MASS SPECTROMETRY OF SUBSTITUTED-AMINO FIVE MEMBERED HETEROCYCLES.

A Thesis presented at the University of Surrey in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Biological and Chemical Sciences

by

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SUMMARY

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The electron impact mass spectral behaviour of 2-[acyl(alkyl)amino]oxazoles has been investigated. When the acyl group is aliphatic, the major fragment ions arise either from cleavage of the substituent or fragmentation of the nucleus with simultaneous elimination of a hydroxyl radical. The elimination of a heterocyclic atom in this way is diagnostic, but does not occur from the molecular ion. Analysis with compounds containing a deuterium label has confirmed that the hydrogen lost in the elimination originates from both a site on the N-alkyl chain and a position adjacent to the carbonyl group. A mechanism accounting for the 1 : 1 participation of these hydrogen atoms is suggested.

For α,ω-bis[N-acyl-N-(4-methyloxazol-2-yl)amino]-alkanes the elimination of a hydroxyl radical depends on the length of the methylene bridge and for 2--dialkylamino-oxazoles the elimination occurs also from the molecular ion.

Although the presence of 5-alkyl substituents does not affect the fragmentation of 2-[acyl(alkyl)amino]-oxazoles, introduction of oxygen into the 5-substituent effects significant changes in mass spectral behaviour; these are detailed for various groupings.

N-Butyl-N-(4-methyloxazol-2-yl)benzamides only lose a hydroxyl radical following extrusion of carbon monoxide. A correlation between the ratio of the relative abundance of the molecular ion to that of the acylium ion, and the

substituent σ constants of groups in the aromatic ring is observed for these molecules at an ionising voltage of 10 eV.

The electron impact mass spectral behaviour of further five-membered heterocycles containing an acyl-(alkyl)amino-substituent has also been investigated. Minimal ring scission is observed for compounds with one heteroatom in the ring. 2-[Acyl(alkyl)amino] thiazoles show elimination of an [SH] radical, whilst isothiazoles only show the elimination when the acylamino-substituent is adjacent to the sulphur atom.

Thiazoles and oxadiazoles show the loss of methyl cyanide from the ring in addition to the loss of either [SH] or [OH] radicals. Elimination of nitrogen is only observed for a tetrazole compound.

Some one hundred and twenty mass spectra are discussed, and representative examples of one quarter of these are appended (as low resolution spectra) for reference.

Acknowledgements

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CONTENTS

ii. Optimisation of ion source parameters

iii. Mass spectrum of the N-d_9-butyl compound

b. The elimination of a hydroxyl radical in the mass spectral behaviour of 2-[acyl-(alkyl)amino]oxazoles 36

i. Introduction

ii. Involvement of hydrogen atoms associated with the oxazole nucleus — variation of the 4,5-dialkyloxazole substituents

iii. Involvement of hydrogen atoms associated with the acyl substituents

(1) The mass spectrum of N-(4-methyloxazol-2-yl)butylamine

(2) The mass spectrum of N-(4-methyloxazol-2-yl)-N-d_1-butylamine

(3) The mass spectra of N-(4-methyloxazol-2-yl)-N-(trimethylsilyl)-butylamine and N-(4-methyloxazol-2-yl)-N-d_9(trimethylsilyl)butylamine

(4) Variation of the N-acyl substituent in 2-[acyl(alkyl)amino]-oxazoles

iv. Involvement of hydrogen atoms associated with the N-alkyl substituents

(1) The mass spectra of 2-methyl-N-alkyl-N-(4-methyloxazol-2-yl)-propanamides

INTRODUCTION

A. INTRODUCTION

1. Organic mass spectrometry

a. Historical development

Initial development of the technique is associated with the work of J.J. Thompson[1] (1911) who noticed that "rays of positive electricity" were deflected by electric and magnetic fields along separate characteristic pathways. It was not until 1931 that the following comments[2] by Stewart and Olsen, "Decomposition of ions in positive ray analysis is due to dissociation by the ionising electrons, rather than the thermal decomposition in the hot cathode or to secondary reaction between ions formed and neutral molecules", heralded the realisation that bombardment of neutral organic molecules with a beam of electrons can produce a characteristic array of ions. A mass spectrometer sorts these ions into a spectrum according to their mass to charge (m/e) ratio and records the relative abundance of each. Mass spectrometers were exploited first in the petroleum industry[3] (in the 1940's) and are now important primary analytical instruments for the determination of organic structures. One of their great advantages is the small sample size that can give a useful spectrum (less than 1 microgram quantities handled by the operator).

b. Instrumental features

Experimentally four features of a mass spectrometer are important, namely those concerned with sample introduction, its ionisation, separation of ions of different m/e and recording of the spectrum.

i. Inlet systems

Early instruments used heated inlet systems to introduce even the most involatile sample into the ionisation chamber of a mass spectrometer. This comparatively slow rate of introduction resulted in considerable loss of sample due to thermal degradation or absorption effects. In modern instruments, rapid introduction of sample as the effluent from a gas-chromatograph (gc-ms) in which a separator preferentially removes the carrier-gas molecule, or by probe introduction of sample directly into the ion-source, minimises these problems.

ii. Ionisation methods

Ionisation, the process whereby the electrically neutral molecule becomes negatively or positively charged, has traditionally been achieved by electron bombardment.[4-5] Organic mass spectrometry is normally concerned with the analysis of the more abundant positive ions. Electrons of a fixed energy between 10 and 100 eV are allowed to collide with the vapour of the compound at a pressure of 10^{-5}-10^{-7} torr. Ionisation of a neutral molecule initially yields the molecular ion $M^{+\cdot}$ which then fragments into further characteristic ions (M_1^+, M_2^+, ... M_n^+).

$$M + e \longrightarrow M^{+\cdot} + 2e$$

$$M^{+\cdot} \longrightarrow M_1^+ \quad M_2^+$$

This mode of ionisation produces a large amount of fragmentation and consequently the greatest amount of structural information, but sometimes at the expense of a molecular ion. Consequently, complementary lower energy ionisation techniques such as chemical ionisation, field desorption or plasma desorption mass spectrometry have supporting structural value, especially for larger molecules.

iii. Ion separation

One approach to the separation of ions of differing $\underline{m}/\underline{e}$ ratios is to accelerate the ions away from the ion source with an electrostatic voltage (E) and to deflect the moving ion with a magnetic field (H). For a single-focussing instrument, the magnetic field is scanned to bring ions of different $\underline{m}/\underline{e}$ values successively to the detector. The equation governing the deflection of a moving charged particle is as follows:

$$\underline{m}/\underline{e} = H^2R^2/2E$$

where R is the radius of a circle in which the charged particles are forced to move. In a double-focussing[6,7] instrument, an additional electrostatic analyser is used to enhance separation. In quadrupole[8] mass spectrometers, separation is achieved by forcing the ion to move between four rods to which a variable direct current and radio frequency voltage is applied.

An important parameter of any instrument is its resolving power or resolution, a measure of its ability to separate adjacent masses. Resolving power may be expressed as $M/\Delta M$, where M is chosen mass and ΔM is its separation from an adjacent mass. Two peaks of equal intensity are

then commonly said to be resolved when the two signals overlap at a position where the intensity is less than 10% of the maximum intensity of one of the ions. In a single-focussing instrument, a resolving power of several thousand is often achieved, whereas in a double-focussing instrument, a resolving power of 30,000-50,000 or even greater is expected. This makes possible the measurement of the relative mass of an ion to an accuracy of several parts per million from which the unique ion composition can be determined.

iv. Signal recording

Ions are detected by the charge they carry. As each positively charged ion arrives at the collector plate or electron multiplier, its charge is given up and the resultant signal is amplified for recording on an oscillograph. However, the technique has the disadvantage of ideally requiring a constant sample supply throughout the determination of the spectrum. The use of a photographic plate has the desirable advantage of simultaneous recording of all parts of the spectrum, but the technique is too time-consuming for everyday application, especially in gc-ms.

Increasingly nowadays, the signal produced from a mass spectrometer is acquired and manipulated by a data system.[9-12] The signal can be processed immediately following collection using a dedicated mini-computer, which will present results either in tabular form or as a line diagram in which the relative intensity of ions is shown graphically, the most

abundant ion in the spectrum (base ion) being given a value of 100%. Alternatively, if a dedicated computer is not available, the signal from the mass spectrometer can be collected and subsequently processed using a non-dedicated facility.

2. Interpretation of a mass spectrum

a. Theories of fragmentation

Two significant theories of mass spectral fragmentation have been suggested. The quasi-equilibrium theory[13] attempts to predict the fragmentation of a molecular ion from basic energy consideration, using statistical theory to determine rate constants and making the assumption that all ions undergo unimolecular decomposition. The alternative, more popular and simpler empirical approach is termed charge localisation.[14,15] It is based on an extension of the use of resonance structures to describe ground-state chemistry and is used throughout this work. In this thesis "α-scission" is defined as cleavage of a bond originating at an atom which is adjacent to the one assumed to bear the charge.[16] The definition of "β- and γ-scission" then follows automatically. A more detailed discussion of specific fragmentations will follow in the ensuing introduction and discussion.

b. Metastable ion peaks

Hipple, Fox and Conden first reported[17] in 1946 the presence of broad peaks at non-integral $\underline{m}/\underline{e}$ values in the mass spectra of hydrocarbons, arising from the spontaneous dissociation of certain ions into lighter ions in the field-free region of the mass spectrometer. A singly-charged ion of mass $\underline{m}_2$ formed after removal from the ion source from an ion of mass $\underline{m}_1$, will give rise to a metastable ion ($\underline{m}^*$) at an $\underline{m}/\underline{e}$ value given by:

$$\underline{m}^* = (\underline{m}_2)^2/\underline{m}_1$$

The presence of these ions gives valuable fragmentation information, although the absence of a metastable ion does not rule out a proposed fragmentation scheme.

c. The use of isotopes

The mass spectrum of any organic compound derives from different molecular species. The presence of certain elements, for example chlorine, containing a high natural abundance of an isotope can be revealed easily by the isotope distribution pattern in the ions concerned. The isotope distribution pattern for a group of ions containing more than one chlorine atom can be calculated using a binomial expansion. Hence, especially in the absence of accurate mass facilities, isotope ion peaks can provide valuable information on the atomic composition of ions and assist in the interpretation of a spectrum.

The addition of a stable isotope can aid the interpretation of a spectrum due to shifts in m/e values. Deuterium is often used as a label to determine the position of hydrogen atoms within a molecule, whereas carbon-13 labelling can be used to follow skeletal rearrangements. Considerable care must be exercised in handling this type of data due to the propensity of ions to scramble before fragmentation.[18] For instance, studies on monodeutero-toluene labelled in the α-, o-, m- or p-position show[19] their mass spectra to be virtually identical, implying all hydrogen atoms in toluene become equivalent in the molecular ion.

3. Applications of mass spectrometry in the pharmaceutical industry

Large numbers of new organic compounds are synthesised each year by the pharmaceutical industry in a search for new drugs. Characterisation of molecular structure is usually achieved using non-destructive techniques, such as nuclear magnetic resonance spectroscopy (n.m.r.) and infra-red absorption spectroscopy. Mass spectrometry is both an expensive and destructive technique which is best used selectively to aid structure identification. It is especially useful in the analysis of compounds for which n.m.r. proton assignments are difficult or in situations where the knowledge of the molecular weight of a compound is important.

A valuable research application occurs in areas where its major advantages of selectivity and sensitivity[20-22] are manifest. Consequently, the smallest by-product of a reaction can be analysed provided prior gc-ms[23,24] separation of components within the sample is achieved. Alternative applications within the pharmaceutical industry occur in drug metabolism and pharmacology, where the technique provides a unique mode of analysing low levels of compound in biological samples or extracts. Increasing use is being made of the quantitative[25-29] application of the technique in which, rather than scanning a complete spectrum, a small number of predetermined ions, characteristic of sample and internal standard, are rapidly and successively monitored, quantitative estimation being made from the relative response.

A commercial facility comparable to gc-ms is now available for the coupling of high pressure liquid chromatography (hplc) with mass spectrometry to handle the many applications which exist within the pharmaceutical industry.

Many new chemical series are designed around novel heterocyclic ring systems. Interpretation of the mass spectrum of a compound within a novel series requires a knowledge of the fragmentation characteristics of that series. This position contrasts with other spectroscopic techniques in which reference to previously tabulated data can either solve or give valuable information on a problem. Although it is possible to draw up certain guide-lines to aid the understanding of a particular mass spectrum, or to draw limited correlation between series of compounds, optimum use of the technique is usually only reached after detailed analysis of the fragmentation characteristics of further representative compounds within the group.

This thesis concerns a detailed analysis of 2-acylamino-oxazoles, a new class of compounds,[30] with anti-allergic action, currently being evaluated under clinical conditions. These compounds reduce the release of certain chemical mediators such as histamine and slow reacting substance of anaphylaxis (SRS-A) within the body. The presence of these mediators gives rise to the clinical symptoms of asthma,[31] such as broncospasms and the presence of mucous plugs which block air passages.

EXPERIMENTAL

B. EXPERIMENTAL

1. Instrumentation

Mass spectra were obtained on an LKB 9000S mass spectrometer equipped with both gas chromatography and solid probe inlet systems. Chromatography was performed on a 5 ft x 4 mm i.d. glass column packed with 1.2% SE30 on Gas Chrom. Q (100-120 mesh), using helium carrier gas (30 ml/min), a column temperature of 150-200°C and an injection port temperature of 210°C. The effluent from the gc column was passed through a Ryhage[32] two-stage, metal jet separator (265°C) before entering the ion source block (230°C). The mass spectrometer (resolution 1500 using 10% valley definition) was set to give an ionising voltage of 20 eV and an accelerating voltage of 3.5 KV. The mass spectra were recorded on a 4-channel Visigraph FR3017 direct reading oscillograph (one channel used for electronic mass marker), and normalised by manual measurement of peak intensities using a Gerber rule. During the latter period of the work, a VG Data Systems computer (2040L), equipped with a Bryan XY recorder output was used to acquire and manipulate mass spectral data. On occasions, additional metastable ion information was obtained using an A.E.I. MS12 mass spectrometer whereas accurate mass data was obtained on a Varian Mat 731 instrument.

2. Chemicals and solvents

Samples of heterocyclic compounds were kindly provided by the organic research chemists at the Lilly Research Centre. Their structures were verified by spectroscopic and microanalytical methods.

3. Synthesis of deuterated compounds

Samples of all compounds were prepared in solution and used directly for gc-ms analysis without prior purification.

a. N-(4-Methyloxazol-2-yl)butylamine

Cyanogen bromide (7 mg) was dissolved in dry tetrahydrofuran (35 µl) in 1 ml reacti-vial (Pierce Chemical Co.) and sodium carbonate (0.15 mg) was added with stirring. N-Butylamine (5 mg) was added to this solution at -10°C, before it was warmed to 25°C (30 minutes), when the supernatant liquid was transferred to a second 1 ml reacti-vial and diluted with water (35 µl). Aqueous hydroxyacetone (50% w/w, 14 mg) and 50% sodium hydroxide solution (2.5 µl) were added with shaking. After 15 minutes the solution was extracted with ether (2 x 300 µl) and the extract evaporated to dryness.

b. N-(4-Methyloxazol-2-yl)N-d_1-butylamine

The N-(4-methyloxazol-2-yl)butylamine residue was dissolved in deuteriochloroform (100 µl) and shaken with deuterium oxide (50 µl) for different periods of time. Varying levels of deuterium exchange of the amino hydrogen were achieved by this method. Samples of the chloroform layer (1 µl) were injected into the gc-ms.

c. N-(4-Methyloxazol-2-yl)N-trimethylsilyl-butylamine and N-(4-methyloxazol-2-yl)N-d_9--trimethylsilylbutylamine

Bis(trimethylsilyl)acetamide or d_{18}-bis--(trimethylsilyl)acetamide (100 µl) and pyridine (100 µl) were added to the N-(4-methyloxazol-2-yl)butylamine residue.

The solution was heated at 60°C for 10 minutes.

d. 2-Methyl-N-1,1-d_2-butyl-N-(4-methyl-oxazol-2-yl)propanamide

Butyronitrile (5 mg) was dissolved in dry tetrahydrofuran (300 µl) and lithium aluminium deuteride (25 mg) added. After 15 minutes, the excess reductant was destroyed with water (100 µl) and the tetrahydrofuran solution was dried with anhydrous sodium sulphate (200 mg). The suspension was centrifuged and the supernatant liquid containing 1,1-d_2-butylamine was removed and evaporated to dryness.

N-(4-Methyloxazol-2-yl)-1,1-d_2-butylamine was prepared as previously described from 1,1-d_2-butylamine and acylated with isobutyric anhydride (12 µl) in benzene (62 µl) under reflux for 3 hours.

e. N-Butyl-N-(4-methyloxazol-2-yl)-d_3-acetamide

2,2,2-d_3-Acetic acid (60 µl) was added to a solution of benzenesulphonyl chloride (100 mg) in pyridine (200 µl) with shaking. After ten minutes, a solution of N-(4-methyloxazol-2-yl)butylamine (50 mg) in pyridine (200 µl) was added and the whole heated for several hours at 60°C.

THE MASS SPECTRA OF OXAZOLES CONTAINING A SUBSTITUTED 2-AMINO GROUP

C. THE MASS SPECTRA OF OXAZOLES CONTAINING A SUBSTITUTED 2-AMINO GROUP

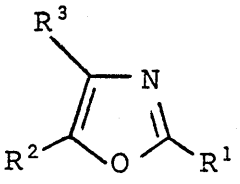
1. Literature survey

Comparatively few studies of the mass spectral behaviour of substituted oxazoles have been reported.

Oxazole itself behaves[33,34] in a manner typical of other unsubstituted aromatic compounds in that the molecular ion m/e 69 constitutes the base ion of the spectrum. Fragment ions m/e 41 [21%] and 40 [37%] respectively are observed corresponding with the elimination of carbon monoxide and a formyl radical. The loss of hydrogen cyanide to give an ion of m/e 42 [13%] is less significant. This behaviour can be contrasted with the much greater prevalence of hydrogen cyanide loss from thiazole[35] [M - HCN (30%)], indicating the greater stability of the C-O bond over the C-S bond.

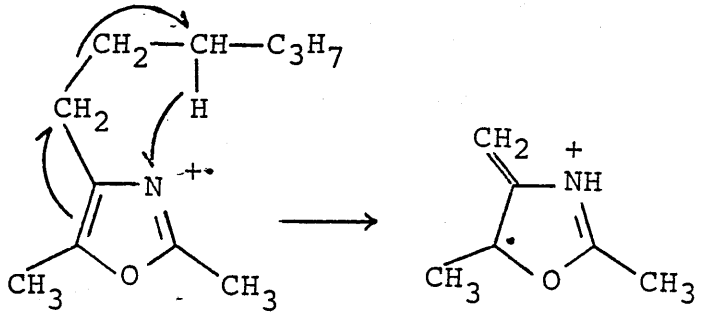
The fragmentation of an aliphatic chain attached to a nitrogen heterocycle varies[36-39] with the site of attachment. Typically isomeric alkylpyridines can be distinguished by their mass spectra whereas alkylbenzenes cannot. The isomeric dialkyl oxazoles, 2,4-dimethyloxazole 2 and 4,5-dimethyloxazole 3, can also be distinguished by their mass spectra.

For 3 the $[M-1]^+$ ion is more abundant than that for 2. In addition, the loss of a methyl radical and hydrogen cyanide, and the abundance of the ion of m/e 43 is only significant for 3.



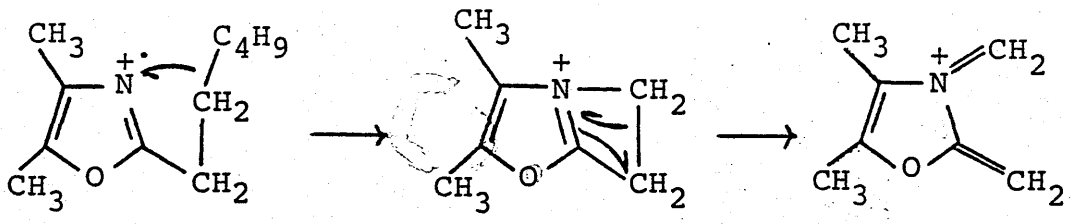
	R^1	R^2	R^3		R^1	R^2	R^3
1	H	H	H	8	C_6H_5	$CO_2C_2H_5$	H
2	CH_3	H	CH_3	9	C_6H_5	H	H
3	H	CH_3	CH_3	10	H	H	C_6H_5
4	CH_3	C_6H_{13}	CH_3	11	CH_3	H	C_6H_5
5	CH_3	CH_3	C_6H_{13}	12	H	C_6H_5	CH_3
6	C_6H_{13}	CH_3	CH_3	13	H	CH_3	C_6H_5
7	C_6H_5	H	$CO_2C_2H_5$				

A more striking example of characteristic differences in the mass spectra of isomeric dialkyloxazoles can be seen in the fragmentation of dimethyl-n-hexyloxazoles 4-6.[33] All the major fragment ions are formed by cleavage of the n-hexyl chain rather than the oxazole nucleus. The most favoured fragmentation for 5 and 6 is the transfer of a hydrogen from the n-hexyl chain to the adjacent nitrogen atom by a rearrangement (Scheme 1).



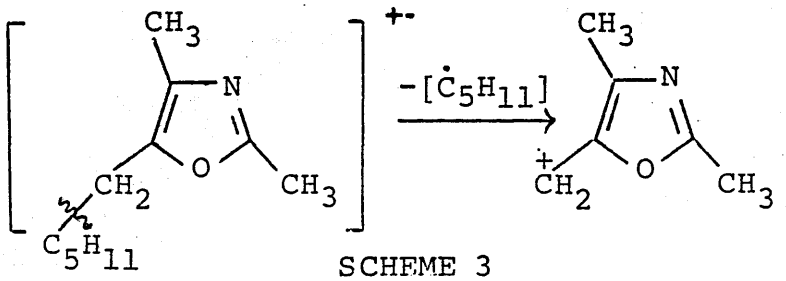
SCHEME 1

In compound 6, γ-scission occurs, again involving the nitrogen atom (Scheme 2).



SCHEME 2

The rearrangement (Scheme 2) is not favoured for 4. Consequently, simple β-fission of the hexyl chain to give a "benzylic type" ion constitutes a third pathway (Scheme 3).



SCHEME 3

The 2-phenyloxazoles 7 and 8 also fragment[40] very differently. For 8, facile α-elimination of the 5- -substituent occurs as the positive charge can be delocalised on the oxygen atom whereas formation of the benzoylium ion is favoured for 7.

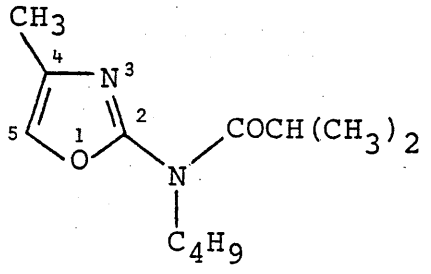
Whereas the spectra of 2-phenyloxazole 9 and 4-phenyloxazole 10 are very similar, the spectra of compounds 11-13 are quite different.[33] All aryl oxazoles[41,42] are characterised by extensive rearrangement and the elimination of hydrogen cyanide and carbon monoxide. High

resolution measurements indicate that for 12 the m/e 103 ion has the composition $[C_8H_7]^+$, whilst for 13 the same ion has the alternative formula $[C_7H_5N]^{+\cdot}$.

