (10 ml) (148). The temperature was maintained at 0° during the addition and for 1 hour after the addition was complete. After stirring the mixture for 3 hours at room temperature the labeled cyanopyridines were extracted with methylene chloride. The aqueous layer was then subjected to continuous liquid-liquid extraction for 24 hours using ether as solvent. The methylene chloride extract was dried over Na_2SO_4 and evaporated to dryness giving a mixture of labeled 2- and 4-cyanopyridines (22% as calculated from $Na^{13}CN$). A vapour chromatogram showed this mixture contained 75-80% of 4-cyanopyridine and 20-25% of 2-cyanopyridine.

The ether extract from the continuous extraction was dried and evaporation of the solvent yielded a solid residue (39% as calculated from $Na^{13}CN$) which on examination by thin layer chromatography (silica, chloroform, 20: methanol, 1) was shown to consist of picolinamide-α-^{13}C and isonicotinamide-α-^{13}C.

Both the amides and the cyano compounds were converted separately to the corresponding methyl esters of picolinic and isonicotinic acid by refluxing in methanolic HCl for 24 hours according to the method of

Winterfield and Flick (149). The overall yield of esters from $Na^{13}CN$ was 36%. The esters were converted to the corresponding alcohols in 58% yield by adding an ether solution of the esters (0.977 g) to a suspension of $LiAlH_4$ (0.039 g) in anhydrous ether at -5° as described by Kaslow et al. (150). The overall yield of alcohols from $Na^{13}CN$ was 21%. The labeled pyridylcarbinols were converted to the hydrochloride salts of 2- and 4-chloromethylpyridine by the method of Winterfield et al. (149) in 18.5% overall yield from $Na^{13}CN$. The mixture of labeled 2- and 4-chloromethylpyridine hydrochlorides was purified by sublimation (60° at 0.1-0.05 mm. Hg). The hydrochloride salts were converted to the labeled picolines using the method of Brown (151). The mixture of 2- and 4-chloromethylpyridine hydrochlorides (0.6 g) was dissolved in acetic acid (5 ml) and added over a period of 15-20 minutes to a stirred solution of zinc (0.256 g), acetic acid (4.5 ml), and water (3 ml). After stirring the mixture overnight at room temperature, it was heated to reflux for 1 hour. The labeled methylpyridines were recovered by basifying the acidic solution with K_2CO_3 and extracting the products by liquid-liquid extraction with ether as solvent. The weight of labeled picolines (0.20 g) constituted an overall yield of 11% from the $Na^{13}CN$. The methylpyridines were separated and collected by preparative g.l.c.

The ratio of 2-methyl to 4-methylpyridine was 3:1. Calculations indicated that the isotopic composition of the first sample of 2- and 4-methylpyridine was: ^{13}C 88.9 ± 0.3%, ^{12}C 11.1 ± 0.2%. A second sample of the labeled methylpyridines was prepared in the same manner but with a sample of $Na^{13}CN$ of different isotopic composition. The composition of the second sample was: ^{13}C 77.8 ± 0.4%, ^{12}C 22.2 ± 0.3%.

SUMMARY

This study has provided more information about the major fragmentation pathways in monomethylquinolines and monomethylpyridines.

Methods were developed for the syntheses of 2-, 4-, and 5-methylquinoline and 2-, and 4-methylpyridine all labeled with ^{13}C in the exocyclic methyl group.

By the use of ^{13}C labeling in this study it has been shown that, in the case of the monomethylquinolines, the loss of ^{13}C as $H^{13}CN$ from the M-1 ion can best be explained by the postulation of a ring-expanded species for this ion. Moreover, the mechanism by which this ring-expanded species is formed, must account for the fact that, regardless of the original position of the methyl group, a substantial amount of the ^{13}C label appears adjacent to the nitrogen atom in the M-1 ion. However, it is not possible to state if the mechanism of ring expansion involves insertion of the exocyclic group into any bond in the molecule giving a tropylium type ion. Ring expansion could occur by initial randomization of the ring atoms followed by 1,2 insertion of the methyl group or by substituent migration followed by a 1,2 insertion.

Three other fragmentation pathways of monomethylquinolines were also studied. The results observed for the loss of ^{13}C as $H^{13}CN$ in the process M→M-HCN are not accurate enough to draw any definite conclusion. The amount of ^{13}C lost as $^{13}C_1{}^{12}C_1H_2$ and $^{13}C_1{}^{12}C_1H_3$ from the monomethylquinolines indicates that ring opening is involved in this fragmentation

pathway. More labeling studies would help to clarify the mechanism.

In the case of monomethylpyridines most of the ^{13}C label is retained in the process M→M-HCN and ring expansion is not a major pathway before the loss of HCN in this process. A larger percentage of ^{13}C is lost as $H^{13}CN$ from the M-1 ion in both 2- and 4-methylpyridine and possibly as much as 33% of the M-1 ions of monomethylpyridines can be regarded as ring-expanded species. Thus with some M-1 ions there is an analogy between monomethylpyridines losing HCN from the M-1 ion and toluene losing C_2H_2 from the M-1 ion.

The loss of ^{13}C as $^{13}C_1{}^{12}C_1H_2$ and $^{13}C_1{}^{12}C_1H_3$ in the labeled pyridines was substantial and can be accounted for by a ring-opened species which loses the exocyclic carbon and the ring carbon to which it is attached. Further mass spectral studies with monomethylpyridines labeled in the nucleus and side chain should provide more information about these fragmentation pathways.

APPENDIX I

Definitions and Symbols (152)

intensity of peak = X

number of measurements = n

mean $\overline{X}$ = $\frac{\Sigma X_i}{n}$

variance = $\Sigma (X_i - \overline{X})^2 / n$

standard deviation = $\sigma = \sqrt{\Sigma (X_i - \overline{X})^2 / n}$

best estimate of σ = $\sqrt{\Sigma (X_i - \overline{X})^2 / n-1}$

calculation of errors where $A_{\overline{X}}$ and $B_{\overline{X}}$ are intensity values and a and b the corresponding best estimates of the standard deviations.

$$(A \pm b) + (B \pm b) = (A + B) \pm \sqrt{(a)^2 + (b)^2}$$

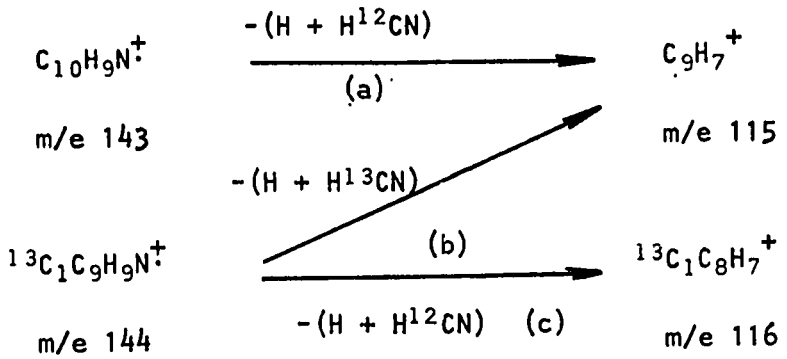
$$(A \pm a) - (B \pm b) = (A - B) \pm \sqrt{(a)^2 + (b)^2}$$

$$(A \pm a) \times (B \pm b) = A.B. \pm A.B. \sqrt{\left(\frac{a}{A}\right)^2 + \left(\frac{b}{B}\right)^2}$$

$$(A \pm a) \div (B \pm b) = \frac{A}{B} \pm \frac{A}{B} \sqrt{\left(\frac{a}{A}\right)^2 + \left(\frac{b}{B}\right)^2}$$

Calculation of the spectrum of 4-methylquinoline-4-α-^{13}C

Intensity measurements of the region m/e 113 - m/e 118 were recorded under low and high resolution conditions for 4-methylquinoline unlabeled and 4-methylquinoline-4-α-^{13}C. The intensity of each ion in the region m/e 113 - m/e 118 in the high resolution was measured relative to the total intensity of m/e 113 - m/e 118 taken as 1.000 after correction for naturally abundant ^{13}C. Table XI shows the corrected spectrum for 4-methylquinoline unlabeled. The spectrum of 4-methylquinoline-4-α-^{13}C is complicated at this stage because of the presence of unlabeled 4-methylquinoline, i.e. the sample of 4-methylquinoline-4-α-^{13}C used in this experiment contained 55.1 ±0.5% of ^{13}C in the exocyclic methyl group. Thus any ion containing only the ^{12}C isotope, e.g. $C_9H_7^+$, might have originated from the labeled or unlabeled compound as indicated in Scheme 23.