Further evidence that the aromatic hydrogens of the oxazole ring do not interchange with the hydrogen atoms of a methyl substituent can be seen in the following two examples.[33]

2-d_1-4-Phenyloxazole fragments by initial loss of carbon monoxide and then by loss of DCN rather than HCN implying there is no randomisation of hydrogen and deuterium atoms for 2-methyl-4-phenyloxazole 11. The intense ion of m/e 90 arises from the loss of carbon monoxide and methyl cyanide. Whereas this ion shifts to m/e 91 (C-5 deuterium probably migrates to C-4) for 5-d_1-2-methyl-4-phenyloxazole, it remains at m/e 90 for 2-d_1-methyl-4-phenyloxazole.

In the present work, the mass spectra of 2-[acyl(alkyl)-amino]oxazoles are not only discussed in relation to the most active member of the series, 2-methyl-N-butyl-N-(4-methyl-oxazol-2-yl)propanamide, 14a, but in comparison with other oxazole and heterocyclic series.



14a

2. Results and discussion

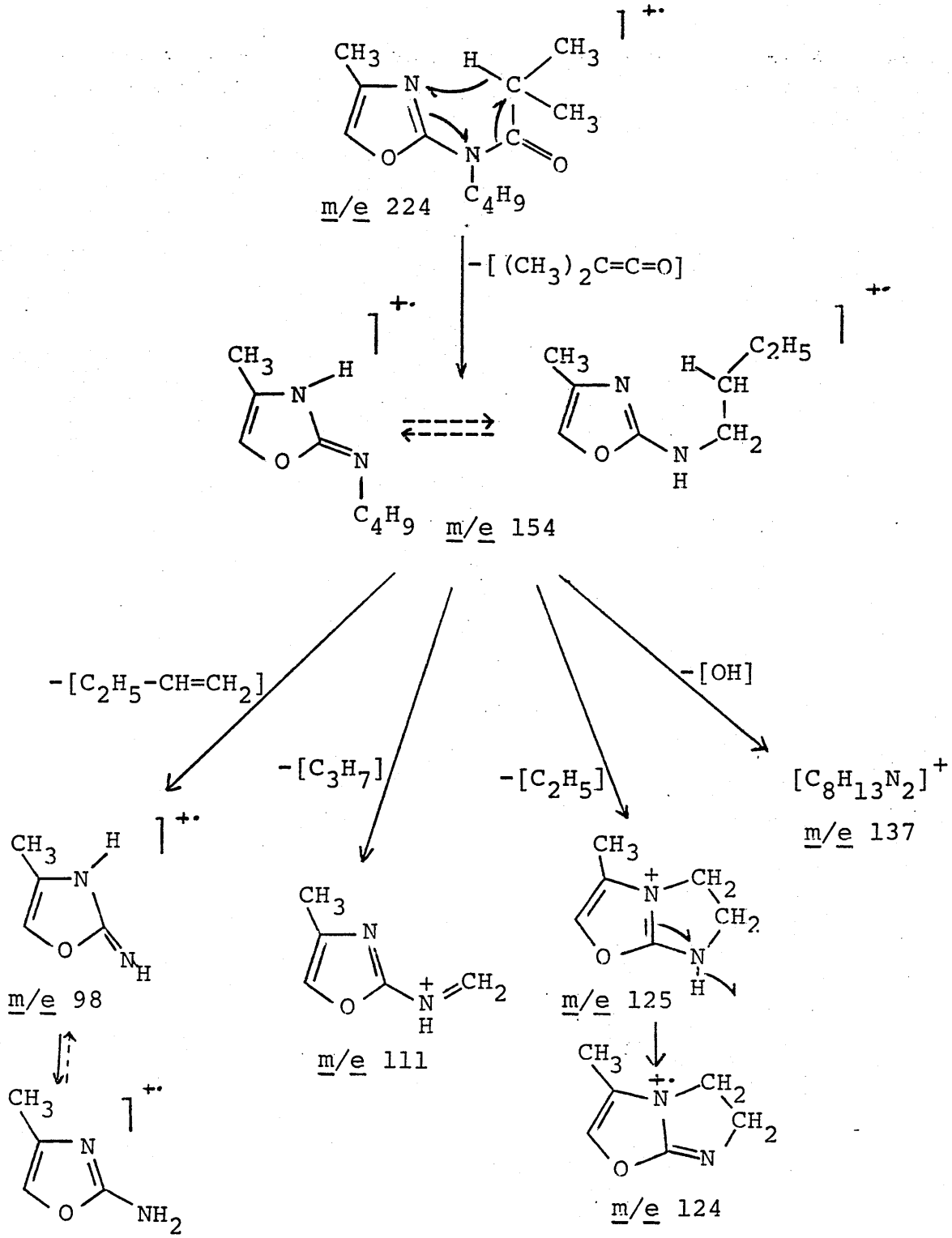
a. 2-Methyl-N-butyl-N-(4-methyloxazol-2-yl)-propanamide

i. Mass spectrum

In contrast to the behaviour of compounds 1-13, the major fragment ions in the mass spectrum (Figure 1) of 2-methyl-N-butyl-N-(4-methyloxazol-2-yl)-propanamide 14a arise from cleavage of the 2-substituent on the oxazole ring rather than the ring itself. Only one significant ion m/e 137 arises from fragmentation of the oxazole nucleus. Fragmentation of the molecular ion to give the base ion m/e 154 involves the transfer by a McLafferty[43] rearrangement of a hydrogen from the propanamide substituent to the adjacent ring nitrogen atom (Scheme 4). Loss of the acyl group by simple scission of the N-CO bond is less significant. Ions containing the oxazole nucleus m/e 153, 6% or the corresponding acylium ion m/e 71, 27% are formed. No comparable fragmentations of the N-C_4H_9 bond are observed.

The ion of m/e 154 can fragment in a number of ways (Scheme 4). Ring-opening of the oxazole nucleus occurs with formation of an ion of m/e 137. Accurate mass data indicates a hydroxyl radical ($C_8H_{14}N_2O \longrightarrow C_8H_{13}N_2$) is eliminated during formation of this ion.

The ion of m/e 111 is formed by α-scission of the side-chain, whilst a second McLafferty rearrangement can give rise to the ion of m/e 98.


m/e 224
-[(CH3)2C=C=O]
m/e 154
-[C2H5-CH=CH2]
-[C3H7]
-[C2H5]
-[OH]
[C8H13N2]+
m/e 137
m/e 98
m/e 111
m/e 125
m/e 124

SCHEME 4

Finally, β-elimination of an ethyl radical can occur with formation of an ion of m/e 125, which metastable ion evidence indicates readily loses a hydrogen to form an ion of m/e 124. No evidence is observed for the formation of the m/e 124 ion from the ion of m/e 153.

As illustrated in Scheme 4, some ions containing the oxazole ring can be shown as having either an exocyclic or more stable endocyclic structure.

ii. Optimisation of ion-source parameters

A comparison of the spectra of compound 14a obtained at ionising voltages of 10, 20 and 70 eV and an ion source temperature of 270°C (Table 1) shows the expected increase in fragmentation of the molecular ion (m/e 224) with an increase in the energy of the bombarding electrons. At an ionising voltage of 10 eV and a source temperature of 210°C, the molecular ion rather than the m/e 154 ion becomes the base ion of the spectrum. The abundance of the ion of m/e 154 increases whilst that of the m/e 224 ion (ions linked by metastable ion peak) decreases with increase in ion source temperature, indicating that thermal effects contribute to this fragmentation. Although the effect is significant at 10 and 70 eV, at 20 eV (Table 2) minimal dependence of the fragmentation on ion source temperature is observed. Consequently, a minimum ion source temperature of 230°C (it was not routinely possible to maintain the ion source below this temperature due to heat conduction from the separator) and an ionising voltage of 20 eV were chosen as optimum conditions and used throughout the work.

Table 1. Effect of ionising voltage on the mass spectra of 2-methyl-N-butyl-(4-methyl-oxazol-2-yl)propanamide

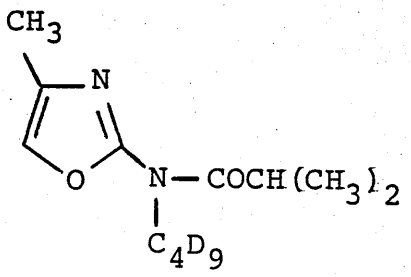
Ion Source Temperature (°C)	Ionising Volt (eV)	% Relative Intensity												
		97	98	111	112	124	125	126	137	138	153	154	155	224
270	10	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	100	8	51
270	20	8	21	38	10	9	9	4	62	6	5	100	10	7
270	70	20	41	65	19	14	8	5	64	10	9	100	11	6
210	10	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	28	<1	100
210	20	6	15	30	7	7	6	<1	62	5	4	100	10	12
210	70	17	37	90	17	11	17	<1	88	7	11	100	7	11

Table 2. Effect of ion source temperature on the mass spectra of 2-methyl-N-butyl-(4-methyloxazol-2-yl)propanamide at an ionising voltage of 20 eV

Ion Source Temperature (°C)	% Relative Intensity												
	97	98	111	112	124	125	126	137	138	153	154	155	224
270	8	21	38	10	9	9	4	62	6	5	100	10	7
250	5	19	34	8	5	7	<1	53	5	4	100	9	9
230	6	17	33	8	7	7	<1	55	5	4	100	10	11
200	6	15	30	7	7	6	<1	62	5	4	100	10	12
190	3	15	33	5	5	6	<1	56	4	3	100	8	16

iii. Mass spectrum of the N-d_9-butyl compound

Supporting evidence for the assignment of ions from 14a is provided by the spectrum (Figure 2) of the deuterium labelled compound, 2-methyl-N-d_9-butyl-N-(4-methyloxazol-2-yl)propanamide 14b.



14b

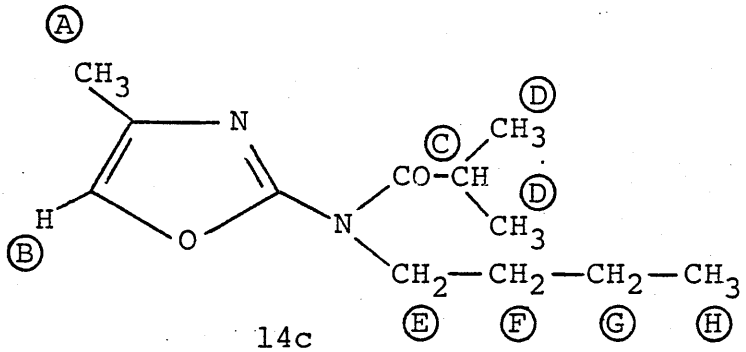
For 14b compared with 14a the molecular ion (m/e 233) and the base ion (m/e 163) have the expected nine a.m.u. increase, as they both contain the butyl group. The peak at m/e 98 for 14a shifts to m/e 99 for 14b as a deuterium rather than a hydrogen is transferred to the oxazole nucleus in the McLafferty rearrangement (Scheme 4).

The peak at m/e 111 in the spectrum of 14a shifts to m/e 113 for 14b consistent with the label of the methylene bonded to the exocyclic nitrogen atom. Whereas fragmentation of the m/e 154 ion for 14a results in the formation of the ion of m/e 137, the corresponding fragmentation for 14b gives two ions (m/e 145 and 146) of similar abundance, whose total intensity is equivalent to that of the ion of m/e 137 for 14a. This result implies an equal probability of losing an [OH] or [OD] radical. The elimination of this radical is discussed in more detail subsequently.

b. The elimination of a hydroxyl radical in the mass spectral behaviour of 2-[acyl(alkyl)-amino]oxazoles

i. Introduction

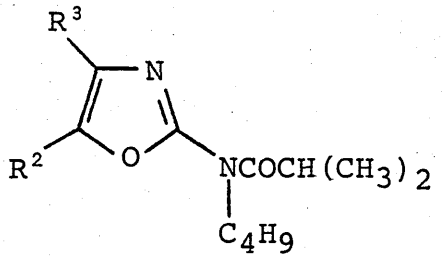
The mass spectra of further groups of oxazoles were examined to determine the extent of the hydroxyl radical elimination observed for 14a and, in particular, to locate the source of the eliminated hydrogen. For convenience of discussion, the eight types of non-equivalent hydrogen atom in 14a have been given a specific identification code as illustrated in 14c. The potential involvement of each hydrogen atom in the ring-scission process is examined in turn.



14c

ii. Involvement of hydrogen atoms associated with the oxazole nucleus-variation of the 4,5-dialkyloxazole substituents

The lack of involvement of hydrogen-A and hydrogen-B (14c) in the elimination of the hydroxyl radical in the mass spectrum of 14a was shown by comparison of the spectra of (4- and/or 5- alkyloxazolyl)propanamides (14-25).



	R^3	R^2		R^3	R^2
15	H	H	20	$C(CH_3)_3$	H
16	H	CH_3	21	$CH(CH_3)_2$	H
17	CH_3	CH_3	22	$C\text{-}C_6H_{11}$	H
18	C_2H_5	H	23	H	$C\text{-}C_6H_{11}$
19	H	C_2H_5	24	C_6H_5	H
			25	H	C_6H_5

Significant details of their spectra are summarised in Table 3. Compounds 15-25 all fragment similarly to 14a (cf. Scheme 4). The behaviour of each compound was characterised by loss of the acyl group and either subsequent loss of a hydroxyl radical or fragmentation of the n-butyl group.

The spectrum of the 5-methyl isomer 16 and of 14a differ only slightly in that 16 displays a less abundant molecular ion and greater secondary fragmentation including formation of the ion of m/e 137. Both the 4,5-dimethyl homologue 17 and 14a itself yield similar relative abundances of the $[M - O{=}C{=}C(CH_3)_2 - 17]^+$ ion. Removal of both 4- and 5-substituents to give 15 favours fragmentation of the butyl chain rather than elimination of a hydroxyl radical. Hence although the mass spectra of 14a-17 are characterised by differences in ion relative abundances, the presence of

either hydrogen-A or hydrogen-B is not a necessary requirement for the elimination of a hydroxyl radical from the oxazole nucleus, indicating these atoms are not directly involved in the elimination.

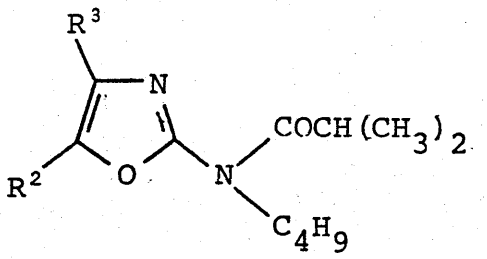
In the spectrum of compounds 18-25, the larger 4- and 5-substituents reduce the elimination of the hydroxyl radical. The spectra of the 4-ethyl (18) and 5-ethyl (19) isomers show characteristic differences. In particular, the relative abundance of the $[M - O{=}C{=}C(CH_3)_2 - OH]^+$ ion is greater for 18 than for 19. A similar situation applies for the spectra of both the isomeric cyclohexyl (22 and 23) and phenyl (24 and 25) compounds.

These larger substituents minimise the formation of the $[M - O{=}C{=}C(CH_3)_2 - OH]^+$ ion such that for 20 the scission of the N-butyl group is significantly more important.

iii. Involvement of hydrogen atoms associated with the acyl substituent

To examine the possible role of hydrogen-C and hydrogen-D in the elimination of the hydroxyl radical, a series of substituted acyl derivatives of 14a was examined. As an ion analogous to that of m/e 154 from 14a theoretically can be produced from the secondary amine (26a) and its derivatives 26b-d, these compounds were also investigated with reference to the function of hydrogen-C.

Table 3. Selected ion relative abundances in the mass spectra of 2-methyl-N-butyl(oxazol-2-yl)-propanamides



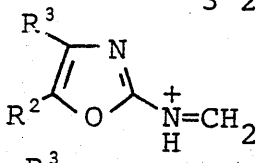
	R^3	R^2	$M^{+\cdot}$	$[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$	c	d	e	f
14a	CH_3	H	11	100	4	61	33	17
15	H	H	6	100	6	49	70	34
16	H	CH_3	6	100	10	83	55	27
17	CH_3	CH_3	15	100	6	56	29	16
18	C_2H_5	H	8	100	8	82	75	21
19	H	C_2H_5	9	100	7	40	30	20
20	$C(CH_3)_3$	H	16	100[a]	8	15	71	6
21	$CH(CH_3)_2$	H	20	100[b]	18	39	53	24
22	cyclo-C_6H_{11}	H	10	100	5	21	20	9
23	H	cyclo-C_6H_{11}	10	100	6	7	27	12
24	C_6H_5	H	22	100	10	57	26	11
25	H	C_6H_5	14	100	9	20	17	14

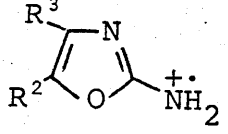
[a] 89 with reference to base ion m/e 43

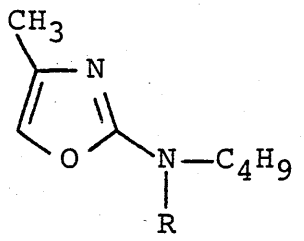
[b] 49 with reference to base ion m/e 154

[c] $[M - O{=}\dot{C}{-}CH(CH_3)_2]^+$

[d] $[M - O{=}C{=}C(CH_3)_2 - OH]^+$

[e] 

[f] 



26a	R = H
26b	R = D
26c	R = $Si(CH_3)_3$
26d	R = $Si(CD_3)_3$

(1) The mass spectrum of N-(4-methyl-oxazol-2-yl)butylamine

The mass spectrum of 26a is similar to that of 14a but with removal of the molecular ion peak to m/e 154 and the formation of more abundant fragment ions. As the loss of a hydroxyl radical is still observed for 26a, it seems reasonable to assume that hydrogens-D, cleaved in the McLafferty rearrangement (Scheme 4) for 14a and not present in 26a, are not involved in this elimination.

(2) The mass spectrum of N-(4-methyl-oxazol-2-yl)-N-d_1-butylamine (26b)

Replacement of the exchangeable hydrogen atom in 26a with deuterium gives N-(4-methyl-oxazol-2-yl)-N-d_1-butylamine (26b). As only partial exchange of the hydrogen atom was obtained, mass spectra of various isotopic mixtures of 26a and 26b were run. The ratio of the abundances of the m/e 155:154 ions (deuterium incorporation) was linearly related to the ratio of the abundances of the m/e 138:137 ions $[M - OH]^+$ or $[M - OD]^+$ (Figure 3). Hence for 26b an [OH] rather than an [OD] radical is lost from the molecular ion and the replaceable hydrogen atom cannot be involved in the elimination.

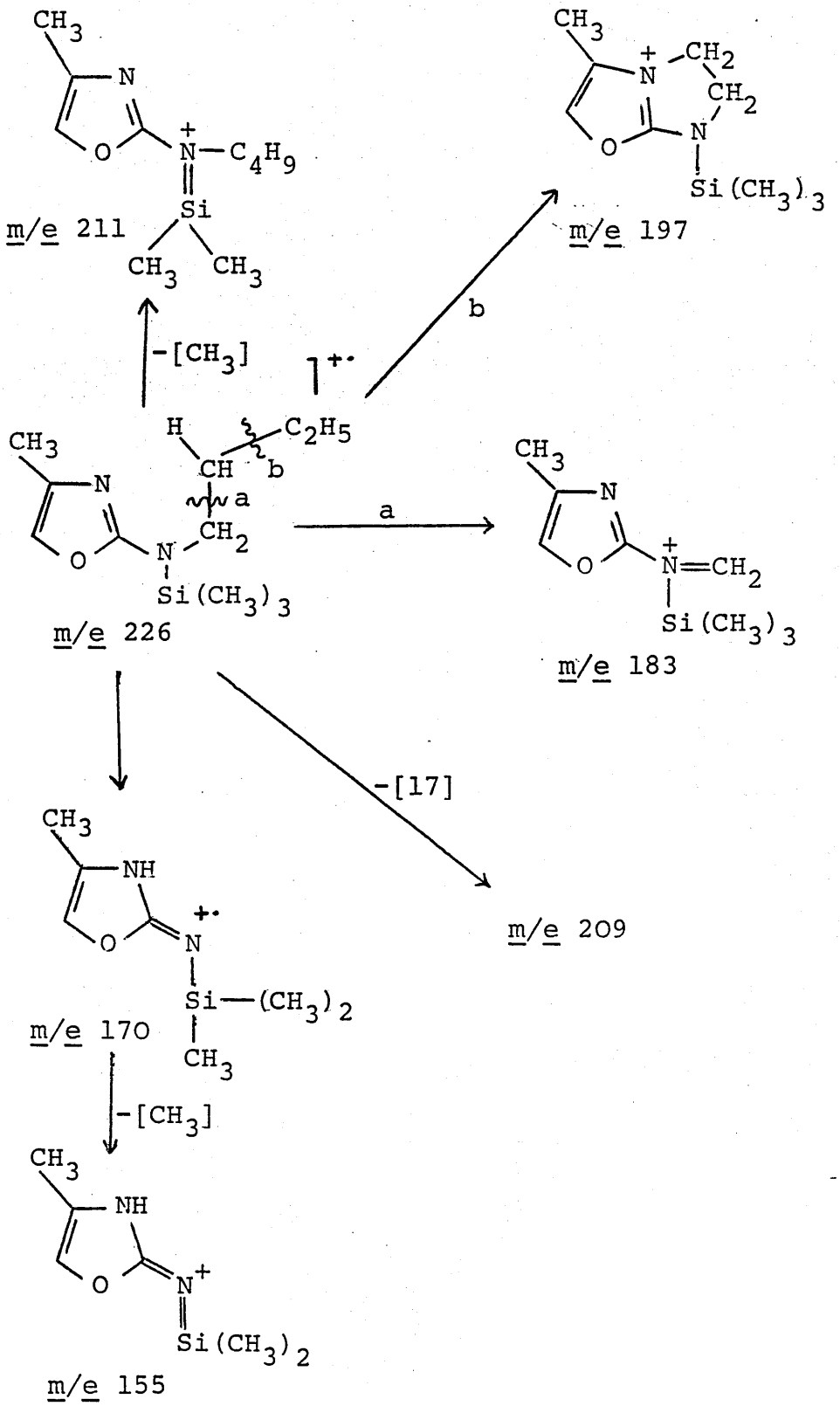
By analogy, the involvement of hydrogen-C (14c) in the elimination of the hydroxyl radical becomes questionable, as this hydrogen, transferred as a radical during the McLafferty rearrangement of the molecular ion becomes the equivalent exchangeable atom not involved in the hydroxyl radical elimination observed in 26a. If one assumes hydrogen-C is now excluded, only hydrogens E-H can be involved in the elimination of the [OH] radical from 14a. However, the loss of both [OH] and [OD] radicals from the d_9-butyl derivative (14b) indicates that both the hydrogen or deuterium atoms associated with the n-butyl group and hydrogen-C are partially involved. This implies that the molecular ion observed for 26a, used to eliminate the involvement of hydrogen-C in the elimination of the hydroxyl radical cannot be a totally satisfactory model for the m/e 154 ion observed in the spectrum of 14a. One explanation for this observation may be that, whereas in 26a the ion of m/e 154 is assumed to have an endocyclic structure, the ion of m/e 154 from 14a, formed as the result of a rearrangement probably has an exocyclic structure (Scheme 4, page 32), which may not rearrange to the more stable endocyclic structure before further fragmentation. Alternatively, 26a may be behaving in a manner similar to that of NN-dialkyl-4-methyloxazol-2-yl-amines (Section C2c), which lose a hydroxyl radical directly from the molecular ion, but by an alternative fragmentation process. Consequently, the precise involvement of hydrogen-C in the elimination of the hydroxyl radical observed for 14a remains uncertain.