Scheme 23

The intensity of an ion such as $C_9H_7^+$ arising from the loss of H+HCN from the unlabeled portion of the partially labeled compound was calculated as follows. The intensity of the ^{12}C isotope ions relative to the total intensity of the ions at m/e 113 - m/e 118 is known from the unlabeled compound. Therefore knowing the percentage of ^{12}C in the partially labeled compound, i.e. 44.9% ^{12}C, the intensity of all the ^{12}C isotope ions due to 44.9% of unlabeled compound was calculated by multiplying the ion intensities for 100% ^{12}C by a factor of 44.9/100.0. The difference between the measured intensities of the ^{12}C isotope ions in the partially labeled spectrum of 4-methylquinoline and the intensities calculated for 44.9% ^{12}C is due to 55.1% of ^{13}C labeled compound, i.e. path (b). We now have a calculated spectrum of 4-methylquinoline labeled with 55.1% ^{13}C in the exocyclic group. Therefore multiplication of both the ions containing ^{13}C and ^{12}C by a factor of 100.0/55.1 will extrapolate them to the case where all the sample molecules have 100% ^{13}C in the exocyclic group and 100% ^{12}C at all ring carbon atoms. Table XII lists the calculated relative abundances for 100% specific enrichment of ^{13}C in the exocyclic group and corrected for the natural abundance of ^{13}C.

TABLE XI

Mass Spectral Peaks of 4-Methylquinoline (Unlabeled)

m/e	Composition	Relative abundance[a,b]
113	C_9H_5	0.045 ±0.002
114	C_8H_4N	0.010 ±0.003
	C_9H_6	0.047 ±0.001
115	C_9H_7	0.663 ±0.003
116	C_8H_6N	0.070 ±0.002
	C_9H_8	0.069 ±0.002
117	C_8H_7N	0.096 ±0.002

[a] Corrected for naturally abundant ^{13}C.

[b] Intensity of each ion relative to $\Sigma_{113-118} = 1.000$

TABLE XII

Mass Spectral Peaks for 4-Methylquinoline-4-α-^{13}C

m/e	Composition	Relative abundance[a-c]
113	C_9H_5	0.005 ±0.002
114	C_8H_4N	0.006 ±0.002
	$^{13}C_1C_8H_5$	0.040 ±0.001
	C_9H_6	0.008 ±0.001
115	$^{13}C_1C_7H_4N$	0.002 ±0.002
	$^{13}C_1C_8H_6$	0.029 ±0.001
	C_9H_7	0.062 ±0.007
116	C_8H_6N	0.034 ±0.001
	$^{13}C_1C_8H_7$	0.594 ±0.007
	C_9H_8	0.020 ±0.003
117	$^{13}C_1C_7H_6N$	0.027 ±0.001
	C_8H_7N	0.061 ±0.004
	$^{13}C_1C_8H_8$	0.070 ±0.002
118	$^{13}C_1C_7H_7N$	0.042 ±0.004

[a] Corrected for naturally abundant ^{13}C.

[b] Intensity of each ion relative to $\Sigma_{113-118} = 1.000$.

[c] Calculated for 100% isotopic enrichment.

APPENDIX II

Recording of High Resolution Spectra with a Time Averaging Computer

Method of Operation

The mass spectrometer is scanned with a time of scan which is slightly longer than the sweep time of the time averaging computer (CAT). For high resolution work this scan is achieved by varying the accelerating voltage which permits only the recording of one nominal mass at a time. The circuit diagram is shown in Figure 6. At the start of each scan of the mass spectrometer a voltage pulse from the function generator scan unit is used to trigger the sweep of the CAT, which awaits this stimulus after completing each sweep. The sweep of the CAT is divided into 1024 equal times (channels) and the information for each channel is summed by the digital adding circuits of the instrument. Improvements of signal to noise ratio is approximately proportional to the square root of the number of scans. After summing a suitable number of scans, the information in the CAT is read out in analog form to an X-Y recorder. For some settings of the mass spectrometer circuits, it was found necessary to use a simple battery and potentiometer DC offset circuit between the output of the driver amplifier for the galvanometer and the analog input of the CAT. The offset circuit is shown in Figure 7. Figure 8a shows the result of one scan of nominal mass m/e 116 of 4-methylquinoline unlabeled as recorded on direct print paper while Figure 8b shows the analog form from the CAT of the same nominal mass after 50 scans.