(3) The mass spectra of N-(4-methyloxazol-2-yl)-N-(trimethylsilyl)-butylamine (26c) and N-(4-methyloxazol-2-yl)-N-(d_9-trimethylsilyl)-butylamine (26d)

For the trimethylsilyl (26c) and d_9-trimethylsilyl (26d) derivatives it was anticipated that in the mass spectrometer transfer of either hydrogen (26c) or deuterium (26d) from the trimethylsilyl group to the oxazole nucleus, would yield ions of m/e 154 and 155 respectively, which would exist as exocyclic structures and hence prove a more satisfactory model for the ion of m/e 154 from 14a.

However, the mass spectra of 26c (Figure 4) and 26d (Figure 5) show preferential loss of the n-butyl group from the molecular ion, either by a McLafferty rearrangement to give peaks at m/e 170 and m/e 179, or by a simple scission to give peaks at m/e 183 and m/e 192 respectively (Scheme 5), rather than loss of the trimethylsilyl group. The participation of the n-butyl group in the elimination of the hydroxyl radical for 14a is again indicated by the absence of an ion of m/e 153 $[M-56-17]^+$ for 26c. The alternative fragmentation of both compounds 26c and 26d preclude their use as a direct model for the interpretation of the mass spectrum of 14a.

The spectrum of the labelled compound 26d indicates that the methyl radical, lost from both the molecular ion and from the $[M-56]^{+\cdot}$ ion originates exclusively from the trimethylsilyl group. The stability of the molecular ion

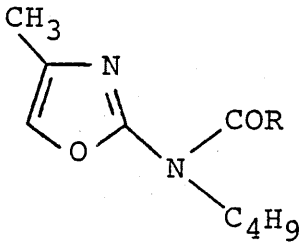


SCHEME 5

shown by the spectra of 26c and 26d indicates that the acyl group triggers the fragmentation of the molecular ion from 14a. The stable molecular ion also encourages the formation of an $[M-17]^+$ ion for both 26c and 26d, the hydrogen atom originating from the n-butyl group. For the spectrum of 26d, the presence of the significant $[M - CD_3]$ peak interferes with the measurement of the ~~elimination of the~~ [M - OD] peak.

(4) Variation of the N-acyl substituent in 2-[acyl(alkyl)amino]oxazoles

The alternative measurement of the involvement of hydrogens-C and -D (14c) in the elimination of the hydroxyl radical observed for 14a was obtained by comparison of the spectrum of 14a with the spectra of N-butyl-N-(4-methyloxazol-2-yl)amides (27-34),



	R		R
27	CH_3	31	$CH(CH_3)CH_2CH_3$
28	C_2H_5	32	$C(CH_3)_3$
29	$(CH_2)_2CH_3$	33	$CH(C_2H_5)_2$
30	$(CH_2)_3CH_3$	34	$(CH_2)_5CH_3$

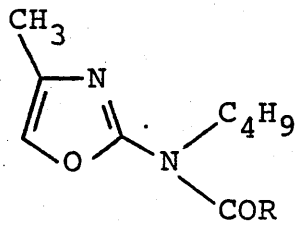
in which the chain length of the acyl group was varied from one to six carbon atoms. The ion of m/e 154 $[M - (COR-1)]^{+\cdot}$ was the base ion for all compounds other than 32 when the butylium ion was the most abundant ion. The relative

abundance of the molecular ion and the fragment ions derived from the base ion decrease with increasing length of the acyl group (Table 4) both for the straight chain and branched chain series. The presence of peaks at m/e 137 $[M - (COR-1) - 17]^+$ and m/e 154 $[M - (COR-1)]^{+\cdot}$ in the spectra of compounds 27-34 further confirms the lack of direct involvement of the hydrogen atoms of the acyl group (hydrogen-D in 14c), other than the atom adjacent to the carbonyl group, in the elimination of the hydroxyl radical for 14a.

In contrast, the direct involvement of the hydrogen atom adjacent to the carbonyl group is observed in the transfer of hydrogen (hydrogen-C in 14c) to the oxazole nucleus during the McLafferty rearrangement and the variation of the relative abundance of the ion of m/e 137 with the acyl substituent.

The mass spectrum of the t-butyl compound (32) (Figure 6) is significantly different from those of other members of the series. Although 32 does not contain a hydrogen alpha to the carbonyl group, its spectrum still exhibits an ion of m/e 154. This ion cannot be formed by a McLafferty rearrangement, but rather by scission of the N-CO bond and transfer of a hydrogen radical. Significant peaks observed at m/e 153 (34%) and m/e 85 (62%) support this conclusion. Once formed, the ion of m/e 154 fragments similarly to the same mass ion observed from compounds 27-31 and 33-34.

Table 4. Selected ion relative abundances in the mass spectra of N-butyl-N-(4-methyloxazol-2-yl)-amides



	R	$M^{+\cdot}$ [a]	m/e 154	153	137	111	98	$[R-C\equiv O]^+$	$[R]^+$
14a	$-CH(CH_3)-CH_3$	11(224)	100	4	55	37	17	71	<1
27	CH_3	44(196)	100	10	90	76	51	8	<1
28	$-CH_2CH_3$	15(210)	100	5	76	46	14	7	1
29	$-(CH_2)_2-CH_3$	18(224)	100	<1	74	58	28	54	62
30	$-(CH_2)_3-CH_3$	8(238)	100	<1	59	27	16	29	40
31	$-CH(CH_3)-CH_2-CH_3$	10(238)	100	15	54	49	22	38	128
32	$-C(CH_3)_2-CH_3$	89(238)	100	34	99	87	45	62	89
33	$-CH(CH_2CH_3)_2$	4(252)	100	3	38	16	9	2	25
34	$-(CH_2)_5-CH_3$	5(266)	100	<1	43	19[b]	12	19[b]	41

[a] Molecular weight in brackets

[b] Doublet ions

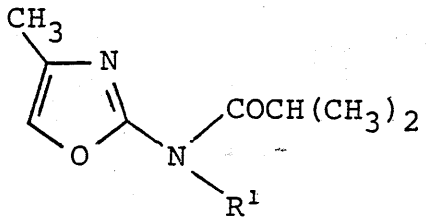
The mass spectra of the corresponding aryl substituted compounds (R = Ph) are characterised by the presence of the acylium ion ($Ph-C\equiv O^+$) and complete absence of ions of m/e 154 and 137. The spectra of these compounds will be discussed in more detail in Section C2g.

iv. Involvement of hydrogen atoms associated with the N-alkyl substituent

The involvement of hydrogens E-H (14c) in the elimination of the hydroxyl radical for 14a was highlighted by the examination of the mass spectra of two further ranges of substituted oxazoles.

(1) The mass spectra of 2-methyl-N-alkyl-N-(4-methyloxazol-2-yl)-propanamides

In the oxazoles 35-43, the N-alkyl group is varied whilst the propanamide group is retained. Table 5 summarises the important features of their mass spectra.



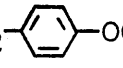
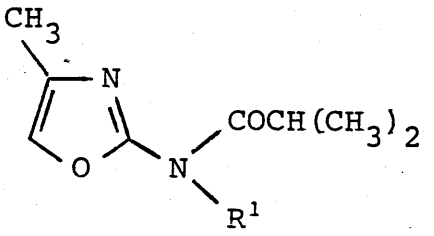
	R^1		R^1
35	$CH_2C\equiv CH$	39	$(CH_2)_2OCH_3$
36	$CH_2CH=CH_2$	40	$(CH_2)_2$- 
37	CH_2-  -OCH_3	41	$(CH_2)_3Cl$
38	$CH_2CH=CH$- 	42	$(CH_2)_3CO_2CH_3$
		43	$CH_2C\equiv C-CH_3$

Table 5. Selected ion relative abundances in the mass spectra of compounds 35-43



	R^1	$M^{+\cdot}$ [a]	b	c	d	m/e 111	m/e 98
35	$CH_2C{\equiv}CH$	5 (206)	100	8	<1	<1	<1
36	$CH_2CH{=}CH_2$	6 (208)	100	16	2	15	<1
37[e]	CH_2-C$_6$H$_4$-OCH_3	7 (288)	11	5	<1	<1	<1
38[f]	$CH_2CH{=}CH$-C$_6$H$_5$	14 (284)	29	29	<1	<1	<1
39	$(CH_2)_2OCH_3$	4 (226)	100	1	2	70	100
40	$(CH_2)_2$-C$_6$H$_5$	10 (272)	100	2	<1	72	75
41	$(CH_2)_3Cl$	4 (244)	100	3	33	35	<1
42	$(CH_2)_3CO_2CH_3$	4 (268)	100	1	8	29	20
43	$CH_2C{\equiv}C{-}CH_3$	3 (220)	100	16	≤1	2	3
14	$(CH_2)_3CH_3$	11 (224)	100	4	55	37	17

[a] Molecular weight in brackets

[b] $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$

[c] $[M - O{=}C{-}CH(CH_3)_2]^{+}$

[d] $[M - O{=}C{=}C(CH_3)_2 - 17]^{+}$

[e] Base ion m/e 121

[f] Base ion m/e 117

All the compounds other than 37 and 38 lose an acyl group from the molecular ion yielding the base ion of the spectrum. In compound 37 scission of the N-CH_2 bond leads to a substituted tropylium ion $[C_8H_9O]^+$ of m/e 121 (100%), whilst for 38 the same fragmentation gives a base ion of m/e 117. No ions are observed of m/e 98, 111 or $[M - O{=}C{=}C(CH_3)_2 - 17]^+$ for either of these compounds.

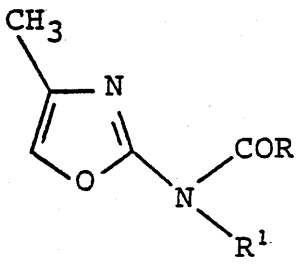
Compounds 41 and 42, which contain three methylene groups, give spectra which demonstrate the elimination of a hydroxyl radical. For 41 simple scission (Scheme 4, page 32) of the $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$ ion occurs to a greater extent than does a second McLafferty rearrangement involving the N-alkyl substituent, the presence of the chlorine atom completely inhibiting this fragmentation (m/e 98<1%). Minimal fragmentation of the $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$ ion is observed for compounds 35 and 36, in which the three terminal carbon atoms are retained.

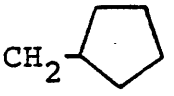
For 40, in which the methylene chain is reduced to only two units, the ion of m/e 202, although not exhibiting a a loss of seventeen mass units, does give significant ions of m/e 98 and 111 following losses of C_8H_8 and C_7H_7. The abundance (>1%) of the $[C_7H_7]^+$ ion is surprisingly low. Hence, elimination of the hydroxyl radical requires an N-alkyl substituent containing three and preferably four (compound 14a) methylene groups.

The elimination of a hydroxyl radical is also not observed for compound 43 which contains neither hydrogen-F nor hydrogen-G (14c). As compound 43 differs from 14a in the absence of these hydrogen atoms, it must be assumed that hydrogen atoms in one or both of these positions play a significant part in the hydroxyl elimination. As there is no hydrogen atom correctly positioned for a McLafferty rearrangement, fragmentation of the butyne chain in 43 only occurs by loss of a methyl radical from the terminal position. Replacement of hydrogen-G in 14c by an oxygen atom (39), causes a significant change in the mass spectrum. The $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$ ion loses a butyl group rather than a hydroxyl radical, and the ion of m/e 98 becomes the base ion of the spectrum. Hence, one of the hydrogens-F,G and in particular hydrogen-H in 14c, must play a significant role in the elimination of the hydroxyl radical.

(2) Effect of the chain length of the N-alkyl substituent on the elimination of a hydroxyl radical

As the acyl group is cleaved prior to the elimination of a hydroxyl radical in the mass spectral behaviour of compounds 44-58, the dependence of the rearrangement on the length of the N-alkyl chain can be measured.



	R^1	R		R^1	R
44	CH_3	CH_3	52	$(CH_2)_2CH_3$	$CH(CH_3)_2$
45	C_2H_5	$(CH_2)_2CH_3$	53	$(CH_2)_2CH_3$	$(CH_2)_4CH_3$
46	C_2H_5	$(CH_2)_4CH_3$	54	$(CH_2)_3CH_3$	$(CH_2)_2CH_3$
47	$CH(CH_3)_2$	CH_3	55	$(CH_2)_3CH_3$	$(CH_2)_4CH_3$
48	$CH(CH_3)_2$	$CH(CH_3)_2$	56	$(CH_2)_4CH_3$	CH_2CH_3
49	$CH(CH_3)_2$	$CH(CH_3)CH_2CH_3$	57	$(CH_2)_5CH_3$	$(CH_2)_3CH_3$
50	$CH(CH_3)_2$	$CH_2CH(CH_3)CH_2CH_3$	58		$(CH_2)_3CH_3$
51	$CH(CH_3)_2$	$(CH_2)_5CH_3$			

The spectra of compounds 44-58 are again characterised by the loss of an acyl group to give the base ion $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$. The relative abundance of the $[M - O{=}C{=}C(CH_3)_2 - 17]^+$ ion is clearly dependent on the chain length of the N-alkyl group (Figure 7). No elimination of the hydroxyl radical is observed for compounds containing an N-alkyl chain of one or two carbons length. As expected, compounds containing the branched N-isopropyl group behave similarly to those containing the N-C_2H_5 substituent. The optimum yield of the $[M - (COR-1) - 17]^+$ ion is observed in compounds containing four or five carbon atoms in the N-alkyl chain. Compound 57, containing six carbon atoms in the N-alkyl chain, shows a lower abundance of this ion. This data verifies the importance of the N-alkyl substituent in the loss of the hydroxyl radical and implies the elimination is optimum for an N-alkyl chain length of four or five carbon atoms.

v. Mechanism of elimination

A comparison of the mass spectra of the oxazoles 14a-58 indicates that the loss of the hydroxyl radical for 14a must not only involve hydrogen-H associated with the terminal methyl group of the N-alkyl chain, but also hydrogen-C. Further information on the mechanism of elimination is provided from the mass spectral behaviour of compounds in which the n-butyl chain in 14a is more specifically labelled. The spectrum of 2-methyl-N-1,1-d_2--butyl-N-(4-methyloxazol-2-yl)propanamide shows only the loss of an [OH] radical confirming that hydrogens-E are not involved in the elimination. Attempts to synthesise a 2,2,3,3-tetradeuterated N-alkyl substituted compound 14a by catalytic reduction of 43 by J.P. Verge (Lilly Research Centre Limited) were unsuccessful. The product obtained was a mixture in which partial deuterium exchange of hydrogen in the butyl group, in addition to reduction of the acetylenic bond, had taken place. The levels of deuterium incorporation (d_2-d_7) can be seen in Table 6. The abundance of ions in the $M^{+\cdot}$ and $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$ clusters were very similar, although a fall in the abundance of the d_7-isotope indicates some deuterium incorporation in the acyl group. The ratio of the m/e 98 to m/e 99 ions remains as in compound 14a indicating no deuterium incorporation in the oxazole ring. Hence, an increase in the abundance of the d_2 and d_3 ions and a decrease of d_7 ions following the loss of the hydroxyl radical, indicates deuterium is preferentially lost in the elimination. Although no specific conclusion can be drawn from this data, it does

Table 6 Selected ion relative abundances in the mass spectrum of compound 14a containing a mixed deuterium isotope label

d_0 (m/e)	d_1	d_2	d_3	d_4	d_5	d_6
224	24	70	100	96	95	70
154	23	71	100	95	97	53
137	33	87	100	100	94	31

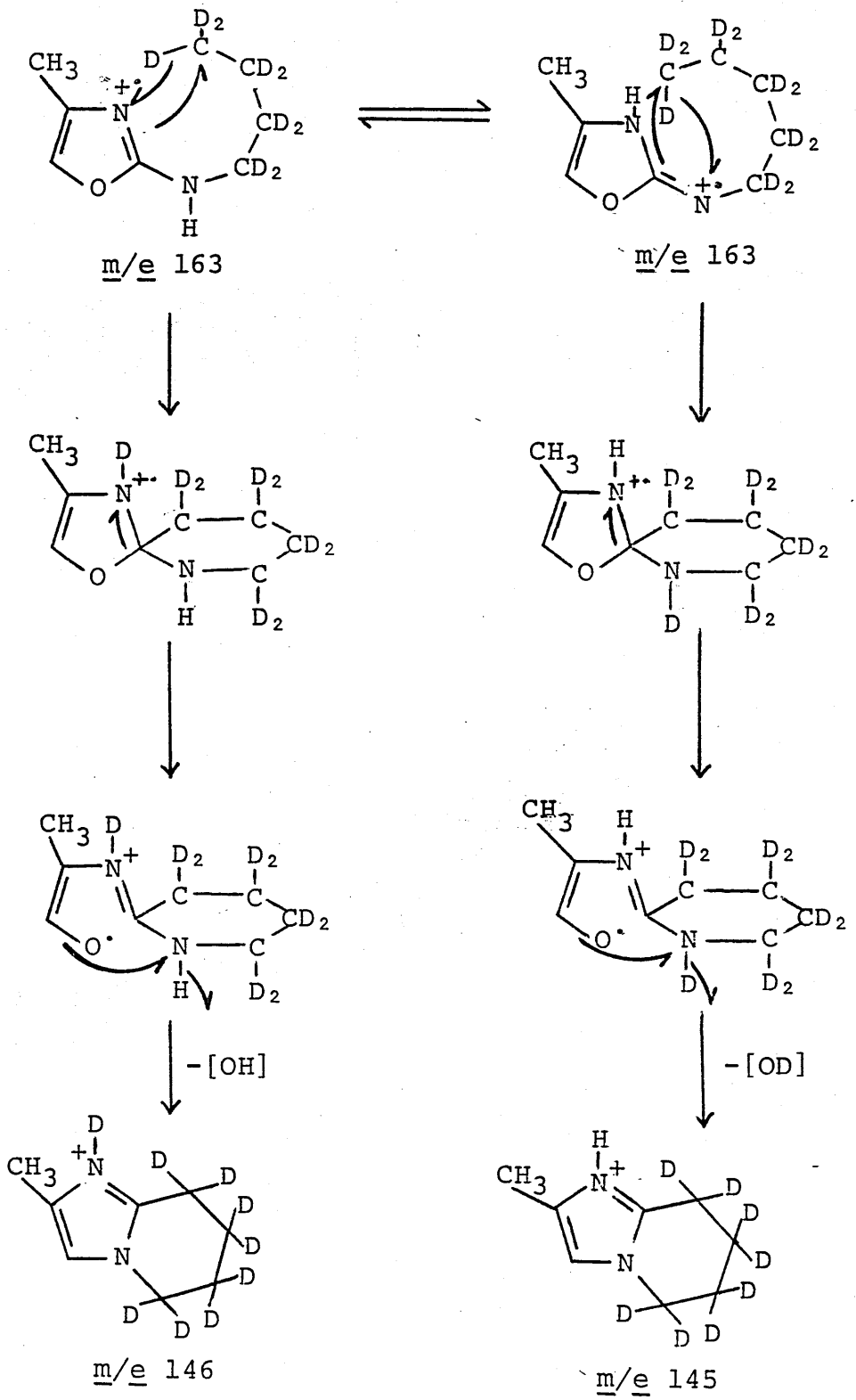
indicate that the loss of hydrogen or deuterium from the butyl chain is not random.

As N-(4-methyloxazol-2-yl)butylamine (26a) did not prove a satisfactory model to study the involvement of hydrogen-C in the elimination of the hydroxyl radical from 14a, the acyl chain in 27 was labelled to give an alternative model compound, N-butyl-N-(4-methyloxazol-2-yl)-d_3-acetamide (27a). The spectrum of 27a shows the loss of equal amounts of [OH] and [OD] radicals from the d_1-McLafferty ion (m/e 155) confirming the involvement of hydrogen-C in the elimination and supporting the 1:1 loss of [OH] and [OD] radicals from 14b. Any mechanism therefore attempting to explain the loss of the hydroxyl radical from 14a must involve hydrogens-C and -H in equivalent positions. Such a mechanism is illustrated in Scheme 6 for 14b which simultaneously involves the two tautomeric forms of the m/e 163 ion. An alternative mechanism in which the final ring fusion step is replaced by the formation of a 3-membered ring system involving cyclisation with the alternative nitrogen is less likely. As the m/e 145 and m/e 146 ions are assigned a fused cyclic structure, they would be expected to be fairly stable. For 14a metastable ion peaks only support further fragmentation of the m/e 137 ion to ions of m/e 57 and m/e 54 (C_3H_4N). Neither of these ions has a high abundance, the m/e 57 ion having the dual composition C_3H_7N and C_4H_9, nor do they give any significant information about the structure of their parent ion. In addition, the spectrum (Figure 8) of 3-methyl-1,5,6,7,8,8a-hexahydroimidazolo—[1,2-a]pyridine, a compound similar in

structure to that proposed for the m/e 137 ion for 14a, does not show signficant fragmentation. The spectrum of this reduced imidazole shows a molecular ion of m/e 138, which loses hydrogen to give a base ion of m/e 136 and lower abundance ions of m/e 135 and 132. Hence, the mass spectral behaviour of the m/e 137 ion from 14a supports its proposed structure and mode of formation.

As the proposed mechanism treats the endocyclic and exocyclic forms of 14a as equivalent, the mass spectral behaviour of 26a is best explained by comparison with that of the (dialkylamino)oxazoles in which an alternative elimination mechanism is assumed.

An analysis of the mass spectra of further heterocyclic series (Section D) suggests that similar eliminations are only observed when the acyl(alkyl)amino-substituents are adjacent to the heterocyclic atom.



SCHEME 6

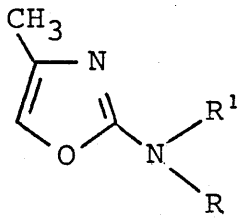
c. N N—Dialkyl-4-methyloxazol-2-ylamines

i. Introduction

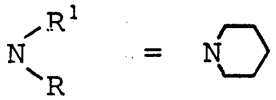
As the molecular ion from 2-[acyl(alkyl)-amino]oxazoles rearranges in losing the acyl substituent, the $[M-(O{=}C{-}R-1)]^{+\cdot}$ ion probably has an exocyclic structure which may tautomerise before further fragmentation. It was anticipated that, in the spectra of 2-(dialkylamino)oxazoles which lack the labile acyl substituent, the endocyclic molecular ion will have greater stability and may show alternative fragmentation.

ii. Results and discussions

The mass spectra of the N,N-dialkyl-4-methyloxazol-2-ylamines (59-63) confirm the influence the acyl group exerts on the fragmentation of N-alkyl-N-(oxazol--2-yl)amides 14a-58.