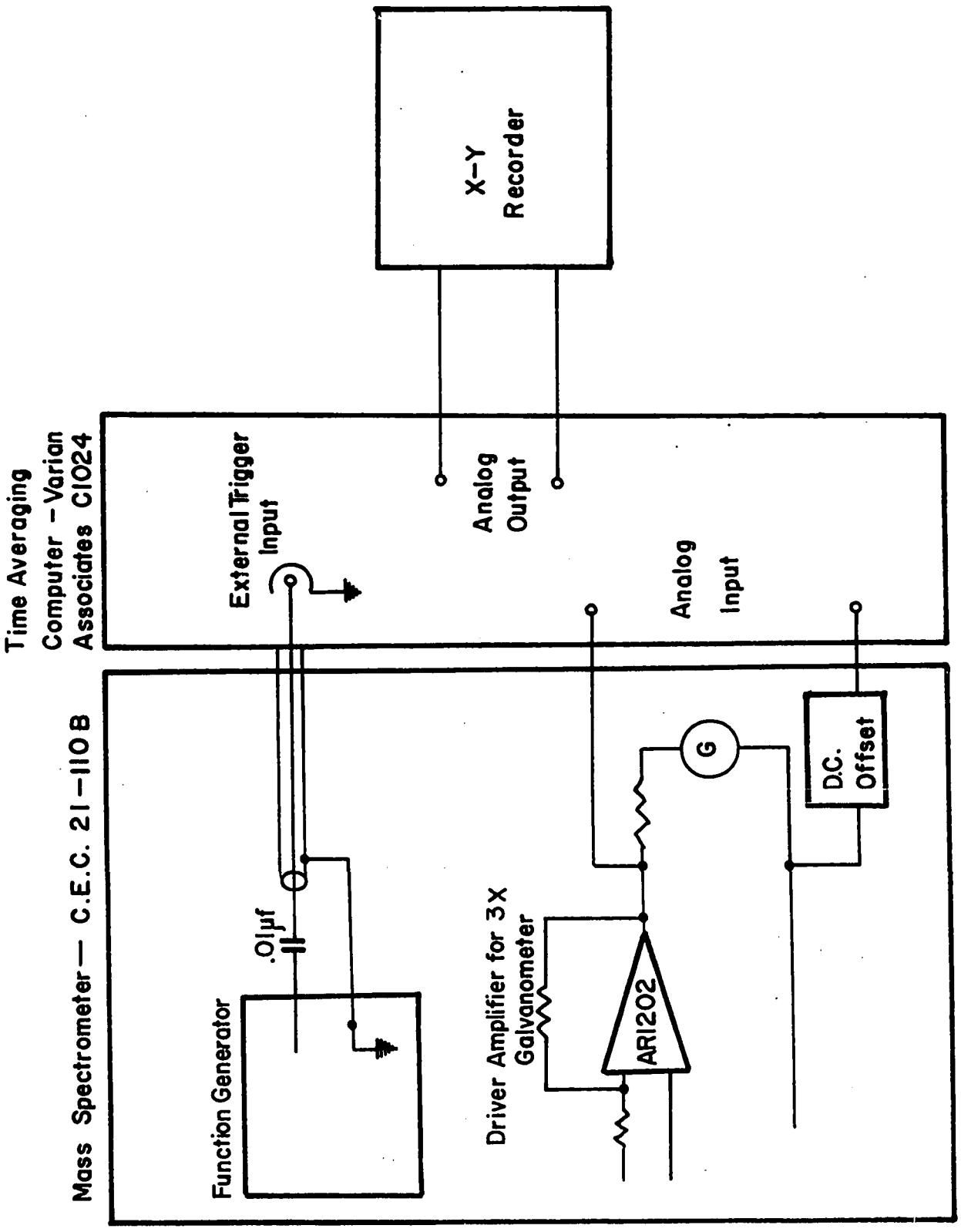


Fig. 6 Diagram of the connections between mass spectrometer, time averaging computer and recorder

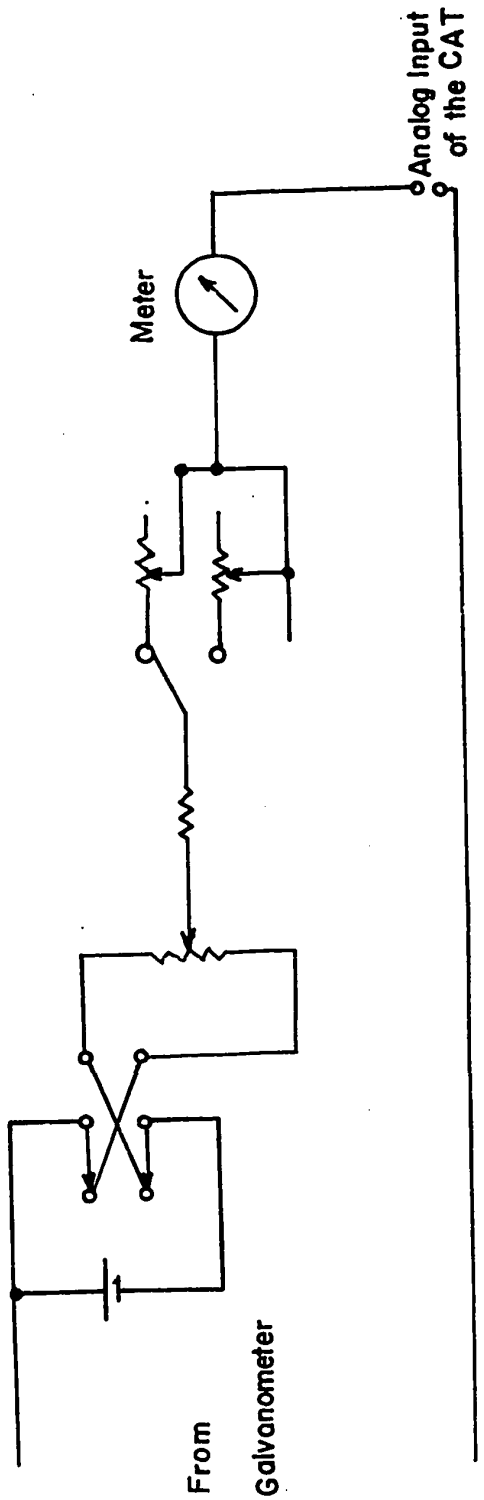


Fig. 7 DC offset circuit

a.

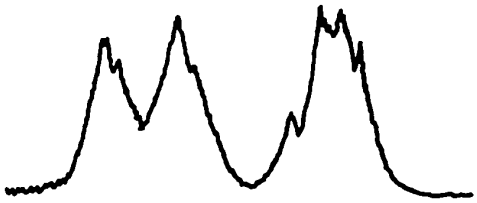


Fig. 8(a) Single scan of mass m/e 116 of 4-methylquinoline

b.