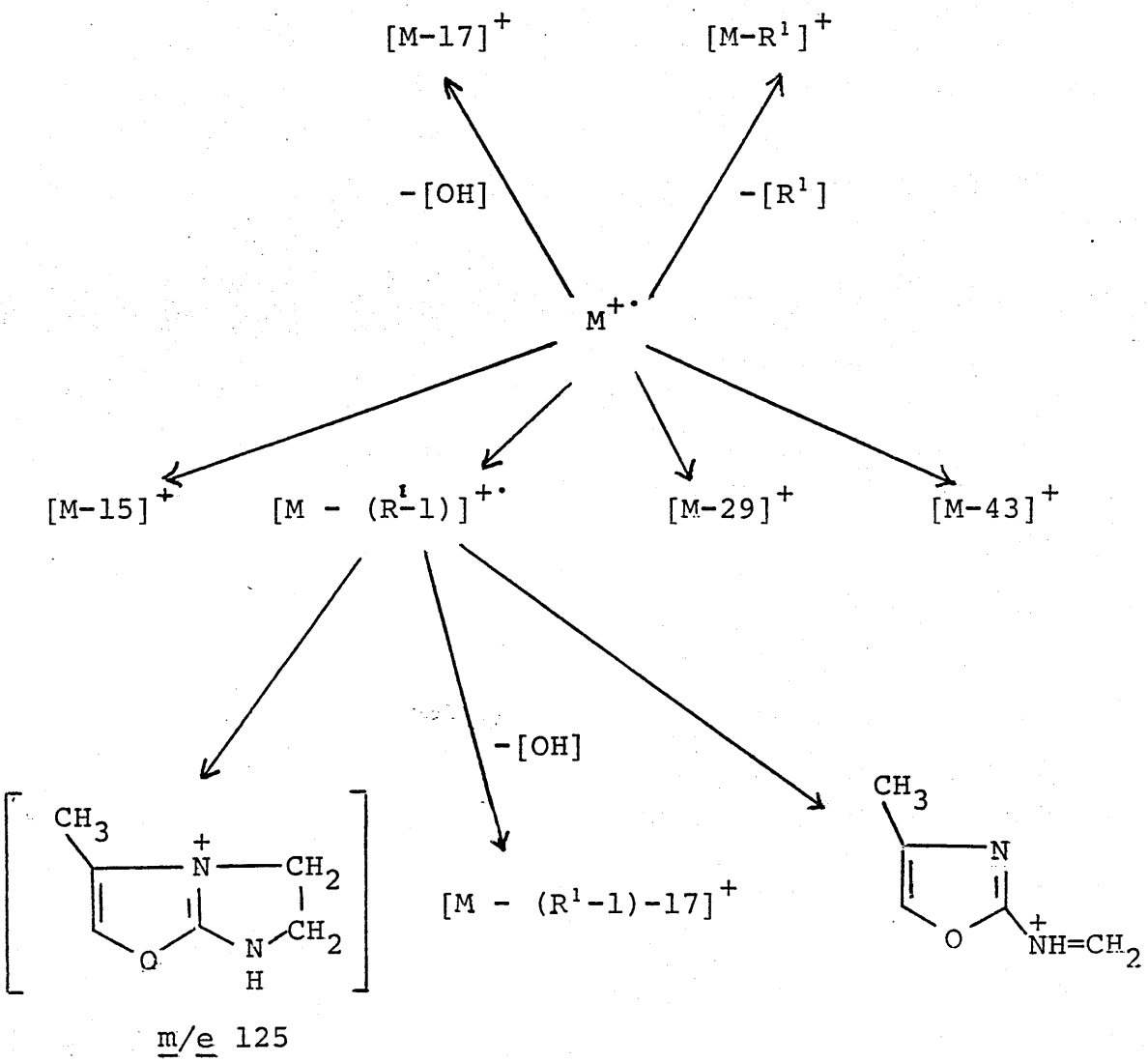


	R^1	R
59	$CH_2CH(CH_3)_2$	$n\text{-}C_4H_9$
60	$CH(CH_3)_2$	$CH(CH_3)_2$
61	$C_2H_4OC_2H_5$	$n\text{-}C_4H_9$
63	CH_2- 	C_2H_5

62 

In the spectra of compounds 59-63 the molecular ion is the base ion, whereas the base ion for compounds 14a-58 is the ion formed following the McLafferty rearrangement involving the acyl group (Scheme 4, page 32). Further significant differences for 59 and 61-63 are the formation of an $[M-17]^+$ ion in addition to an $[M - (R-1)-17]^+$ ion and the α-, β-, γ-scission of the N-alkyl chain. By analogy with 14c for which hydrogen-A and -B can be excluded, the loss of a hydroxyl radical from the molecular ion in 59 and 61-63, compounds which contain a tertiary substituted exocyclic nitrogen atom, can only involve the hydrogen atoms associated with the N-alkyl substituents. Scheme 7 shows the principal fragmentation pathways of compounds 59-63.

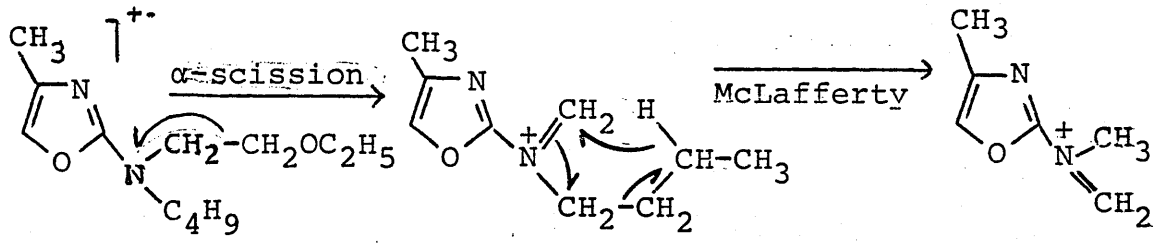
The mass spectrum (Figure 9) of 59 shows significant ions of m/e 167 $[M - C_3H_7]^+$ and m/e 153 indicating simple scission of the alkyl chain. Other important peaks can be seen at m/e 210 $M^{+\cdot}$, 193 $[M-17]^+$, 154 $[M - C_4H_8]^{+\cdot}$ and 125 $[M - C_4H_8 - C_2H_5]^+$. Both alkyl substituents in 60 have an effective chain length of only two carbon atoms and consequently, as in the corresponding amides, the mass spectrum (Figure 10) does not show the elimination of a hydroxyl radical. Significant ions are observed at m/e 182 $M^{+\cdot}$, 167 $[M - CH_3]^+$, 139 $[M - C_3H_7]^+$, 125 $[M - C_4H_9]^+$, 98 and 97, the latter ion fragmenting to an ion of m/e 70 probably by loss of hydrogen cyanide.



m/e 125

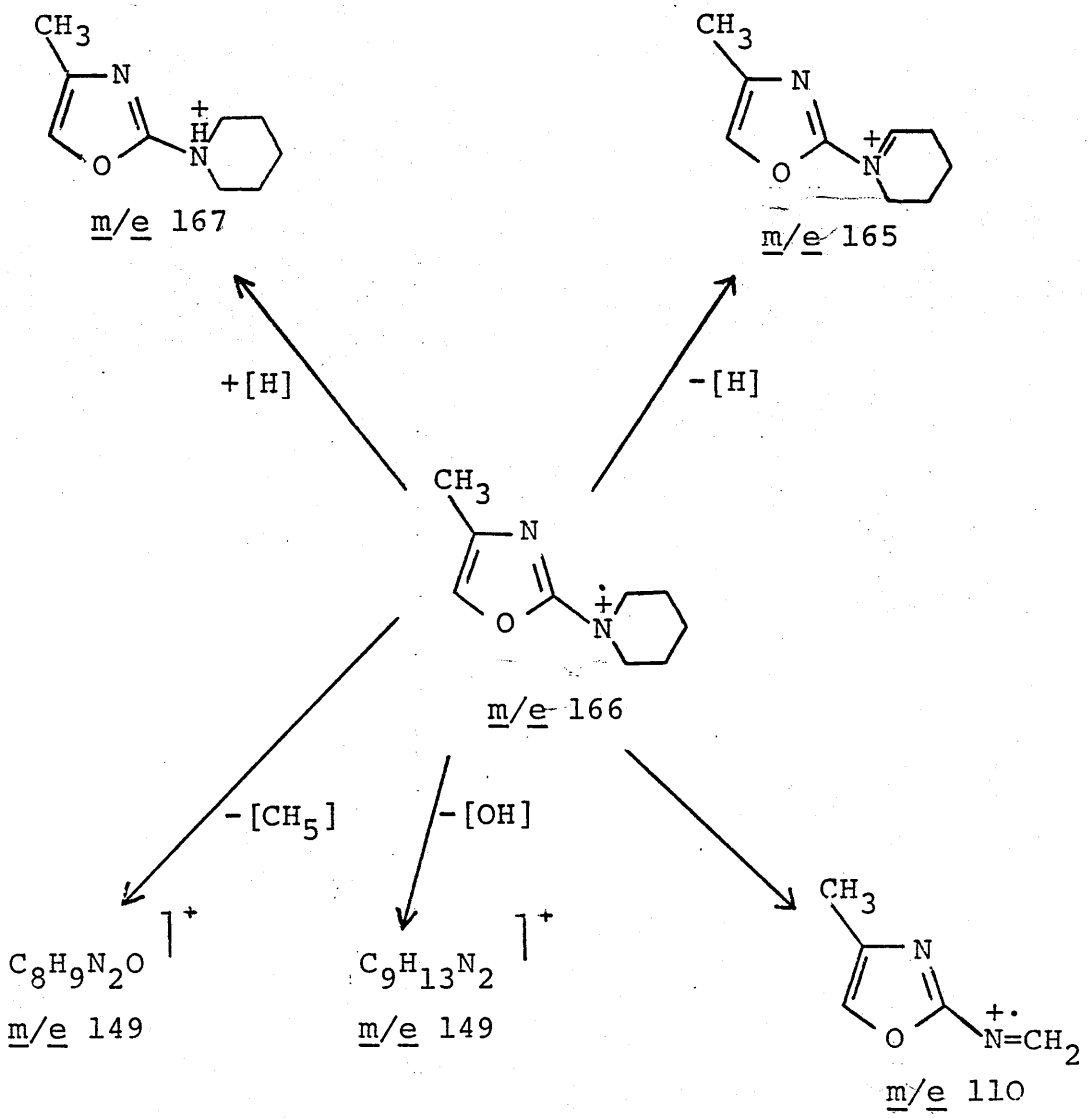
SCHEME 7

In the spectrum of 61 (Figure 11), the loss of 17 mass units is more easily observed after rather than before the McLafferty rearrangement (Scheme 7). A metastable ion indicates that for 61 the ion of m/e 125 is formed on fragmentation of the m/e 167 ion (Scheme 8), whereas for other members of the series it is formed from the $[M - (R^1-1)]^{+\cdot}$ ion (Scheme 7). Other significant ions are observed at m/e 226 $M^{+\cdot}$, 197 $[M-29]^+$, 154 $[M - H_2C{=}CHOC_2H_5]^{+\cdot}$, 137 $[M - H_2C{=}CHOC_2H_5 - OH]^+$ and 111.



SCHEME 8

A McLafferty rearrangement is not observed for compound 62 as the piperidine ring must undergo a second rearrangement before a neutral molecule is eliminated (Figure 12). However, the piperidine substituent is responsible for the formation of the ion of m/e 110, the high abundance of the $[M+1]^+$ and $[M-1]^+$ ions, and the elimination of a hydroxyl radical from the molecular ion (Scheme 9) to give an ion of m/e 149 $[C_9H_{13}N_2]^+$. Accurate mass measurements indicate that the peak at m/e 149 exists as a doublet and that the other ion has the composition $[C_8H_9N_2O]^+$ corresponding to the elimination of the elements CH_5 from the molecular ion, presumably in at least a two step process.


CH3
N
O
H
N
m/e 167
CH3
N
O
N
m/e 165
+[H]
-[H]
CH3
N
O
N
m/e 166
-[CH5]
-[OH]
C8H9N2O
m/e 149
C9H13N2
m/e 149
CH3
N
O
N=CH2
m/e 110

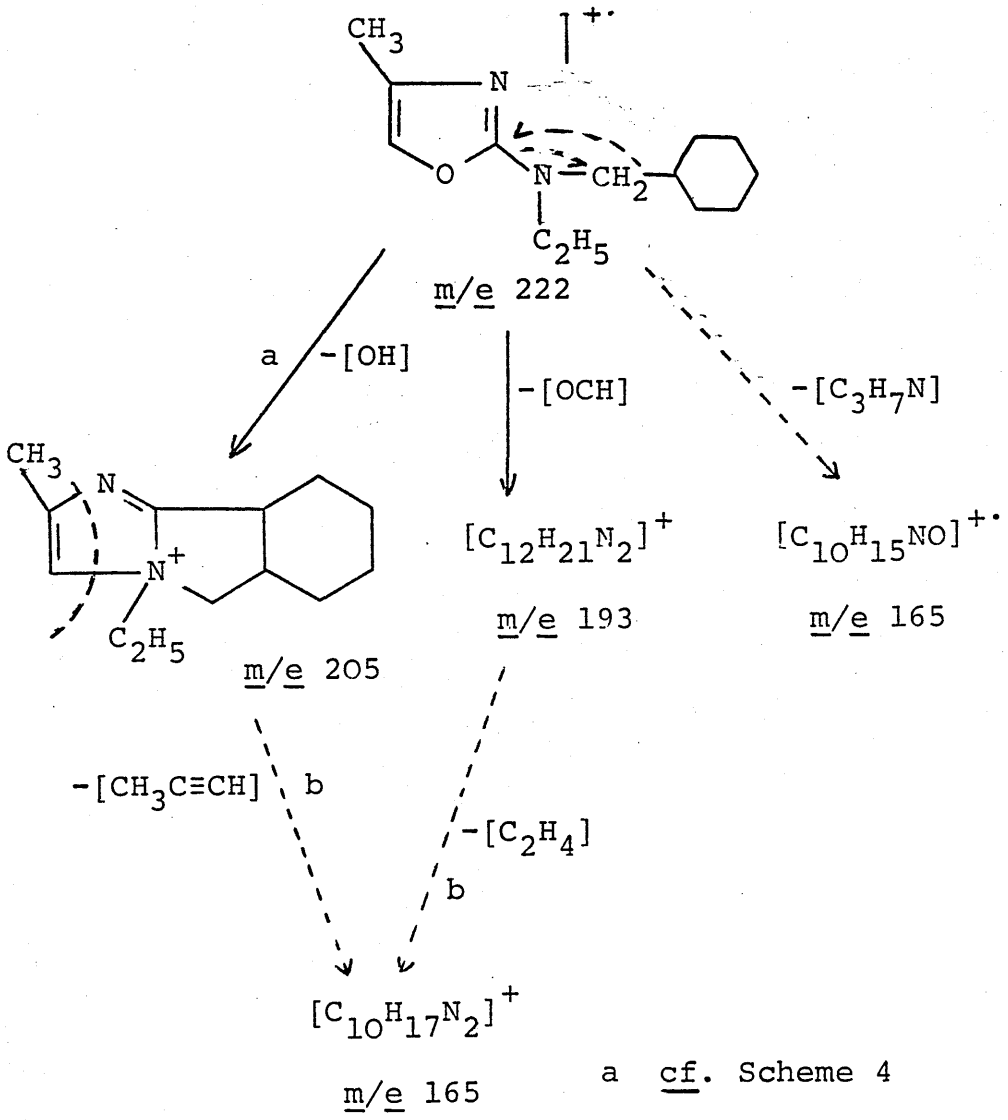
SCHEME 9

The spectrum of compound 63 differs from that of the other members of the series 59-63 in that the larger N-alkyl substituent is lost both by α-scission to give the ion of m/e 139 $[M - C_6H_{11}]^+$ and by a McLafferty rearrangement to give an ion of m/e 126 (Figure 13). Fragmentation of the oxazole ring is indicated by the presence of the two ions m/e 205 $[M - OH]^+$ and m/e 193 $[M - CHO]^+$. Major ions are also observed of m/e 222 $M^{+\cdot}$ and m/e 111. No metastable ion information is available to confirm the genesis of the peak at m/e 165. However, accurate mass data suggests that the ion has the dual composition $C_{10}H_{17}N_2$ and $C_{10}H_{15}NO$, the former component being twice as abundant as the latter. The loss of the elements C_3H_5O from the molecular ion $[C_{13}H_{22}N_2O]^{+\cdot}$ to give the oxygen deficient ion of m/e 165 is highly significant as the peak probably arises from fragmentation of either the ion of m/e 205 $[M - OH]^+$ or m/e 193 $[M - CHO]^+$. Whereas formation of the m/e 165 ion from the $[M - CHO]^+$ ion would entail loss of ethylene, its formation from the $[M - OH]^+$ ion would require the elimination of $CH_3C{\equiv}CH$ and provide evidence for the structure of the ion of m/e 205 (Scheme 10).

iii. Conclusion

The elimination of a hydroxyl radical directly from the molecular ion in compounds 59, 61-63 indicates that a structure incorporating an exocyclic C=N bond is not an essential requirement for its loss from 2-[dialkylamino]oxazoles. Consequently, any attempt to explain the same elimination for 2-[acyl(alkyl)amino]oxazoles following loss of the acyl group should not necessarily be

confined to consideration of exocyclic structures. The difference in mass spectral behaviour between 2-[dialkylamino]- and 2-[acyl(alkyl)amino]oxazoles may be a more plausible explanation for the lack of [OD] radical elimination from the molecular ion of the mono-alkyl compound 26b rather than the alternative consideration of its existence solely as an endocyclic structure.



a cf. Scheme 4

b no metastable ion evidence

SCHEME 10

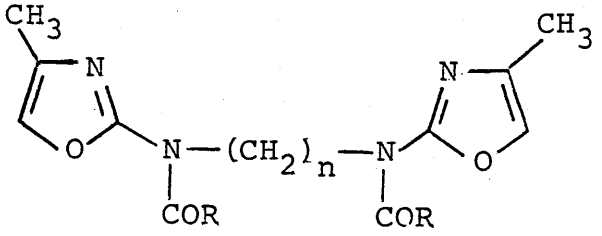
d. α,ω-Bis-[N-acyl-N-(4-methyloxazol-2-yl)amino]-alkanes

i. Introduction

The mass spectra of seven α,ω-bis-[N-acyl-N-(4-methyloxazol-2-yl)amino]alkanes (64-70) were examined to determine the relationship between the length of the methylene bridge and the ease of elimination of the hydroxyl radical in a series of oxazoles more sterically hindered than 14a-56.

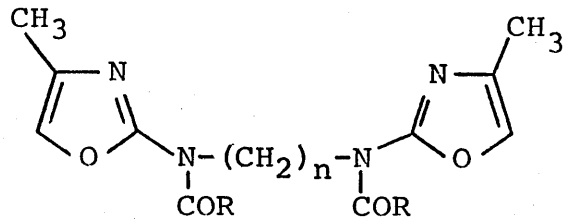
ii. Results and discussions

The spectra of the oxazoles 64-70 are considerably more complex (Scheme 11) than those of the 2-[acyl(alkyl)amino]oxazoles 14a-58. For instance, a hydroxyl radical can be eliminated from at least four different ions, whilst a [CHO] radical can also be eliminated from a ring. The relative abundance of significant ions in the spectra of 64-70 are shown in Table 7.



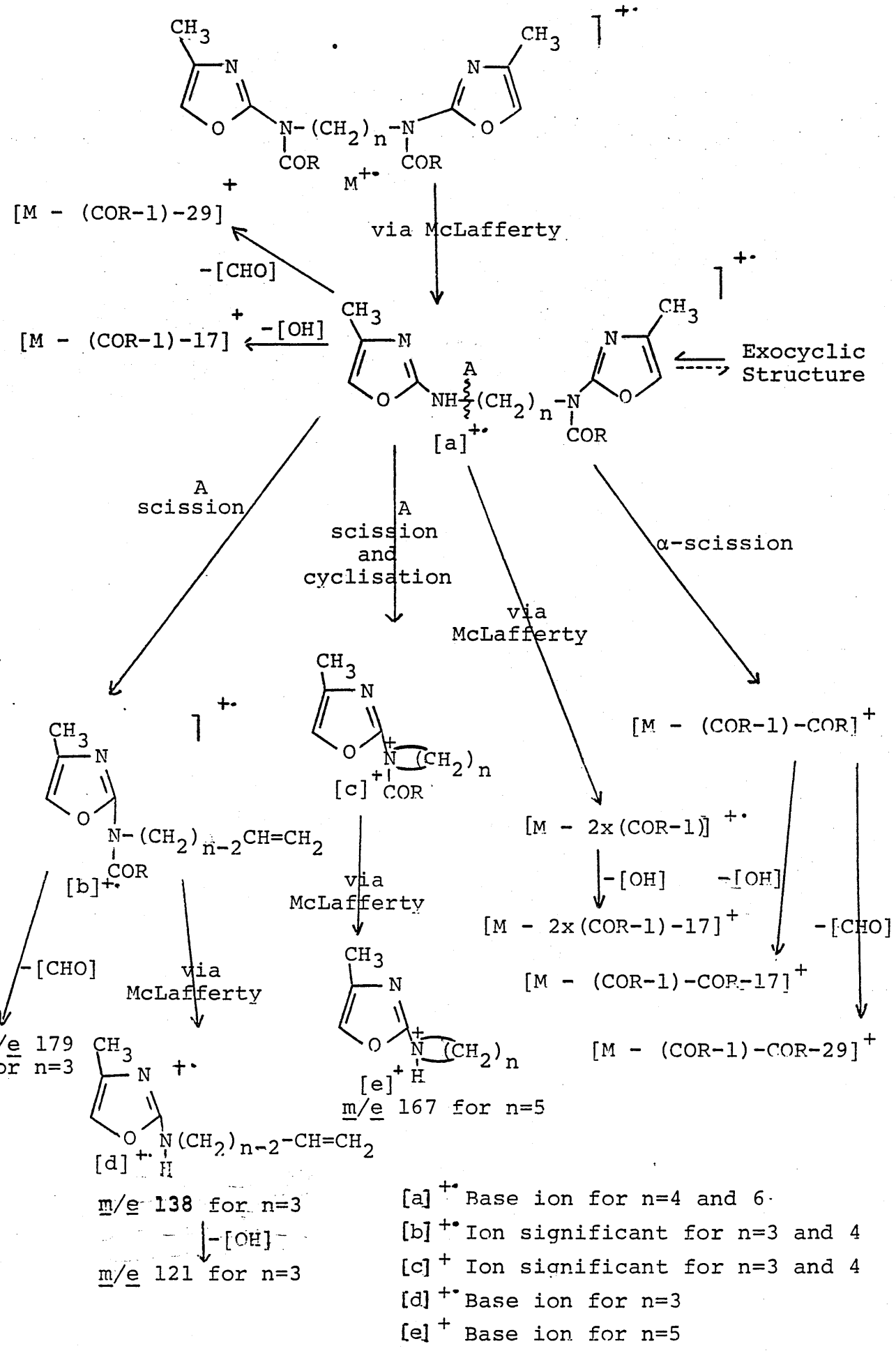
64	n = 3;	R = CH_3	68	n = 5;	R = $CH(CH_3)_2$
65	n = 3;	R = $CH(CH_3)_2$	69	n = 6;	R = $CH(CH_3)_2$
66	n = 4;	R = $CH(CH_3)_2$	70	n = 6;	R = C_4H_9
67	n = 4;	R = C_4H_9			

Table 7. Selected ion relative abundances in the mass spectra of compounds 64-70



n	3	3	4	4	5	6	6
R	$-CH_3$	$-CH(CH_3)_2$	$-CH(CH_3)_2$	$-n-C_4H_9$	$-CH(CH_3)_2$	$-CH(CH_3)_2$	$-n-C_4H_9$
	64	65	66	67	68	69	70
$[M]^{+\cdot}$	13	12	18	7	6	38	8
$[M - (COR-1)]^{+\cdot}$	94	59	100	100	56	100	100
$[M - (COR-1)-17]^{+}$	12	18	57	21	8	30	12
$[M - (COR-1)-29]^{+}$	45	30	25	13	3	33	19
$[M - (COR-1)-COR]^{+}$	8	13	33	15	5	16	4
$[M - (COR-1)-COR-17]^{+}$	6	13	16	8	2	2	<1
$[M - (COR-1)-COR-29]^{+}$	37	30	13	3	<1	23	13
$[M - 2x(COR-1)]^{+\cdot}$	3	7	15	12	5	16	11
$[M - 2x(COR-1)-17]^{+}$	10	17	29	12	2	12	6
$*[b]^{+\cdot}$	59	35	50	16	2	3	3
$*[c]^{+}$	28	19	36	16	11	16	8
$*[d]^{+\cdot}$	100	100	82	73	31	13	7
$*[e]^{+}$	25	19	67	25	100	73	49
$*[b-29]^{+}$	55	20	25	1	7	10	3
$*[d-17]^{+}$	20	21	29	10	3	8	<1

* For nature of these ions, see Scheme 11



[a]+· Base ion for n=4 and 6
[b]+· Ion significant for n=3 and 4
[c]+ Ion significant for n=3 and 4
[d]+· Base ion for n=3
[e]+ Base ion for n=5

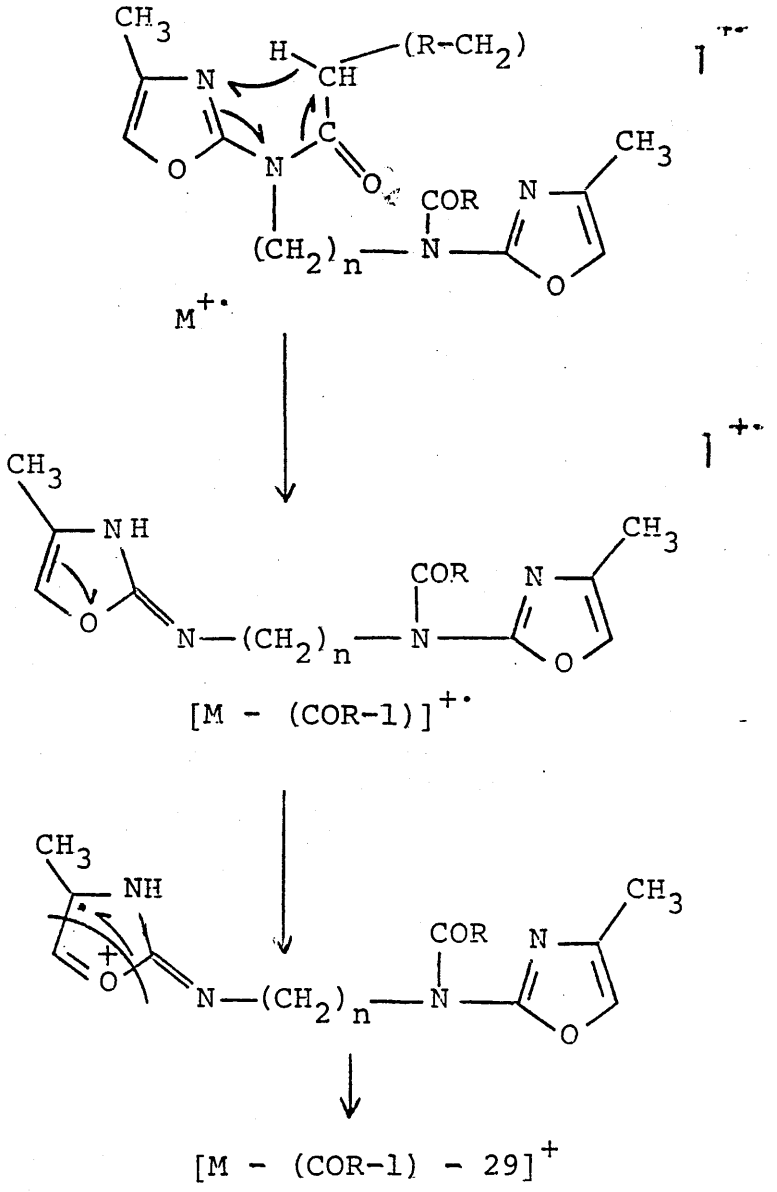
SCHEME 11

As the acyl substituents in 64-70 very readily undergo a McLafferty rearrangement, the spectra have a low intensity molecular ion which does not appear to eliminate a hydroxyl radical. In compounds 66, 67, 69 and 70, when n = 4 or 6, the base ion of the spectrum is the McLafferty rearrangement ion. However, in compounds 64 and 65, when n = 3, and in compound 68, when n = 5, the $[M - (COR-1)]^{+\cdot}$ ion fragments by simple scission of the N-CH_2 bond to give the base ions of m/e 138, 138 and 167 respectively (Scheme 11). The enhanced stability of the ion of m/e 138 is probably due to its existence as a 6--membered fused-ring structure, whilst the ion of m/e 167 probably has a piperidinium structure.

An alternative fragmentation of the oxazole ring involving the loss of 29 mass units (m/e 278→249) was shown with compound 64 (Figure 14) to correspond to the loss of the [CHO] radical. The loss of this radical was observed from several ions for compounds 64-70. The $[M - (COR-1)-29]^{+}$ ion was most abundant for compounds 64, 65, 69 and 70, ie. when n = 3 or 6, whereas in compounds 66-68, when n = 4 or 5, the loss of the hydroxyl radical was favoured. As the loss of the [CHO] radical is not dependent on the length of the methylene bridge, the eliminated hydrogen atom may originate from the oxazole ring (Scheme 12) rather than from the methylene groups.

Although the mass spectra of compounds 64-70 show a second McLafferty rearrangement, the second acyl substituent is more readily lost by simple scission of the N-COR bond. Both the $[M - (COR-1) - COR]^{+}$ and $[M - 2\chi(COR-1)]^{+\cdot}$ ions

lose a hydroxyl radical, but the former ion preferentially loses a [CHO] radical. Ions [b-e] (Scheme 11) are formed following either one or two McLafferty rearrangements and the scission of the N-CH_2 bond. Whereas ion $[b]^{+\cdot}$ eliminates a [CHO] radical, ion $[d]^{+\cdot}$ preferentially loses a hydroxyl radical, perhaps indicating the involvement of the exchangeable hydrogen in the latter elimination as discussed in Section C2biii.

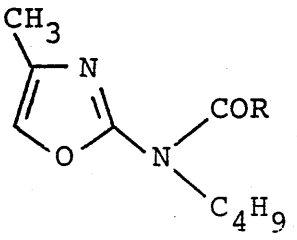


SCHEME 12

In view of the numerous competing fragmentations of 64-70 so far discussed, no correlation was expected between the abundance of the ions formed following loss of a hydroxyl radical and the length of the methylene bridge. When the methylene bridge contains three or four carbon atoms 64-67 the abundance of the $[M - (COR-1) - 17]^+$ ion is similar to its level observed for 2-[acyl(alkyl)amino]oxazoles, whilst for five and six carbon atoms, the formation of this ion is less favoured. Hence, a graph of the abundance of this $[M - (COR-1) - 17]^+$ ion plotted against the length of the methylene bridge (Figure 15) shows a significant maximum at n = 4. Consequently, assuming the elimination of the hydroxyl radical proceeds by a mechanism similar to that suggested for 14a, little steric influence on the formation of the cyclic intermediate prior to loss of the radical is observed for 64-67 when n = 3 or 4. A preferred chain length of four methylene units for optimum hydroxyl radical elimination is also observed for the further fragmentations $[M - (2\ COR-1) - COR - 17]^+$, $[M - 2(COR-1) - 17]^+$ and $[d-17]^+$. As with the 2-[acyl(alkyl)amino]oxazoles, the abundance of the ions from 66-67 and 69-70 (n = 4 and 6 respectively) formed following loss of a hydroxyl radical, are significantly higher for the isopropyl than for the butyl substituents.

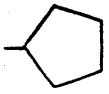
e. N-Butyl-N-(4-methyloxazol-2-yl)cycloalkyl-amides

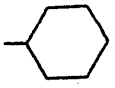
Compounds 71-75 and compound 14a fragment in an analogous manner (Scheme 4, page 32), although the spectrum (Figure 16) of compound 71 shows an additional $[M-CO]^{+\cdot}$ ion and abundant m/e 137 and acylium ions.

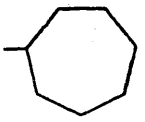


71 R = 

72 R = 

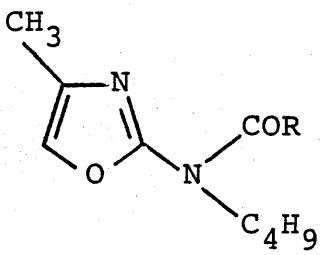
73 R = 

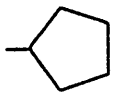
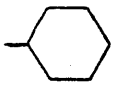
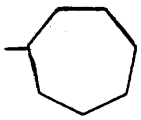
74 R = 

75 R = 

The enhanced abundance of the c-C_3H_5-acylium ion can be attributed to the well-known stability of the cyclopropyl cation. The relative intensity of the molecular ion from 71-75 increases with decreasing ring size of the substituent whilst the abundance of the $[R-C\equiv O]^+$ ion (Table 8) formed following scission of the N-COR bond is only significant for the cyclopropyl compound. For the two compounds containing the largest rings, significant amounts of the carbonium ion $[R]^+$ are observed. This data complements the previous findings that the m/e 154 and m/e 137 ions vary in relative abundance with the acyl substituent, although the latter substituent does not itself lose hydrogen directly in the elimination of the hydroxyl radical.

Table 8 Selected ion relative abundances in the spectra of compounds 71-75



	R		m/e						
		$M^{+\cdot}$ [a]	154	137	124	111	98	$[R]^+$	$[R-C\equiv O]^+$
71		32(222)	100	64	9	29	25	11	67
72		10(236)	100	26	>1	12	8	9	5
73		9(250)	100	30	3	11	7	11	6
74		3(264)	100	19	3	15[b]	8	34	15[b]
75		1(278)	100	31	5	17	13	29	6

a Molecular ion in brackets.

b Both $[C_5H_7N_2O]^+$ and $[R-C\equiv O]^+$ ions contribute to abundance.

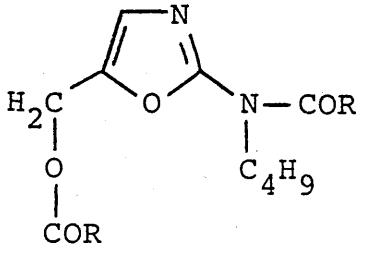
f. 2-[Acyl(alkyl)amino]oxazoles containing a 5-substituent

i. Introduction

Although 5-alkyl substituted 2-[acyl(alkyl)-amino]oxazoles fragment similarly to 14a, it was anticipated that introduction of an oxygen-containing substituent into the 5-position on the oxazole ring might encourage fragmentation at this site and hence affect the elimination of the hydroxyl radical. Consequently, compounds containing an appropriate hydroxy, alkoxy or acetoxy substituent were analysed.

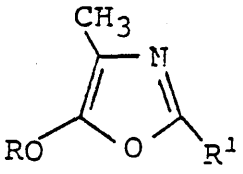
ii. Results and discussions

The presence of a 5-alkyl substituent does not significantly affect the fragmentation of 2-[acylamino]-oxazoles (Scheme 4, page 32), although the abundance of the $[M - (COR-1) - 17]^+$ ion is reduced relative to that of 14a in compounds 23 (5-cyclohexyl) and 25 (5-phenyl). However, the introduction of a 5-acetoxymethyl (76) or 5-isobutyroxymethyl (77) substituent into the oxazole ring considerably modifies the mass spectral behaviour (Figures 17 and 18).

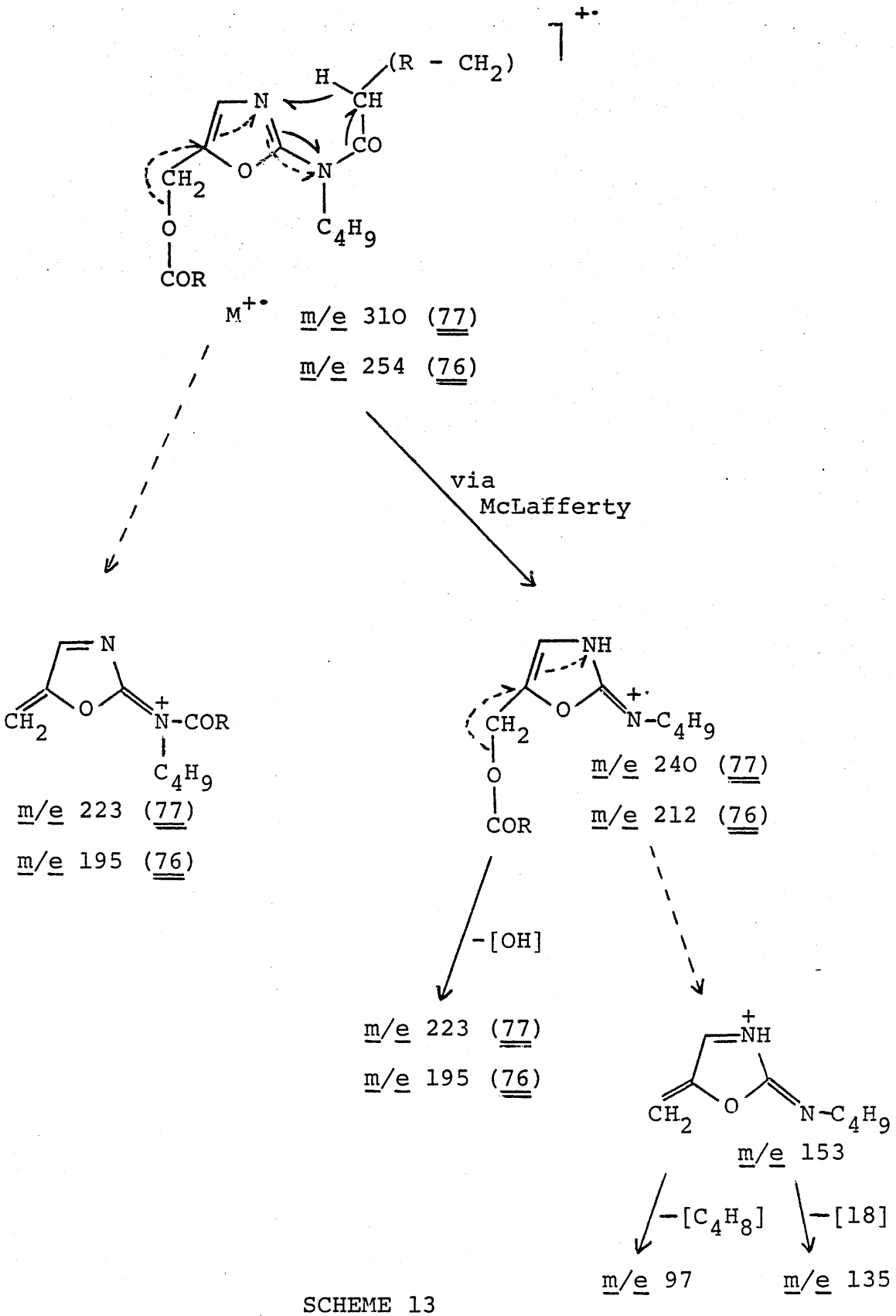


76 R = CH_3 77 R = $CH(CH_3)_2$

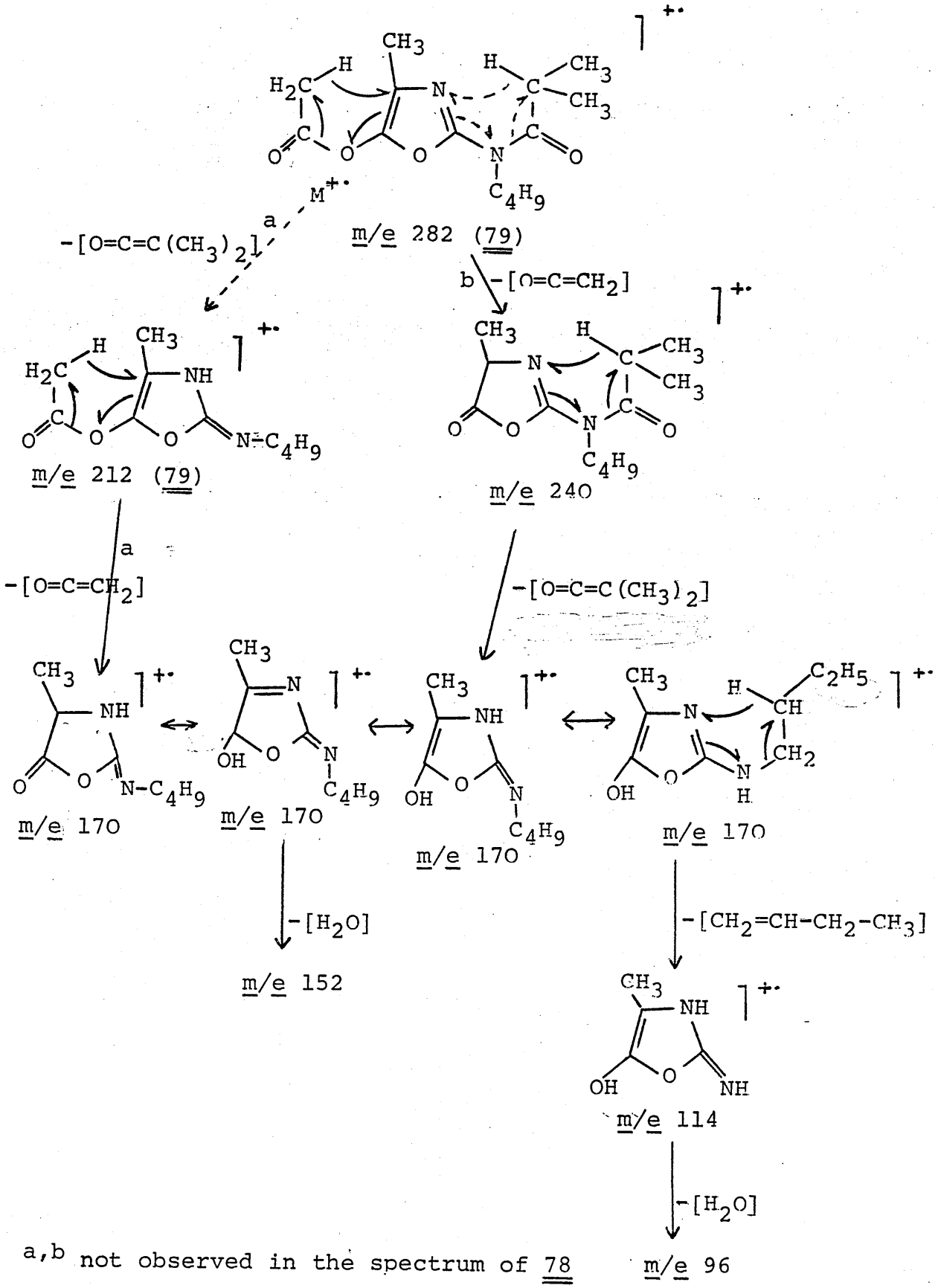
The acyl substituent attached to the nitrogen atom is lost following a McLafferty rearrangement (Scheme 4, page 32), but the $[M - (COR-1)]^{+\cdot}$ ion then fragments by scission of the CH_2-O bond to give an ion of m/e 153 (Scheme 13). The stability of the latter conjugated ion probably encourages this fragmentation. Ions of m/e 195 and 223 are formed following initial loss of the O-acyl substituent. The loss of a hydroxyl radical from the $[M - (COR -1)]^{+\cdot}$ ion is not significant, whereas the ion of m/e 153 loses 18 a.m.u., probably water. A more significant fragmentation of this ion involves formation of the ion of m/e 97. In contrast, the mass spectrum of 14a shows a significant ion of m/e 98 (see section C2ai). The mass spectra of both 2-methyl-N-butyl-N-(5-hydroxy-4-methyloxazol-2-yl)propanamide 78 and 2-methyl-N-(5-acetoxy-4-methyloxazol-2-yl)-N-butylpropanamide 79 (Figure 19) reflect the presence of a 5-substituent linked to the oxazole ring by an oxygen atom. The spectrum of 79 shows that the molecular ion undergoes two McLafferty rearrangements (Scheme 14) to form the base ion of m/e 170. The same base ion is observed for the 5-hydroxy compound following only one rearrangement, but without the aid of labelling studies, no conclusion can be made on the origin of the oxygen atom lost in the subsequent elimination of water from the m/e 170 ion.



	R	R^1
78	H	$N(C_4H_9)$-$COCH(CH_3)_2$
79	$COCH_3$	$N(C_4H_9)$-$COCH(CH_3)_2$
80	C_2H_5	$CH(CH_3)_2$


(R - CH2)
M+•
m/e 310 (77)
m/e 254 (76)
via McLafferty
m/e 223 (77)
m/e 195 (76)
m/e 240 (77)
m/e 212 (76)
-[OH]
m/e 223 (77)
m/e 195 (76)
m/e 153
-[C4H8]
-[18]
m/e 97
m/e 135

SCHEME 13

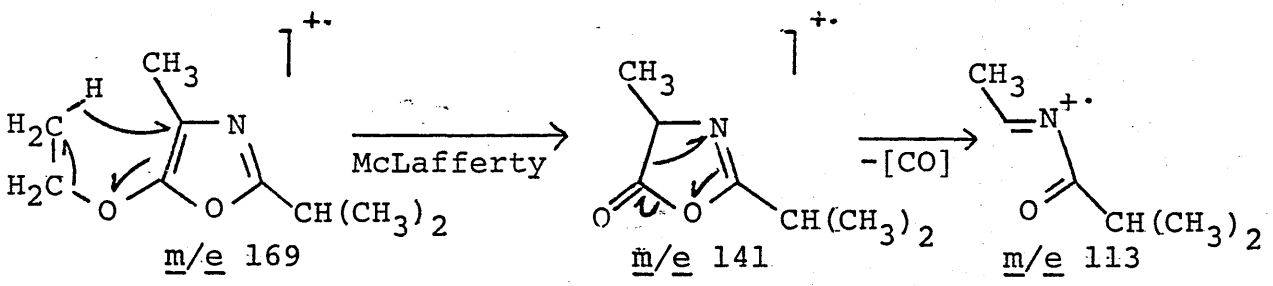


a,b not observed in the spectrum of 78

SCHEME 14

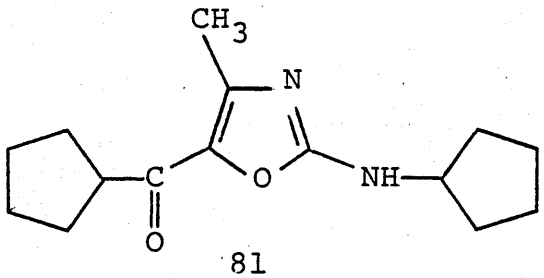
Alternatively, the ion of m/e 170 can undergo a further McLafferty rearrangement to form the ion of m/e 114, which then eliminates water to form an m/e 96 ion.