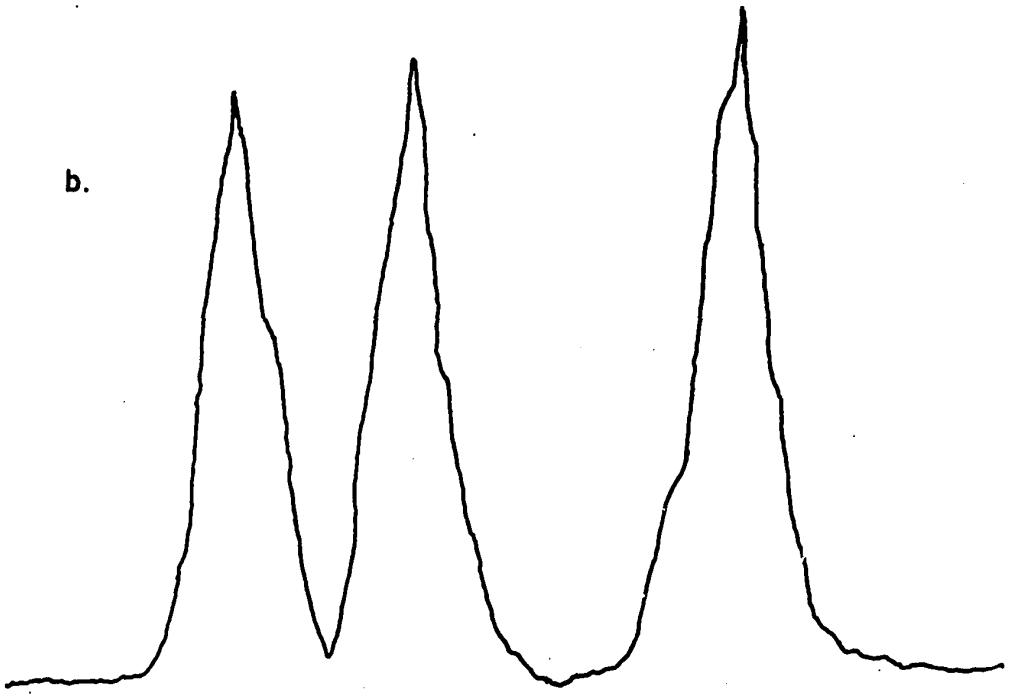


Fig. 8(b) Sum of 50 scans of mass m/e 116 of 4-methylquinoline after time averaged processing

The system was designed and built by Mr. I. Thompson, Mr. C. Schonfeld, and Mr. F. Ramelan.

Tests of the Method

To date the application of a time averaging computer for recording high resolution mass spectral data has not been reported. The validity of this system for recording high resolution spectra was checked by two methods. The nominal masses m/e 115 and m/e 116 of 4-methylquinoline of natural isotopic abundance were recorded separately. The main peak at mass m/e 115 is due to the loss of HCN from the M-1 ion of 4-methylquinoline, namely $C_9H_7^+$. At mass m/e 116 three peaks are observed, $C_8H_6N^+$, $^{13}C_1C_8H_7^+$, and $C_9H_8^{+\cdot}$. Thus the relative intensities of $C_9H_7^+$ and the ^{13}C isotope peak due to naturally abundant ^{13}C, $^{13}C_1C_8H_7^+$, can be measured from the low and high resolution spectra of 4-methylquinoline of natural isotopic abundance. By using the figure of 1.08 for the percentage of naturally abundant ^{13}C it is possible to calculate the intensity of the $^{13}C_1C_8H_7^+$ ion relative to the $C_9H_7^+$ ion. The intensity of the $^{13}C_1C_8H_7^+$ ion measured relative to $C_9H_7^+$ as 100.0 ±0.2 was 9.9 ±0.2 and the calculated value was 9.9 ±0.2.

A separate experiment to check the validity of the method involved the recording of mass m/e 92 present in the spectrum of a mixture of toluene and xylene. Under high resolution conditions (1 in 20,000) two ions are present at this mass, namely $C_7H_8^{+\cdot}$ and $^{13}C_1C_6H_7^{+\cdot}$. The former ion is the molecular ion of the toluene while the latter is the naturally abundant ^{13}C isotope peak of $C_7H_7^+$ arising from loss of CH_3 from the molecular ion of xylene and from the M-1 ion of toluene.

By examining the nominal mass m/e 92 of toluene alone it is possible to measure the intensity of $^{13}C_1C_6H_7^+$ due to the naturally abundant ^{13}C of the M-1 ion $C_7H_7^+$ relative to the intensity of the $C_7H_8^{+\cdot}$ ion. Thus it is possible to calculate the intensity of the $^{13}C_1C_6H_7^{+\cdot}$ due to xylene relative to the intensity of the molecular ion of toluene, $C_7H_8^{+\cdot}$, from the mass spectrum of mixtures of toluene and xylene.

Several mixtures of toluene and xylene of known composition were examined under high resolution conditions. The two peaks at m/e 92 were recorded 50 times on the CAT. Several sets of 50 scans were recorded for each injection. By varying the amounts of toluene and xylene in the mixtures it was hoped to show a direct correlation between changes in the relative proportions of toluene and xylene and the relative intensities of the ions $C_7H_8^{+\cdot}$ and $^{13}C_1C_6H_7^{+\cdot}$. The results are listed in Table XIII. A plot of the ratio of molar concentrations of xylene and toluene versus the ratio of intensities of xylene and toluene is shown in Figure 9. It is seen that the points of the plot lie on a straight line indicating a direct relationship between molar ratio of the constituents of the mixtures and the relative intensities of the ions $C_9H_7^{+\cdot}$ and $^{13}C_1C_8H_6^{+\cdot}$.