A 2-[acyl(alkyl)amino]oxazole containing a 5-alkoxy group was not available for analysis. However, the mass spectrum of 5-ethoxy-2-isopropyl-4-methyloxazole (80) suggests that the formation of a 5-oxazolidone prior to the elimination of carbon monoxide (Scheme 15) may be a likely mode of fragmentation.



SCHEME 15

Whilst the elimination of a hydroxy radical is considerably lowered by the presence of a 5-cyclohexyl-carbonyl group, it is negligible for N-(5-cyclopentylcarbonyl--4-methyloxazol-2-yl)cyclopentylamine (81). Although the 2-cyclopentylamine substituent reduces the same elimination for 81 (cf. compound 73), the 5-cyclopentylcarbonyl substituent is responsible for its suppression to negligible levels.



81

Hence, 76-81 show different mass spectral behaviour to that of 14a, in particular suppressing or eliminating the hydroxyl radical elimination.

g. N-Butyl-N-(4-methyloxazol-2-yl)benzamides

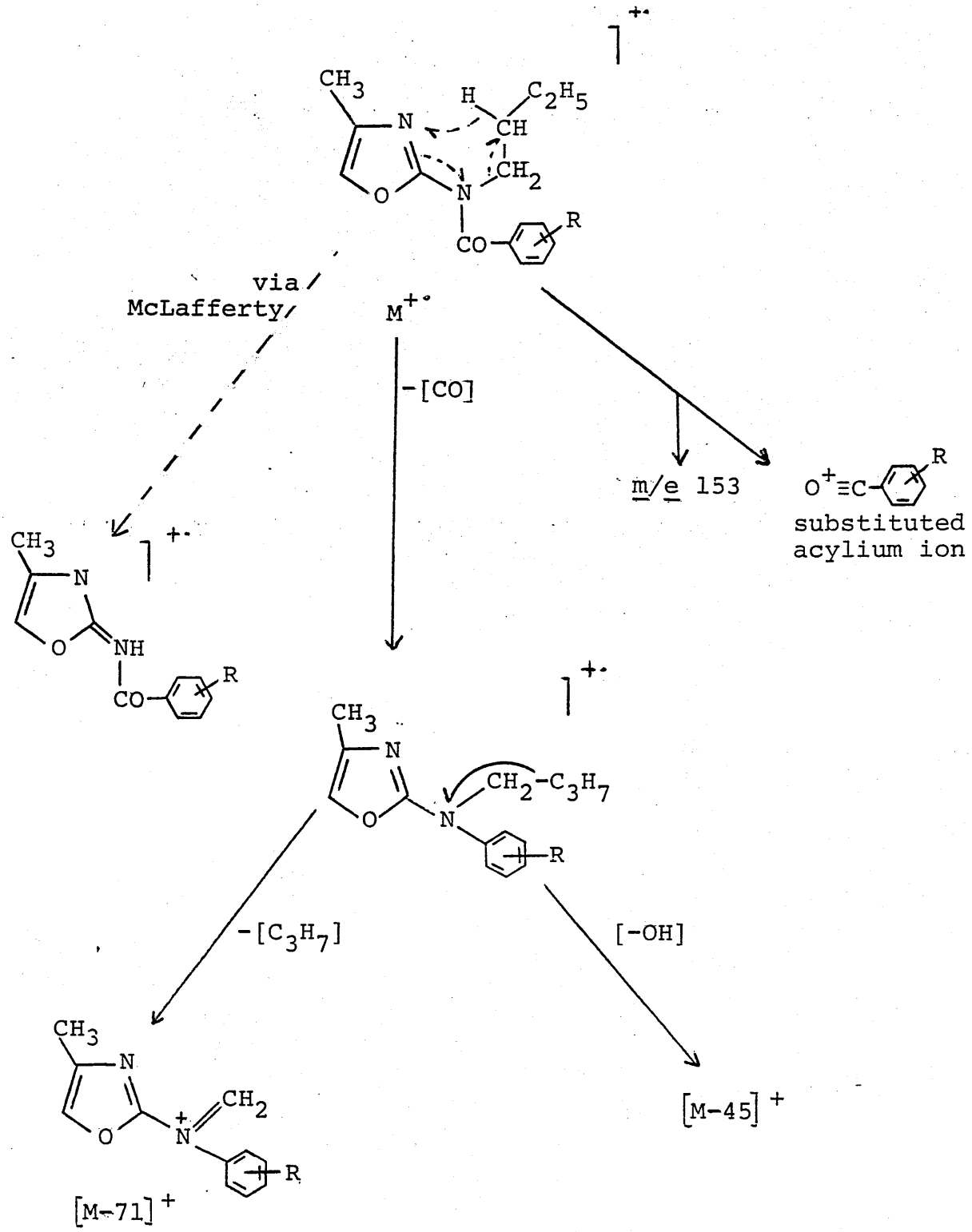
i. Introduction

The mass spectra of the N-butyl-N-(4--methyloxazol-2-yl)benzamides (82-93) are compared with the spectra of the 2-[acyl(alkyl)amino]oxazoles. The absence of a hydrogen in the acyl group in a γ-position to the endocyclic nitrogen precludes the McLafferty rearrangement (Scheme 4, page 32).

ii. Results and discussions

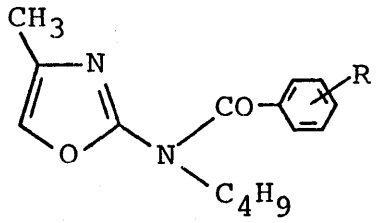
The mass spectra of oxazolylbenzamides 82-93 are very simple (Table 9) in which the m/e 153 ion and corresponding acylium ion, formed by scission of the N-CO bond, are prevelant. The molecular ion also loses carbon monoxide to form an ion which, in turn, eliminates a hydroxyl radical to give an $[M-45]^+$ ion. An $[M-17]^+$ ion is observed for 92-93, the oxygen probably arising from the nitro-group.

In the absence of a γ-hydrogen atom on the benzene ring, selected compounds undergo a McLafferty rearrangement involving the butyl chain to give an $[M-56]^{+\cdot}$ ion. Ions of m/e $[M-71]^+$ probably arise from the loss of both carbon monoxide and a propyl radical. The mass spectra (Figures 20 and 21) of the 2-chloro (85) and 2-methoxy (86) compounds can be readily distinguished from their 3- and 4-isomers 82 and 89 (Figures 22 and 22b) and 85 by the presence of $[M-35]^+$ and $[M-31]^+$ ions, the enhanced stability of the ortho-substituted compounds being due to the formation of ions with a fused ring structure (Scheme 17).


via McLafferty
M+·
-[CO]
m/e 153
substituted acylium ion
-[C3H7]
[-OH]
[M-71]+
[M-45]+

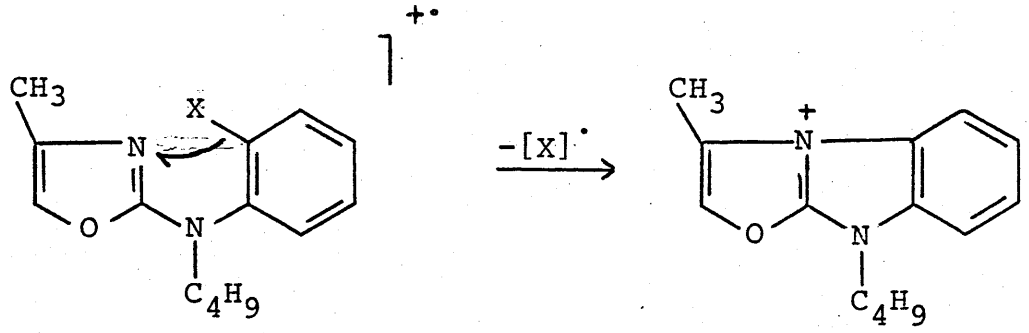
SCHEME 16

Table 9. Selected ion relative abundances in the mass spectra of N-butyl-N-(4-methyloxazol--2-yl)benzamide at 20 eV



	R	$M^{+\cdot}$ [a]	$[M-28]^{+\cdot}$	$[M-45]^{+}$	$[M-56]^{+\cdot}$	$[M-71]^{+}$	$[R-C\equiv O]^{+}$	m/e 154	153	137	97
82	3-Cl	43 (292)	11	21	6	8	100	5	45	12	23
83	4-F	32 (276)	7	10	4	3	100	2	19	10	11
84	H	24 (258)	9	10	2	1	100	2	10	6	5
85	2-Cl	7 (292)	7	12	<1	7	100	1	15	1	6
86	2-OCH_3	<1 (288)	<1	2	<1	<1	100	<1	<1	1	<1
87	4-OCH_3	17 (288)	2	1	<1	<1	100	<1	<1	1	<1
88	4-CH_3	8 (272)	2	<1	<1	<1	100	<1	1	1	<1
89	4-Cl	27 (292)	2	12	3	3	100	1	12	8	10
90	3-CF_3	21 (326)	6	15	7	7	100	6	60	17	46
91	3,4-diCl	37 (326)	9	9	20	<1	100	6	60	12	29
92	3-NO_2	38 (303)	8	24	18	16	100	16	135	27	104
93	4-NO_2	86 (303)	26	5	25	28	100	15	152	25	86

[a] Molecular ion in brackets



SCHEME 17

h. Substituent effects on the relative intensity of the molecular and acylium ions in the mass spectra of N-butyl-N-(4-methyloxazol-2-yl)-benzamides

i. Introduction

The most frequently employed quantitative correlation in solution chemistry is the Hammett equation,[44] which relates the rules of reaction of meta and para substituted aromatic compounds with changing substituent

$$\log K/K_0 = \rho\sigma \qquad (1)$$

where K and K_0 are rates of reaction of substituted and unsubstituted compounds respectively, σ is a substituent constant which gives a measure of the ability of the substituent to influence the electronic distribution at the reaction site and ρ is a reaction constant which is a measure of the sensitivity of the reaction to changes in the electron density at the reaction site.

McLafferty was able to extend this concept to correlate the electron impact mass spectra of a number of substituted benzophenones.[45-47] He showed that the rate of fragmentation, measured as a parent to daughter ion ratio, was related to the substituent constant of the group (R).

$$[R\text{-}C_6H_4COX]^{+\cdot} \xrightarrow{K} [COX]^+ + R\text{-}C_6H_4\cdot \qquad (2)$$

Further applications[48-50] of this simple steady state kinetic approach are limited, as it is assumed in (2) that the fragmentation of the molecular ion alone affects the relative abundance of the $[COX]^+$ ion. In practice, other

parameters[51] such as the internal energy distribution of the $M^{+\cdot}$ ion, competitive fragmentation of the $M^{+\cdot}$ ion and further fragmentation of the product ion, minimise the success of attempted correlations.

ii. Results and discussion

No correlation was observed between the relative intensity of ions present in the mass spectra (20 eV) of N-butyl-N-(4-methyloxazol-2-yl)benzamides. However, on reducing the ionising voltage to 10 eV, only three ions, $M^{+\cdot}$, $[M - CO]^{+\cdot}$ and $[R-C_6H_4-C\equiv O]^{+}$, (Scheme 16) were observed. Calculation of relative ion intensities from the lower voltage spectra showed that the ratios of ions $M^{+\cdot}$ over $[R-C_6H_4C\equiv O]^{+}$ were related to the substituent constants of the group R (Table 10). At 20 eV the same calculation produced only a scatter of data. Figure 23 indicates that a Hammett correlation is obtained for the $M^{+\cdot}$ and $[R-C_6H_4-C\equiv O]^{+}$ ions except for the nitro-compounds (92 and 93). Previous workers[52] have also observed a similar lack of correlation for these compounds, which they believe is due to the ability of the nitro-substituent to form intermediate resonance ions and hence stabilise the molecular ion.

No correlation was observed in the fragmentation involving the elimination of carbon monoxide. Lack of correlation in this latter fragmentation may imply the occurrence of a rearrangement reaction, prior to or during fragmentation of the molecular ion, which loses the orientation of the substituent.

Table 10. Calculation of the effect of the substituent (R) on the fragmentation of the molecular ion to the $[R\text{-}C_6H_4\text{.}C{\equiv}O]^+$ ion, in the mass spectra of N-butyl-N-(4-methyloxazol-2-yl)benzamides at 10 eV

	R	$\frac{10^2\,[R\text{-}C_6H_4\text{-}C{\equiv}O^+]}{M^{+\cdot}}$	$2+\log \frac{[R\text{-}C_6H_4\text{-}C{\equiv}O^+]}{M^{+\cdot}}$	σ
82	3-Cl	2.10	0.320	0.37
83	4-F	6.70	0.826	0.06
84	H	4.59	0.661	0.00
87	4-OCH_3	40.00	1.602	-0.27
88	4-CH_3	24.90	1.396	-0.17
89	4-Cl	4.30	0.633	0.23
90	3-CF_3	1.45	0.161	0.43
92	3-NO_2	0.01	<0.001	0.71
93	4-NO_2	2.10	0.322	0.78

THE MASS SPECTRA OF OTHER 5-MEMBERED HETEROCYCLES CONTAINING AN ACYL(ALKYL)AMINO-SUBSTITUENT

D. The Mass Spectra of other 5-membered Heterocycles Containing an Acyl(alkyl)amino-substituent

1. Introduction

The mass spectra of further 2-[acyl(alkyl)amino]-heterocycles were examined to determine to what extent these compounds also fragment by loss of the heteroatom with scission of both carbon-hetero bonds. Compounds were analysed in which the N-alkyl substituent contained at least three methylene groups, and whose spectra, by analogy to those of the oxazole series, might be expected to show the loss of a simple radical containing the heteroatom. In all, a further twelve 5-membered heterocyclic series were examined.

To aid comparison with the oxazole series, the mass spectral behaviour of these additional heterocyclics was examined at 20 eV although literature spectra were invariably obtained using an ionising voltage of 70 eV.

2. Compounds with one heteroatom in the ring

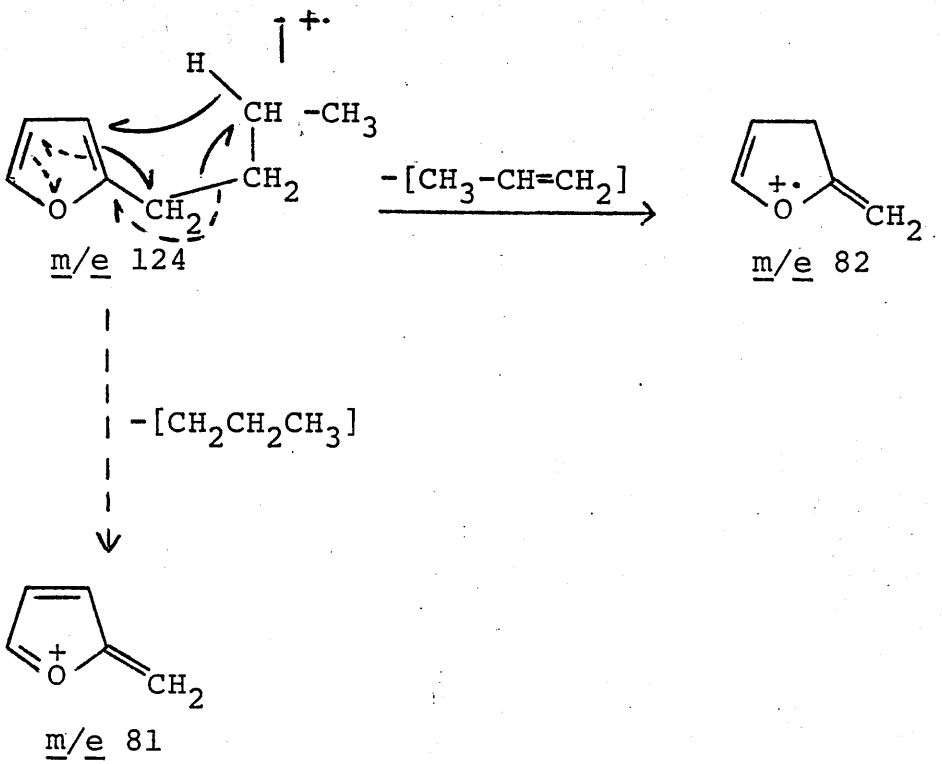
a. Furans, thiophenes and N-methylpyrroles containing a 2-acyl(alkyl)amino-substituent

i. Literature survey of selected furans, thiophenes and pyrroles

The mass spectrum of furan[53,54] shows an intense molecular ion which fragments by elimination of a formyl radical, thereby forming a cyclopropenyl ion. 2-Alkylfurans containing only small substituents (methyl or ethyl) fragment[55,56] similarly, but with larger substituents[55,57] ring fragmentation becomes less important and scission of the side-chain dominates. Typically for 2-butylfuran,[58] a propyl radical is lost by β-scission or propene is lost by a McLafferty rearrangement (Scheme 18). Alkyl 2-furyl ketones[55] will similarly undergo a rearrangement. Loss of a hydroxyl radical has not been reported for 2-substituted furans.

Thiophene has a spectrum[59] similar to that of furan, losing the [CHS] radical and acetylene from the molecular ion. For 2-alkylthiophenes[60] the base peak is the $[C_5H_5S]^+$ ion (m/e 97), resulting from β-scission of the alkyl substituent. This ion probably has a thiabenzene ~~thiopyrilium~~[61] structure and is analagous to the ring expanded tropylium ion formed from alkylbenzenes. Only for compounds such as thienyl ketones containing a large aliphatic side-chain, for instance, 2-acetyl-5-isovalerylthiophene,[62] is the alkyl group lost by rearrangement. Loss of the sulphur heteroatom in thiophenes as an [SH] radical has again not been reported.

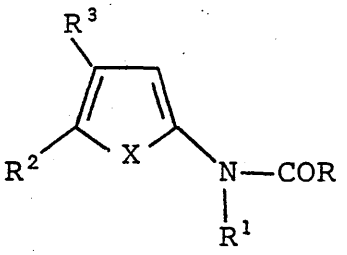
The molecular ion from pyrrole[63] fragments in a variety of ways by loss of HCN, C_2H_2 and the radicals $[C_2H_3]$, $[C_3H_3]$ and $[CH_2N]$. β-Cleavage is the predominant fragmentation of long-chain 2-alkylpyrroles, although in contrast to 1-alkylpyrroles, no detailed study has yet been reported.



SCHEME 18

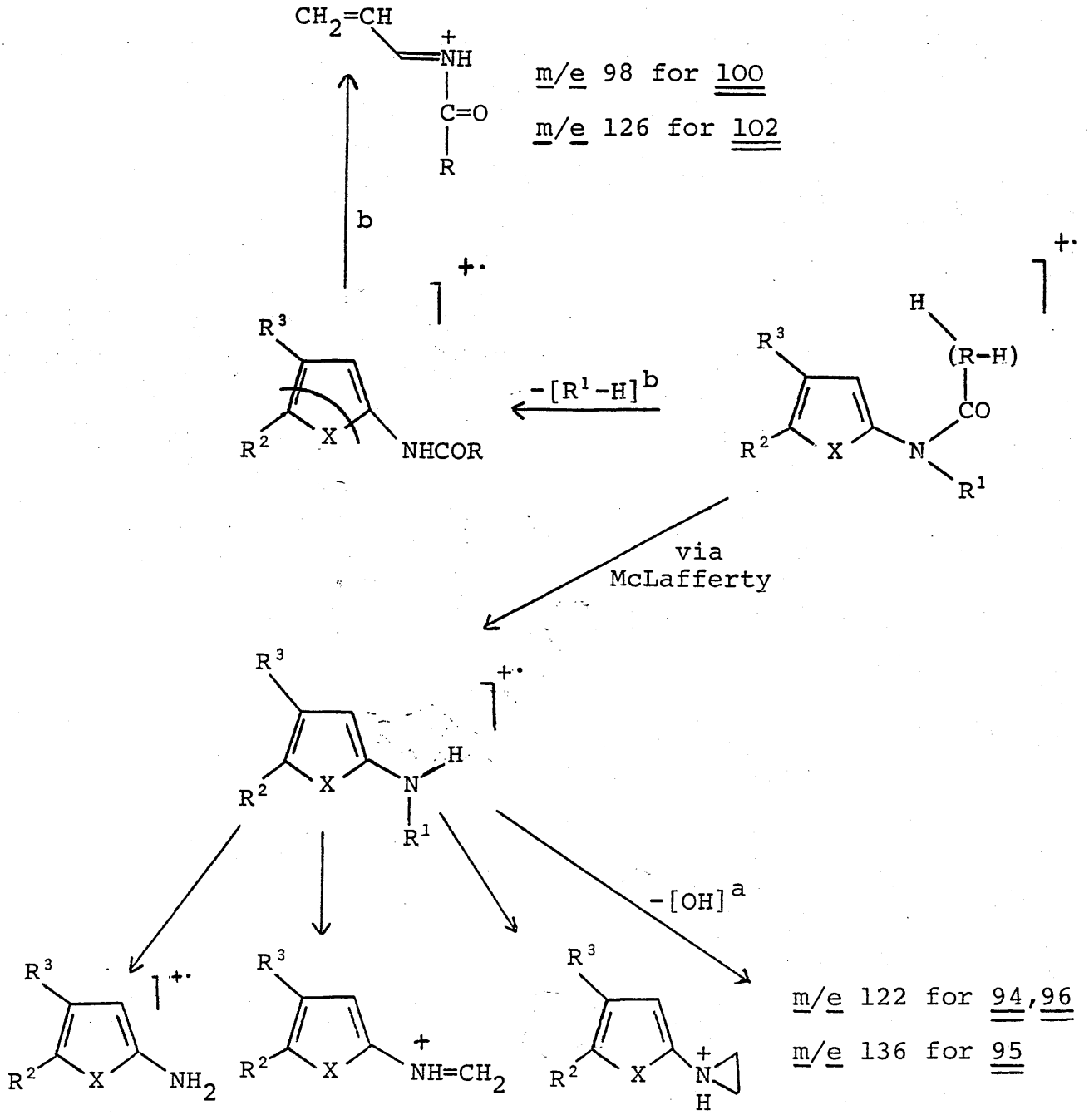
ii. Results and discussion

The mass spectra of furans and thiophenes containing a 2-acyl(alkyl)amino-substituent (Figures 24 and 25 for 94 and 97) are characterised by the loss of the acyl group (Scheme 19) through a McLafferty rearrangement and subsequent fragmentation of the N-alkyl group. Scission of the CH_2-CH_2 bond adjacent to the nitrogen atom is then the ensuing more abundant fragmentation pathway.



	X	R	R^1	R^2	R^3
94	O	CH_3	C_4H_9	H	H
95	O	i-C_3H_7	C_4H_9	CH_3	H
96	O	i-C_3H_7	C_4H_9	H	H
97	S	cyclo-C_3H_5	C_4H_9	CH_3	H
98	S	i-C_3H_7	$(CH_2)_5CH_3$	CH_3	H
99	S	i-C_3H_7	C_4H_9	CH_3	H
100	N-CH_3	CH_3	C_4H_9	H	H
101	N-CH_3	i-C_3H_7	C_6H_{13}	H	H
102	N-CH_3	i-C_3H_7	C_4H_9	H	H

2-[Acyl(alkyl)amino]N-methylpyrroles (e.g. 100, Figure 26) have a more abundant molecular ion and lose the acyl group both by rearrangement (Scheme 19) and simple scission. Fragmentation of both heterocyclic C-X bonds and elimination of an [XH] radical is only observed for the furans 94-96 through loss of a hydroxyl radical. Although the transition is supported by a metastable ion peak, the resultant m/e 122 (94, 96) and m/e 136 (95) ions are of low abundance (<1%). The absence of a comparable elimination and a more abundant molecular ion (Table 11) for the thiophenes 97-99 may reflect the greater aromatic character of thiophenes compared with furan.



[a] furans only

[b] significant for N-methylpyrroles only

SCHEME 19

An even more abundant molecular ion is observed in the spectra of 2-[acyl(alkyl)amino]pyrroles, which fragment by an alternative ring scission process (Scheme 19) to that of the corresponding furans, possibly analagous to the loss of $[CH_2N]$ from pyrrole. Although the scission process is significant for 100 and 102, it is not observed for 101 for which the longer N-alkyl chain encourages cleavage of the side-chain. The absence or minimal loss of a heteroatom for furans, thiophenes and N-methylpyrroles containing a 2-acyl-(alkyl)amino-substituent probably reflects their greater stability compared with oxazoles.

Table 11. Selected ion relative abundances in the mass spectra of furans, thiophenes and N-methylpyrroles containing a 2-acyl(alkyl)amino-substituent

	$M^{+\cdot}$ [a]	$[M - (R^1-1)]^{+\cdot}$	$[M - O{=}C{-}R]^{+\cdot}$	d	e	f	g	h	j
94	21(181)	<1	<1	100	6	<1	27	30	9
95	23(223)	7	3	100	<1	<1	<1	16	8
96	9(209)	3	<1	100	<1	<1	5	17	12
97	30(237)	<1	9	100	-	<1	2	22	2
98	71(267)	1	<1	100	-	4	4	63	13
99	84(239)	<1	39	100	-	7	9	60	50
100[b]	49(194)	8	20	15	-	15	10	32	22
101	100(250)	27	17	43	-	6	9	39	4
102[c]	100(222)	1	85	61	-	32	2	15	8

[a] molecular ion in brackets

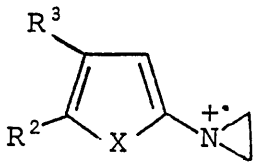
[b] base ion m/e 98 $[CH_2{=}CH{-}CH{=}\overset{+}{N}H{-}COCH_3]$; m/e 42 (55%)

[c] significant ions at m/e 126 (98%) and 70 (23%)

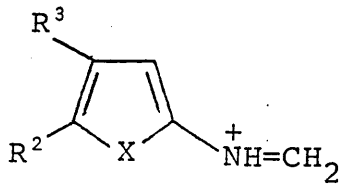
[d] $[M - (O{=}C{-}R - 1)]^{+\cdot}$

[e] $[M - (O{=}C{-}R - 1) - XH]^{+}$

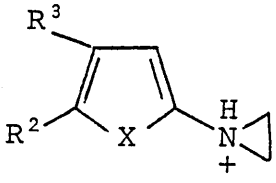
[f]



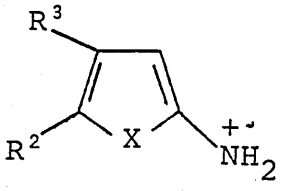
[h]



[g]



[j]



3. Compounds with two heteroatoms in the ring

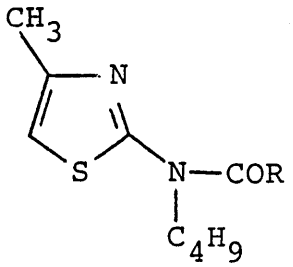
a. Thiazoles and isothiazoles

i. Literature survey of thiazoles and isothiazoles

The molecular ion of thiazole[35] provides the base peak of the spectrum and the only important fragmentation is the loss of HCN. Simple 2-alkylthiazoles also show an intense base ion and only when the alkyl group size is increased to propyl[64] does fragmentation of the substituent by a rearrangement process produce a new base ion. A rearrangement with the loss of acetaldehyde is also an important process for ethyl 4-methylthiazole-2--carboxylate.[35] Although loss of an [SH] radical is not reported for thiazoles, 2-aminothiazole-3-oxides[65] eliminate a hydroxyl radical but the loss does not require scission of the heterocyclic ring. No reference to the mass spectral behaviour of isothiazoles was observed in the literature.

ii. Results and discussion

The 2-[acylamino]thiazoles 103 and 104 show similar spectral behaviour to 2-[acylamino]oxazoles, although their molecular ions are relatively more abundant.

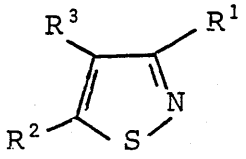


103 R = i-C_3H_7

104 R = CH_3

Their spectra (Figure 27 for 104) show an increase in loss of the N-alkyl group and a decrease in the elimination of the [SH] radical compared with that of the [OH] radical from oxazoles. No ion comparable to that of m/e 154 (Scheme 20) is observed in the oxazole series. The latter ion probably exists in a fused cyclic structure and is the only significant ion not formed via the McLafferty rearrangement.

The mass spectral characteristics of isothiazoles vary with the position of the acylamino-substituent. The spectrum (Figure 28) of the 3-[acylamino]isothiazole (105) shows $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$, $[M - O{=}C{=}C(CH_3)_2 - C_2H_5]^+$, $[M - O{=}C{=}C(CH_3)_2 - C_3H_7]^+$ and $[M - O{=}C{=}C(CH_3)_2 - C_4H_9]^+$ ions of m/e 156, 127, 113 and 100 respectively, similarly to the spectra of the thiazoles 103 and 104. The lower abundance of the molecular ion suggests the isothiazole is less stable than the corresponding thiazole, whilst the elimination of the [SH] radical is barely discernible.

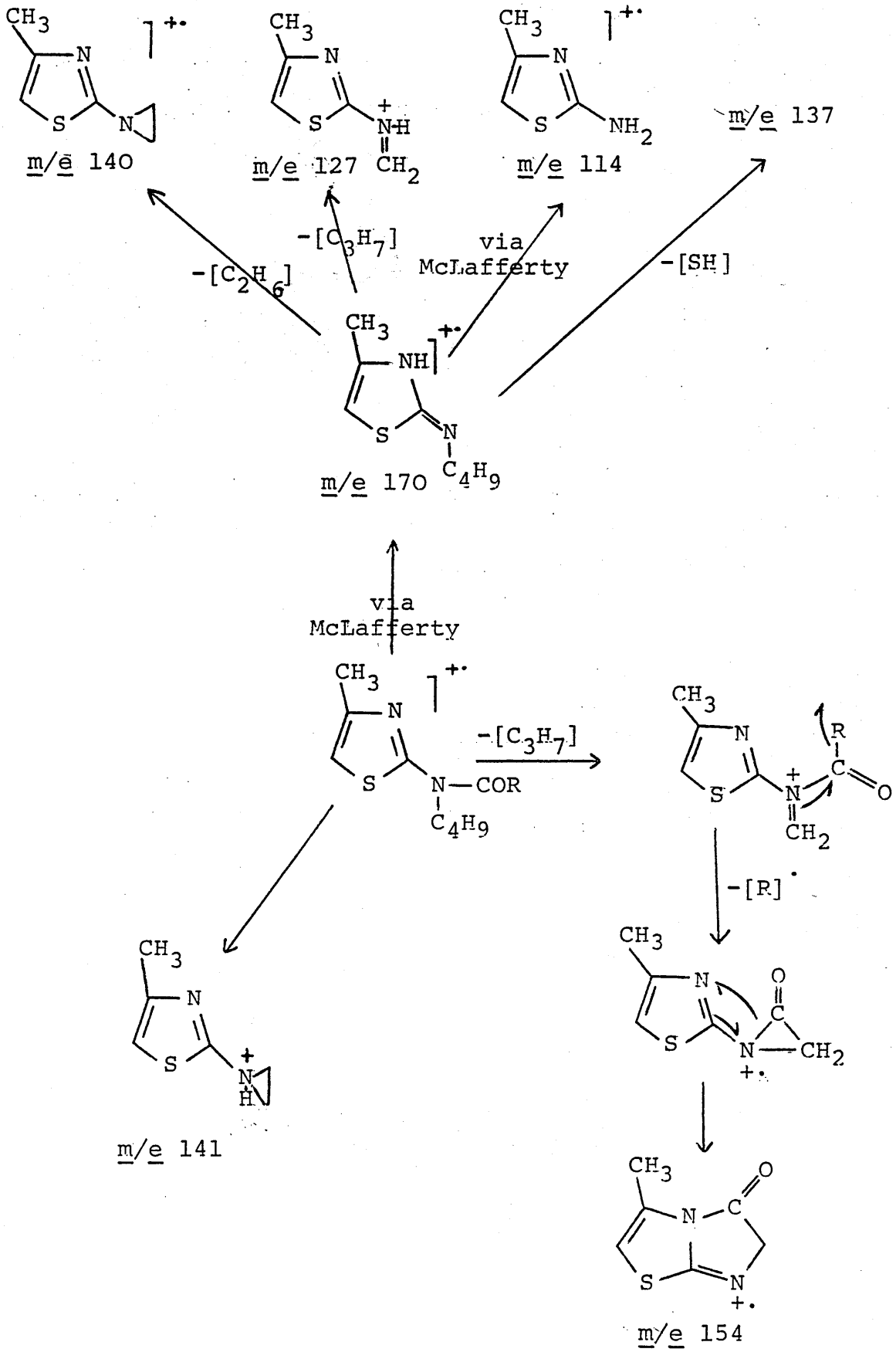


	R^1	R^2	R^3
105	$N(C_4H_9)COCH(CH_3)_2$	H	H
106	CH_3	$N(C_4H_9)COCH(CH_3)_2$	H
107	CH_3	H	$N(C_4H_9)COCH(CH_3)_2$

For compound 106 (Figure 29) the $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$ ion is the most abundant, which although eliminating an [SH] radical shows less of this fragmentation than the comparable ion from 103. Hence, a proximal effect is confirmed for [SH]

extrusion as the radical is only eliminated from isothiazoles when the acylamino group is adjacent to the sulphur atom. In contrast the lack of elimination of a comparable nitrogen containing radical from 105 suggests such a moiety is not lost from [acyl(alkyl)amino]isothiazoles.

For 107 (Figure 30) loss of both the alkyl and acyl substituents by consecutive McLafferty rearrangements is probably encouraged by the relatively small difference in energy between the exocyclic and endocyclic structures involved in the rearrangement. Interestingly, butene rather than the acyl fragment is lost first. No loss of an [SH] radical is observed from this isothiazole.


m/e 140
m/e 127
m/e 114
m/e 137
-[C3H7]
via McLafferty
-[C2H6]
-[SH]
m/e 170
via McLafferty
-[C3H7]
-[R]
m/e 141
m/e 154

SCHEME 20

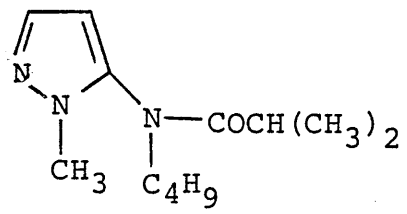
b. 2-Methyl-N-butyl-N-(imidazol-2-yl) propanamide and 2-methyl-N-butyl-N-(1-methylpyrazol-5-yl)-propanamide

i. Literature survey of imidazoles and pyrazoles

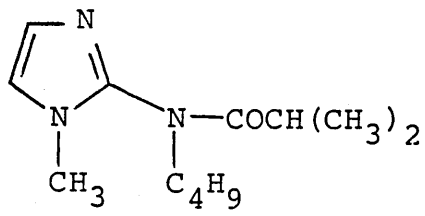
The mass spectra of a limited number of imidazoles and pyrazoles have been reported. The spectrum of imidazole[66] is dominated by loss of HCN whereas the fragmentation of pyrazole[67,68] follows two distinct pathways. Loss of HCN is again the most significant feature, but ions of m/e 28 $[CH_2N]^+$ and m/e 39 $[C_3H_3]^+$ indicate an alternative mode of scission of the molecular ion. Deuterium labelling studies[69-71] indicate that for both imidazoles and pyrazoles, minimal hydrogen scrambling of the molecular ion occurs prior to fragmentation. Significant side-chain rearrangements[72] are reported for 5-styryl and 5-acylpyrazoles involving formation of polycyclic heteroaromatic rings.

ii. Results and discussions

The mass spectral behaviour of the 2-[acyl(alkyl)amino]pyrazole (108) and the 2-[acyl(alkyl)amino]-imidazole (109) is compared with that of the corresponding 2-[acyl(alkyl)amino]oxazole (14a).

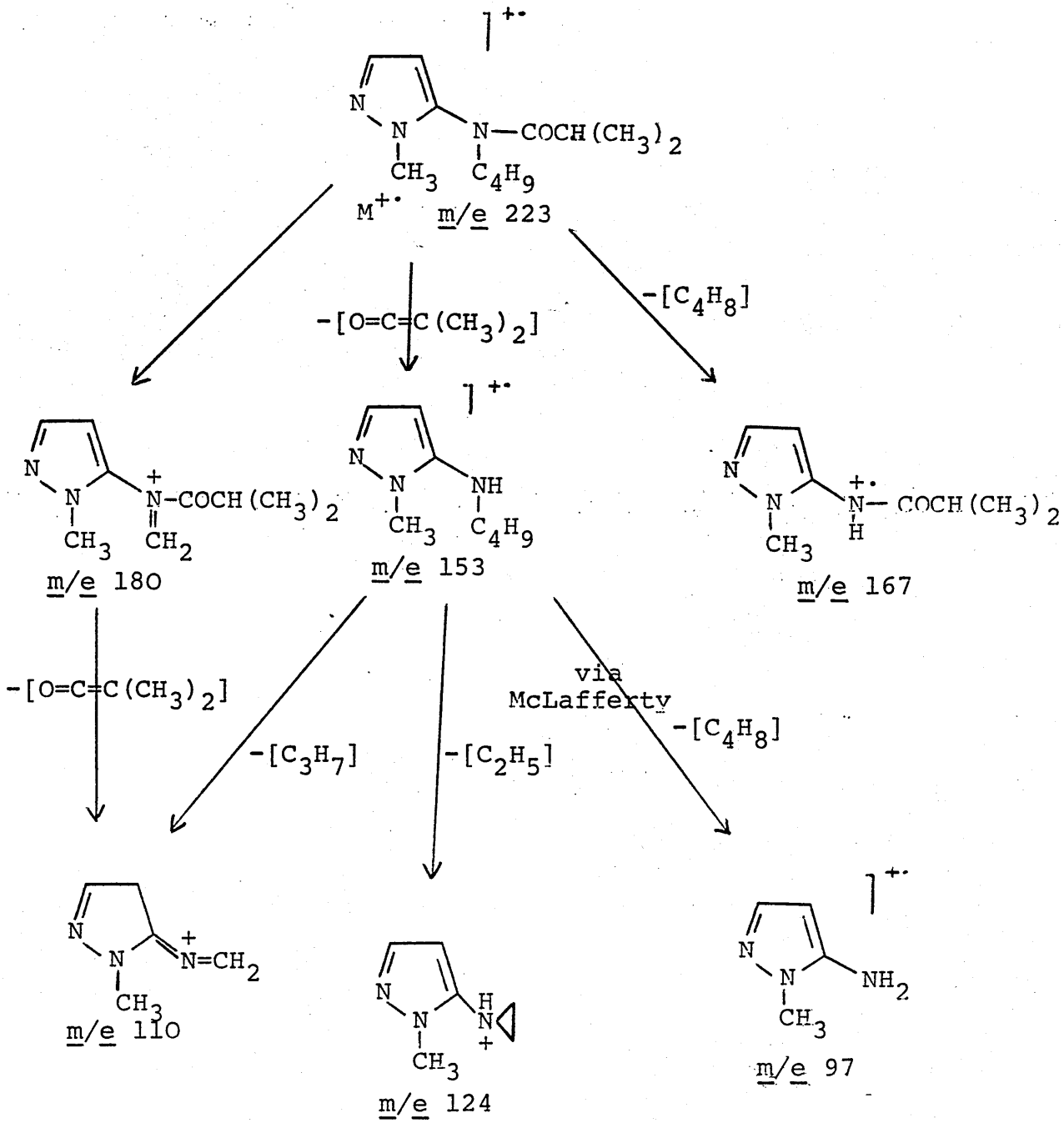


108



109

The spectra (Figures 31 and 32) of 108 and 109 are significantly different although loss of a ring heteroatom is not observed for either molecule. Whereas the fragmentation of the molecular ion from oxazole 14a follows only one pathway *via* the initial McLafferty rearrangement, compound 108 fragments in three ways (Scheme 21). Two pathways involve a McLafferty type rearrangement to lose N-alkyl or N-acyl groups. The fragmentation to give the peak at m/e 180 must arise from simple α-scission of the N-butyl group rather than from loss of the isopropyl radical, as the m/e 180 ion subsequently loses the acyl group to give the base ion of the spectrum of m/e 110. This ion is also formed from the m/e 153 ion $[M - O{=}C{=}C(CH_3)_2]^{+\cdot}$, as observed for the 2-[acyl(alkyl)amino]oxazole (14a). The spectrum of the isomeric 2-[acyl(alkyl)amino]imidazole is considerably simpler, the m/e 180 being the base ion. The increased stability of this ion compared with the similar pyrazole ion is probably due to the ease of delocalisation of the positive charge over the three adjacent nitrogen atoms.


M+· m/e 223
-[O=C=C(CH3)2]
-[C4H8]
m/e 180
m/e 153
m/e 167
-[O=C=C(CH3)2]
-[C3H7]
-[C2H5]
via McLafferty
-[C4H8]
m/e 110
m/e 124
m/e 97

SCHEME 21

4. Compounds with three heteroatoms in the ring

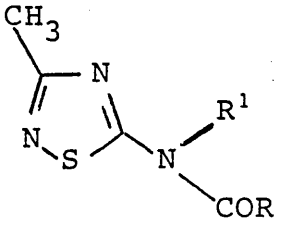
a. 1,2,4-thiadiazoles and 1,3,4-thiadiazoles containing a 2-acyl(alkyl)amino-substituent

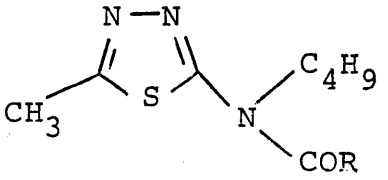
i. Literature survey of 1,2,4-thiadiazoles and 1,3,4-thiadiazoles

The mass spectra of only a small number of 1,2,3- and 1,2,4-thiadiazoles have been reported. As expected the increase in the number of heteroatoms within the 5-membered ring increase the number of fragmentation pathways. Typically, following expulsion of nitrogen, 4,5-alkyl and -acyl substituted 1,2,3-thiadiazoles[73] eliminate both sulphur and the [SH] radical. The loss of a mercapto radical is reported for a series of 3,5-bis(alkyl)isothiazoles but by a mechanism involving elimination of the exocyclic rather than ring sulphur atom.

ii. Results and discussions

The spectra of a group of three 5-[acyl-(alkyl)amino]-1,2,4-thiadiazoles (110-112) and two 2-[acyl-(alkyl)amino]-1,3,4-thiadiazoles (113-114) are compared with those of the 2-[acyl(alkyl)amino]oxazoles.





	R^1	R
110	C_4H_9	i-C_3H_7
111	C_4H_9	$(CH_2)_5CH_3$
112	$(CH_2)_5CH_3$	CH_3

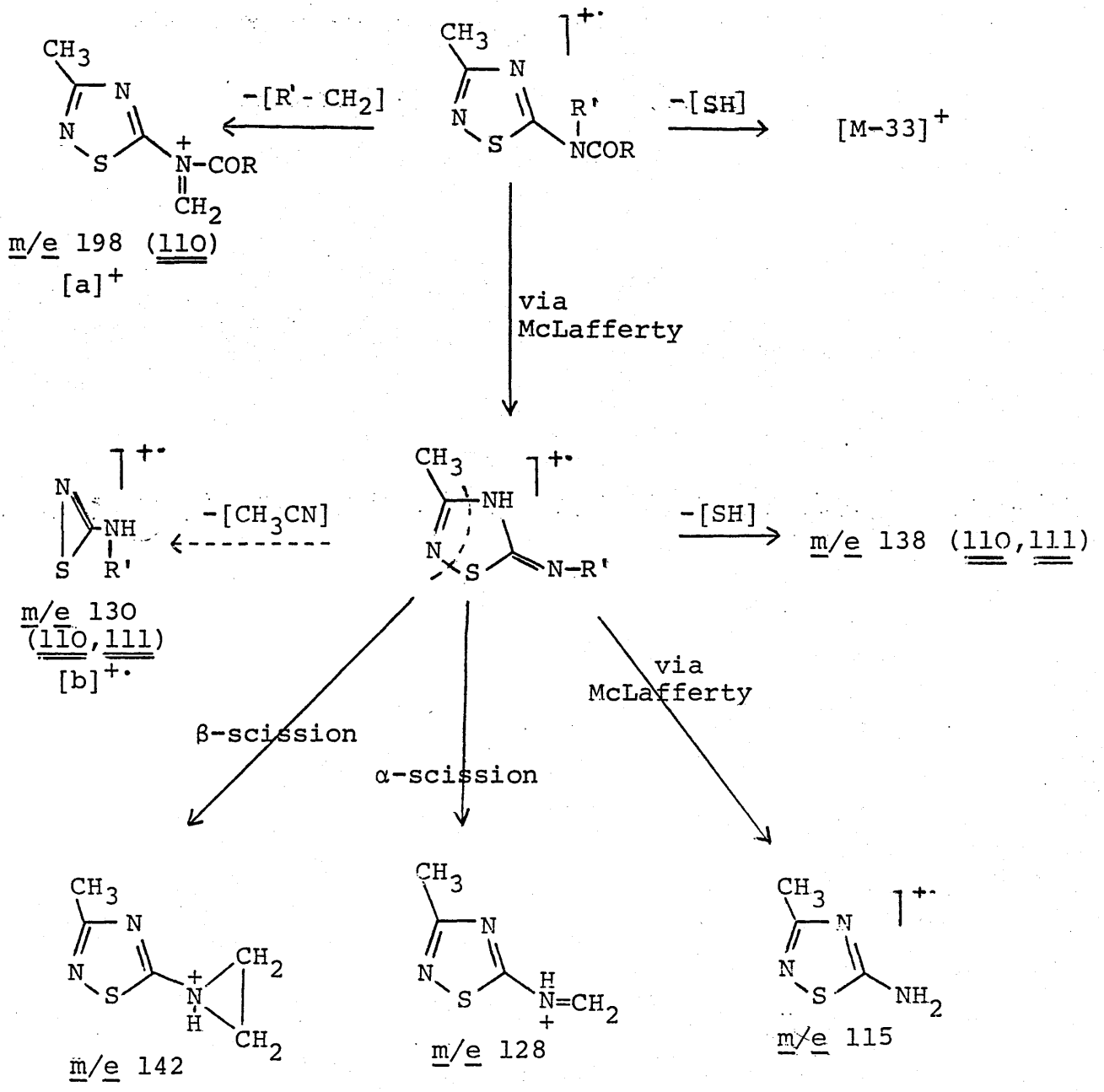
	R
113	i-C_3H_7
114	c-C_3H_5

In addition to the rearrangement of the 2-acylamino--substituent as observed in the spectra of the corresponding oxazoles, 110-112 show the loss of both [R - CH_2] and [SH] radicals (Figure 33 for 110) from the molecular ion (Scheme 22). The $[M - (O{=}C{-}R - 1)]^{+\cdot}$ ion also further fragments not only by scission of the N-alkyl group but by loss of methyl cyanide and the [SH] radical further confirming the greater stability of the oxazole ring over the 1,2,4-thiadiazole ring.