TABLE XIII

Analytical Data for Toluene and Xylene Mixtures

Mixture No.	$\frac{\text{Moles of xylene}}{\text{Moles of toluene}}$	$\frac{\text{Intensity of } {}^{13}C_1C_6H_7^+}{\text{Intensity of } C_7H_8^+}$
1	0.937 ±0.001	0.085 ±0.003
2	4.381 ±0.001	0.420 ±0.006
3	9.825 ±0.001	0.965 ±0.011
4	15.678 ±0.001	1.525 ±0.013

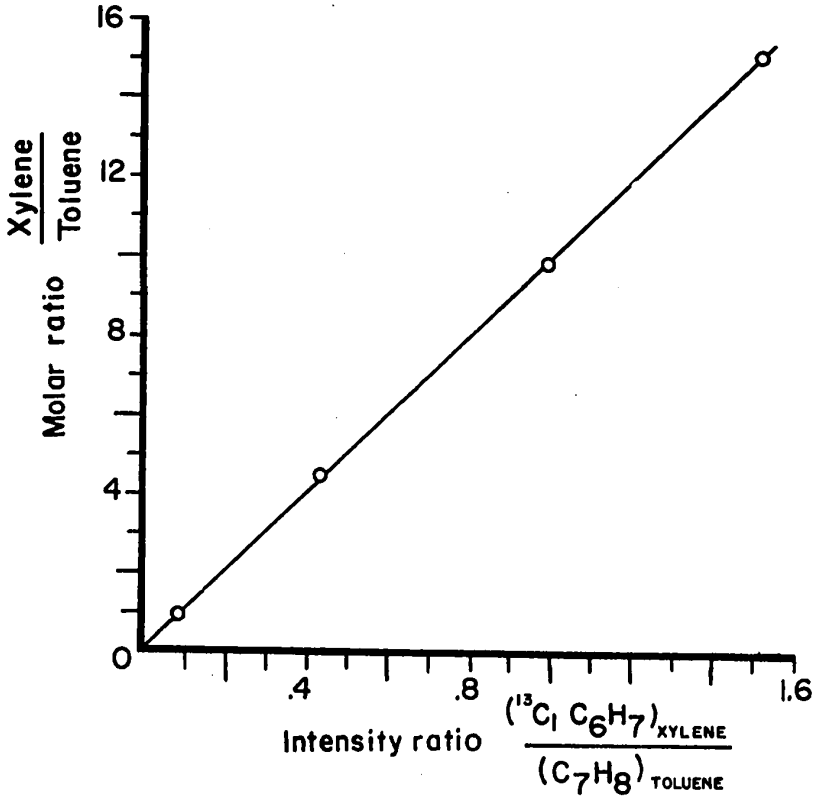


Fig. 9 Plot of molar ratio xylene/toluene vs intensity ratio $^{13}C_1C_6H_7/C_7H_8$

APPENDIX III

Thermal Gradient Collecting Device

In preparative gas-liquid chromatography the usual method of sample collection is simple condensation inside a glass tube inserted into the chromatograph outlet. Brownlee and Silverstein (153) have described a device using capillary tubes and a linear thermal gradient to minimize aerosol formation. The device (Figure 10) consists of two parallel 215 mm long aluminum tubes (A), one 1.7 mm i.d., 3.17 o.d. to accept thin-wall glass capillary (30 cm by 1.6 mm o.d.), and the other, 3.4 mm i.d., 6.34 mm o.d. to accept a 25 cm length of 3 mm o.d. glass tubing. The aluminum tubes are insulated from the ambient air by a 35 mm by 160 mm porcelain or ceramic tube (B). At one end, the aluminum tubes pass through a 38 mm cubic aluminum block (C) containing a 100 watt cartridge heater and a thermocouple probe. At the other end, the tubes pass through a 38 mm by 38 mm by 50 mm aluminum block (D) that has a 178 mm x 19 mm aluminum rod (E) extending down into a cooling bath (F). Both blocks are mounted on, but insulated (G) from, a length of aluminum angle (H), which is supported rigidly in a horizontal position by a bracket (I) fastened with screws to the side of the chromatograph and by another bracket (J). The bracket (I) is insulated from the chromatograph. Provision is made for vertical and lateral alignment of the aluminum tubes with the exit port of the gas chromatograph. The exit port is fitted with a Swagelok fitting containing a Teflon ferrule (K)

to ensure a gas-tight joint with the inserted glass collector tube. A short length of Teflon rod (L) is placed on the distal ends of the aluminum tubing to prevent the accumulation of frost.

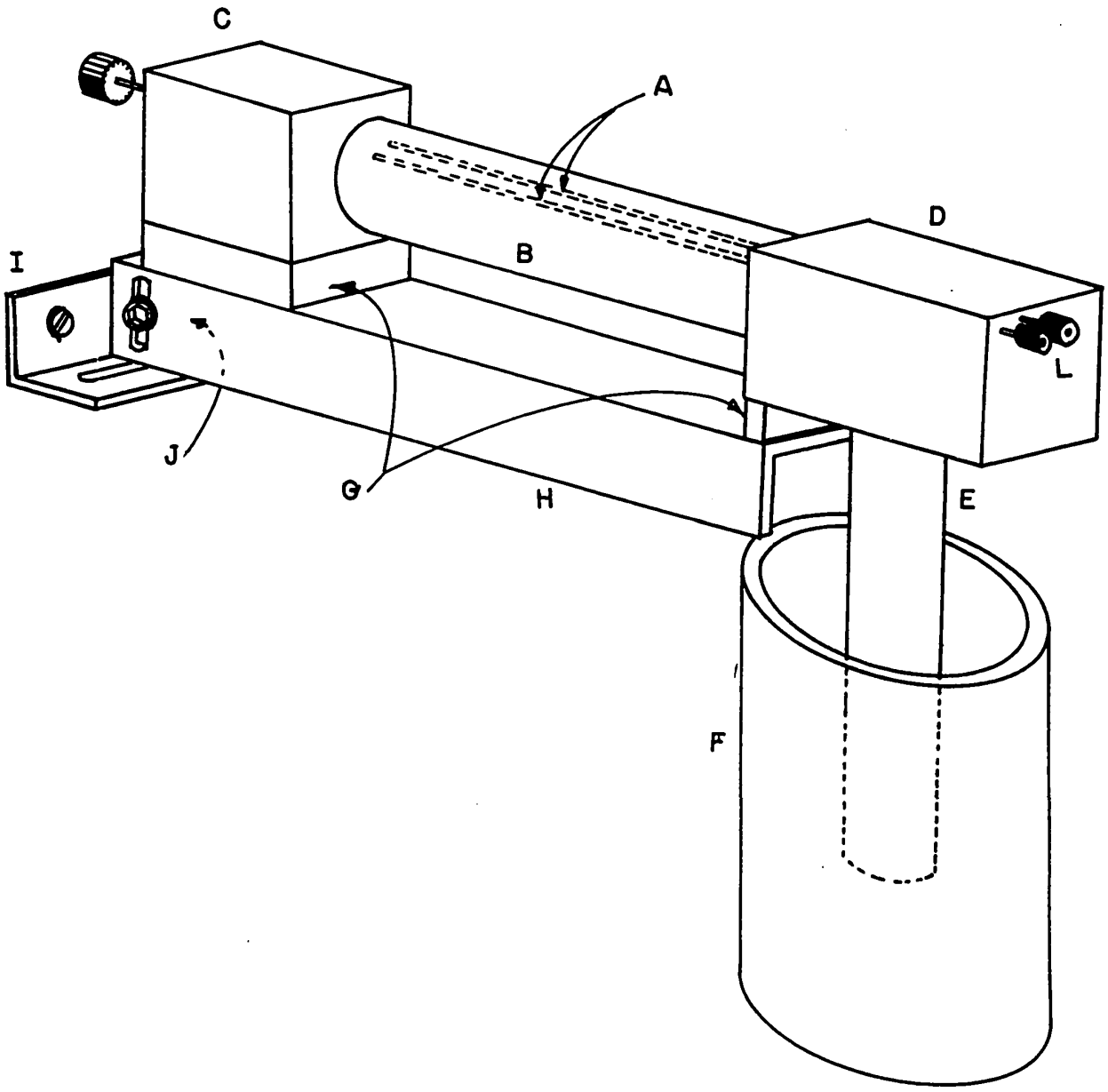


Fig. 10 Thermal gradient collector

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