The 1,3,4-thiadiazoles show an even greater number of fragmentation pathways (Scheme 23). For 113 and 114 (Figure 34) the molecular ion loses CO and CH_3CN in addition to loss of the [C_3H_7] and [SH] radicals and rearrangement of the acylamino group. Consecutive losses of CH_3CN and the [SH] radical are observed from the molecular ion. The loss of the [SH] radical before and after CH_3CN elimination can take place by similar mechanisms, as the 1, 2 and 3 positions in the ring-opened heterocyclic ion can still participate in the elimination of an [SH] radical.

The greater stability of the 1,2,4-thiadiazoles over the 1,3,4-thiadiazoles is exemplified in the abundances of their respective molecular ions (Table 12). Whereas for 110-112, [SH] radical loss is more significant from the $M^{+\cdot}$ ion than from the $[M - (O{=}C{=}R - 1)]^{+\cdot}$ ion, it is less significant for the 1,3,4-thiadiazoles (113 and 114). Interestingly, for the 1,2,4-thiadiazoles, loss of the [SH] radical is most significant for 112 ($R^1 = (CH_2)_5CH_3$), when the $[M-33]^+$ ion becomes the base ion. If it is assumed that the acyl group does not play a significant role in the elimination, reduction

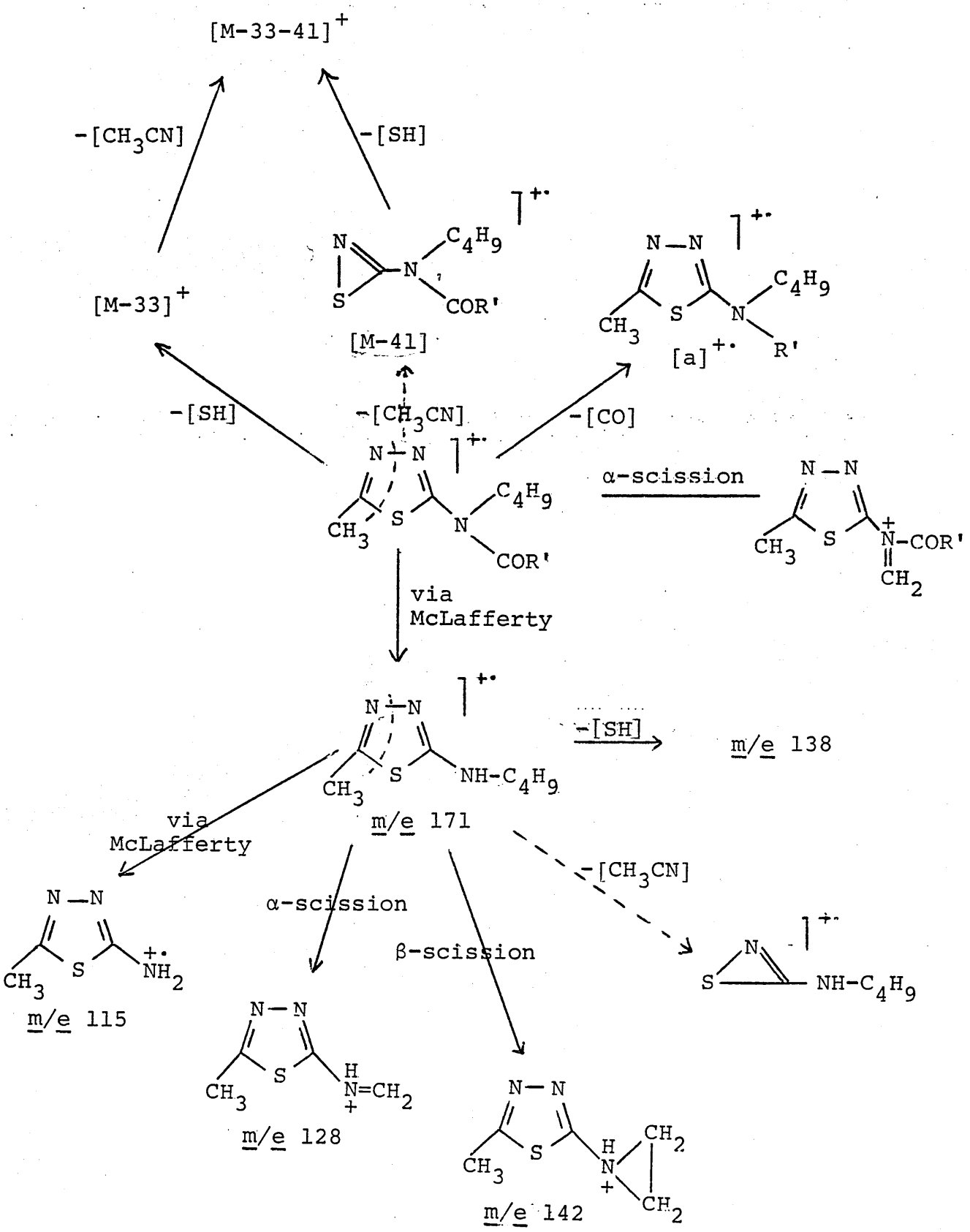
of the N-alkyl chain length to four carbon atoms reduces the level of the $[M-33]^+$ ion. This situation contrasts with that for the 2-[acyl(alkyl)amino]oxazoles, when maximum elimination of the [OH] radical occurs with a corresponding N-alkyl group chain length of 4-5 carbon atoms, although this latter elimination does not occur from the molecular ion.



[a]$^{+}$ Significant only for compound 111

[b]$^{+\cdot}$ Base ion for compound 111

SCHEME 22



[a]+· Significant only for 113

SCHEME 23

Table 12. Selected ion relative abundances in the mass spectra of 5-[acyl(alkyl)amino]--1,2,4-thiadiazoles and 2-[acyl(alkyl)amino]-1,3,4-thiadiazoles

	$M^{+\cdot}$ [a]	$[M - SH]^+$	$[M - (O{=}C{-}R{-}1)]^{+\cdot}$	$[M - (O{=}C{-}R{-}1) - CH_3CN]^{+\cdot}$	$[M - (O{=}C{-}R{-}1) - SH]^+$
110[b]	38(241)	39	58	77	13
111	20(283)	35	85	100	25
112	32(241)	100	31	51	24
113[c]	14(241)	3	45	53	54
114[d]	2(239)	2	7	7	11

[a] molecular ion in brackets

[b] base ion m/e 71

[c] base ion m/e 128

[d] base ion m/e 69

b. 2-Methyl-N-butyl-N-(5-methyl-1,3,4-oxadiazol-2-yl)propanamide and 2-methyl-N-butyl-N-(3-methyl-1,2,4-oxadiazol-5-yl)propanamide

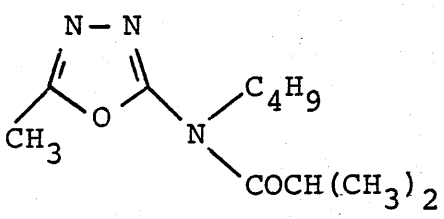
i. Literature survey of oxadiazoles

The mass spectra of phenyl-substituted oxadiazoles only have been studied in great depth. 1,3,4-Oxadiazole fragments[74] by loss of CO whilst aryl-substituted 1,3,4-oxadiazoles[75,76] lose the corresponding benzoylium ion. The simultaneous loss of nitrogen may be an important driving force. Phenyl-1,2,4-oxadiazoles[76-80] undergo ring scission to form both the $[C_6H_5CN]^{+\cdot}$ and $[C_6H_5]^+$ ions.

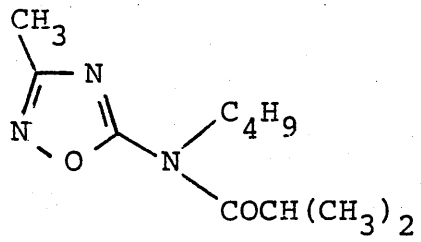
ii. Results and discussion

The mass spectral behaviour of two isomeric 2-[acyl(alkyl)amino]oxadiazoles is compared with that of 14a and previously reported oxadiazoles.

The spectrum (Figure 35) of the 1,3,4-oxadiazole (115) is complicated by the presence of groups of peaks corresponding to differing levels of protonation of the three adjacent nitrogen atoms. For the 1,2,4-oxadiazole (116), formation of protonated ion clusters is even more pronounced (Figure 36). For both 115 and 116 fragmentation involving the N-butyl and N-isobutyryl groups is similar to that for oxazole 14a. Additionally significant peaks of m/e 182 [M-43] and m/e 183 can be seen for 115 (Scheme 24). Both ions are linked by metastable ion peaks to the m/e 140 ion (cf. Scheme 21 for pyrazole 108).

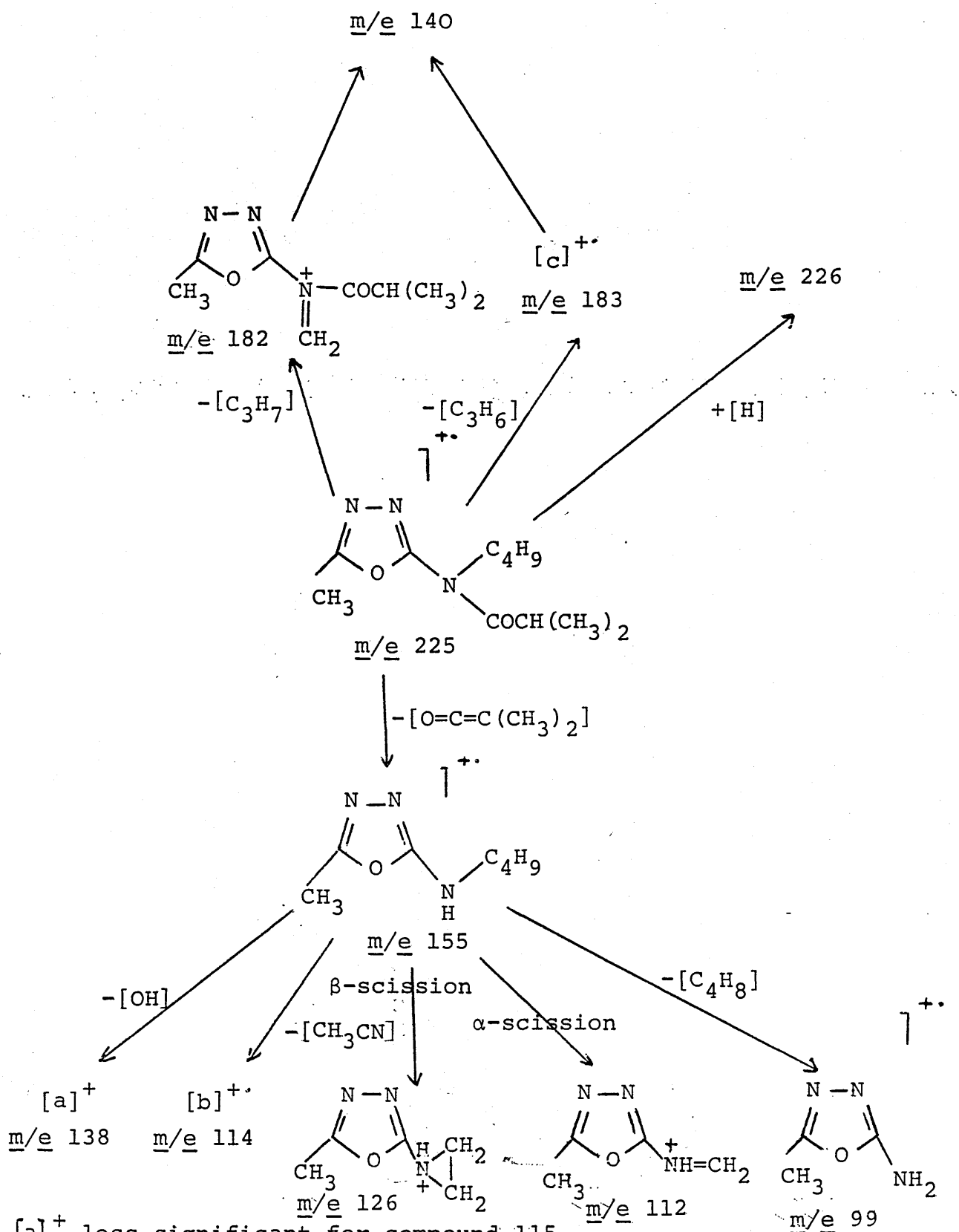


115



116

Scission of each oxadiazole ring occurs with elimination of either methyl cyanide or a hydroxyl radical from the $[M - O{=}C{=}C(CH_3)_2]^{+\bullet}$ ion. Similar competitive elimination is observed for the thiadiazoles 110-114. The elimination of CH_3CN to give a peak at m/e 114 is most significant for the 1,2,4-oxadiazole, whereas the 1,3,4-oxadiazole preferentially loses a hydroxyl radical. Hence, oxadiazoles 115 and 116 undergo ring fragmentations very different to those of previously reported aryl oxadiazoles, but show similarities with comparable oxazoles 14a-58.



[a]$^{+}$ less significant for compound 115

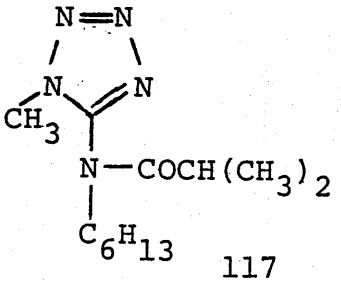
[b]$^{+\cdot}$ more significant for compound 115

[c]$^{+\cdot}$ not significant for compound 115

SCHEME 24

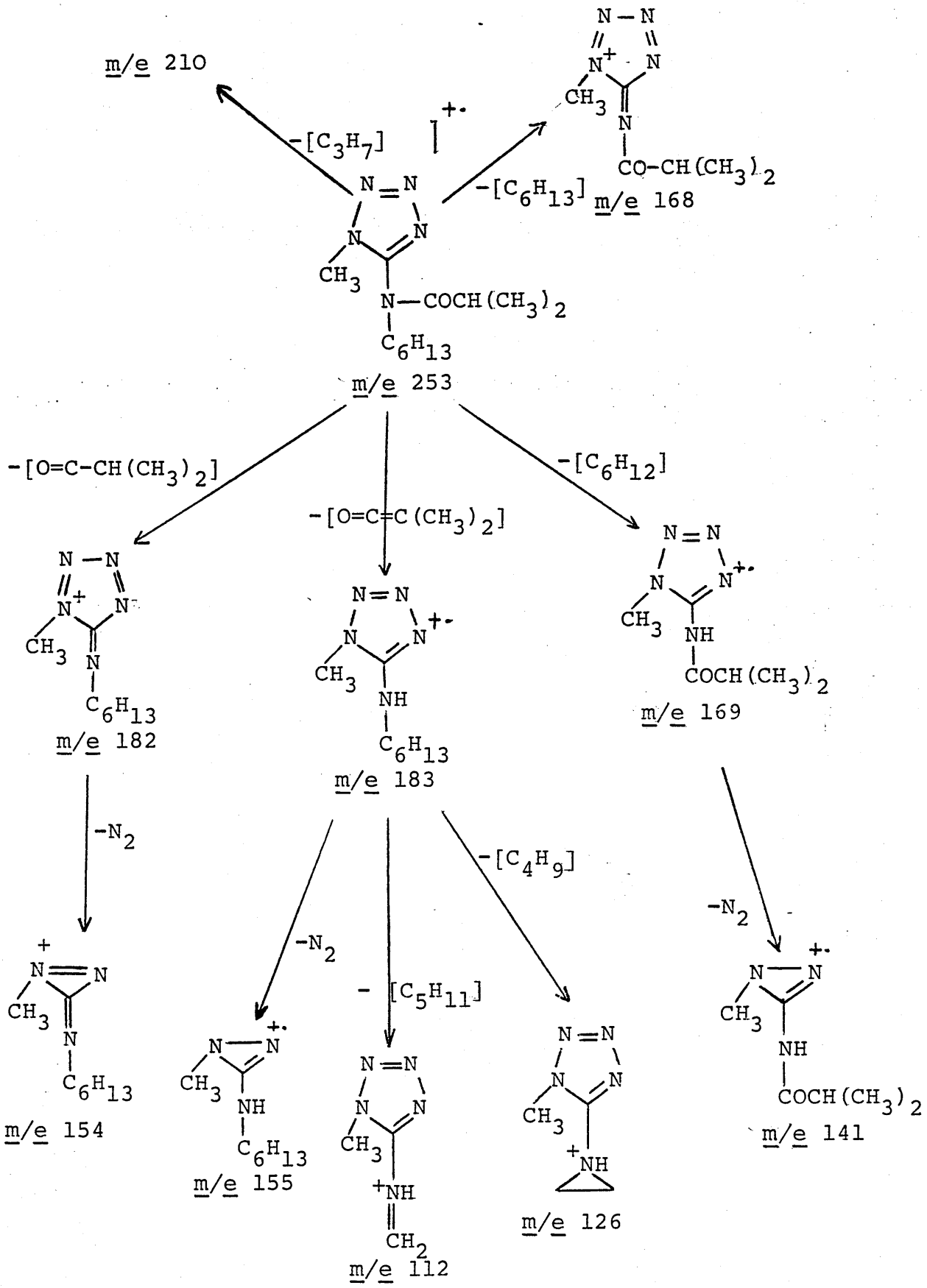
5. Compound with four heteroatoms in the ring

a. 2-Methyl-N-hexyl-N-(1-methyltetrazol-5-yl)-propanamide



117

The mass spectral behaviour of the tetrazole derivative 117 is characterised by the elimination of nitrogen from ions formed following loss of the acyl or alkyl substituent (Scheme 25). The spectrum (Figure 37) shows that ions formed following simple scission of these groups are more abundant than those formed following rearrangements, e.g. m/e 154 [M-71-28].

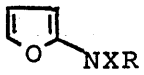
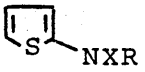
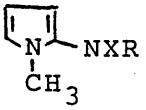
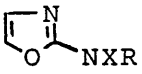
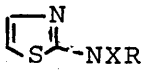
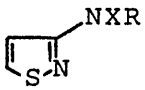
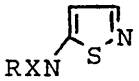
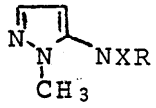
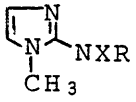
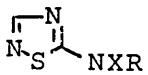
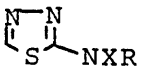
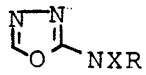
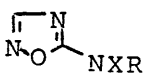

m/e 210
-[C3H7]
-[C6H13]
m/e 168
m/e 253
-[O=C-CH(CH3)2]
-[O=C=C(CH3)2]
-[C6H12]
m/e 182
m/e 183
m/e 169
-N2
-N2
-N2
-[C4H9]
-[C5H11]
m/e 154
m/e 155
m/e 112
m/e 126
m/e 141

SCHEME 25

6. Ring fragmentation of 5-membered heterocyclic compounds containing an acyl(alkyl)amino-substituent

Table 13 summarises the ring fragmentation observed for the 5-membered heterocycles. These results indicate that the loss of a hydroxyl radical from specific ions in the mass spectra of selected 2-[acyl(alkyl)amino]-oxazoles (e.g. 14a) is mimicked by heterocyclic compounds containing the acylamino-substituent adjacent to the oxygen atom. For furans the loss of a hydroxy radical is insignificant (<1%) whereas for the oxadiazoles the elimination is reduced due to competitive methyl cyanide extrusion. A similar but reduced loss of the [SH] radical was observed for 2-(acylamino)thiazoles and for the (acylamino) thiadiazoles but not for the more stable thiophene. Participation of the adjacent acylamino-substituent in the elimination of the radical was again indicated for the 3-, 4- and 5-(acylamino) isothiazoles, as only the mass spectrum of the 5-substituted compound showed loss of a [SH] radical. However, loss of nitrogen as a molecule of methyl cyanide or of nitrogen was only observed for the less stable oxadiazoles, thiadiazoles and tetrazoles.

Table 13. Ring scission and concomitant mass loss of 5-membered heterocycles containing an acyl-(alkyl)amino-substituent

Heterocycle	Elimination	Observation	
	$[M - (X-1) - OH]^+$	Detectable	
	$[M - (X-1) - SH]^+$	Not observed	
	$[M - (X-1) - NHCH_3]^+$	Not observed	
	$[M - (X-1) - OH]^+$	Significant	
	$[M - (X-1) - SH]^+$	Significant	
	$[M - (X-1) - SH]^+$	Detectable	
	$[M - (X-1) - SH]^+$	Significant	
	$[M - (X-1) - SH]^+$	Not observed	
	$[M - (X-1) - NHCH_3]^+$	Not observed	
	$[M - (X-1) - NHCH_3]^+$	Not observed	
	$[M - SH]^+$	Significant	CH_3CN eliminated
	$[M - SH]^+$	Significant	CH_3CN eliminated
	$[M - (X-1) - OH]^+$	Significant	CH_3CN eliminated
	$[M - (X-1) - OH]^+$	Significant	CH_3CN eliminated
	$[M - (X-1) - NH]^+$	Not observed	N_2 eliminated

X = acyl group R = alkyl group

REFERENCES

E. References

1. Thompson, J.J., Phil. Mag., 1911, 21, 225.
2. Stewart, H.R. and Olsen, A.R., J. Amer. Chem. Soc., 1931, 53, 1236.
3. Washburn, H.W., Wiley, H.F. and Rock, S.M., Ind. Eng. Chem. Anal. Ed., 1943, 15, 541.
4. Dempster, A.J., Phys. Rev., 1921, 18, 415.
5. Nier, A.O., Rev. Sci. Instr., 1947, 18, 398.
6. Herzog, R.F.K., Z. Physik ,1934, 89, 447.
7. Mattauch, J. and Herzog, R.F.K., Z. Physik ,1934, 89, 786.
8. Paul, W. and Reather, M., Z. Physik , 1955, 140, 262.
9. Stenhagen, E., "Mass Spectrometry in Biochemical Research," Chimia (Switzerland), 1965, 37, 1037.
10. Biemann, K., Bommer, P., Desiderio, D.M. and McMurray, W.J., Advan. Mass Spectry., 1966, 3, 639.
11. McLafferty, F.W., Science, 1966, 151, 641.
12. Barber, M., Powers, P., Wallington, M.J. and Wostenholme, W.A., presented at Mass Spectrometry Group Meeting, September 13-15th, 1966, Birmingham, England.
13. Rosenstock, H.M., Wallenstein, M.B., Wahrhaftig, A.L. and Eyring, H., Proc. Nath. Acad. Sci. U.S.A., 1952, 38, 667.
14. Svec, H.J. and Junk, G.A., J. Amer. Chem. Soc., 1967, 89, 790.
15. Baldwin, M., Kirkien-Konasiewioz, A., Loudon, A.G., Maccoll, A. and Smith, D., J. C. S. Chem. Comm., 1966, 574.

16. Budzikiewicz, H., Djerassi, C. and Williams, D.H., "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, 1967, p. 2.

17. Hipple, J.A., Fox, R.E. and Condon, E.U., Phys. Rev., 1946, 69, 347.

18. Bursey, M.M. and Hoffman, M.K., Mass Spectrom.: Tech. Appl., Interscience, New York, 1971, p. 373.

19. Rylander, P.N., Meyerson, S. and Grubb, H.M., J. Amer. Chem. Soc., 1957, 79, 842.

20. McAdams, D.R., Lane, L. and Lemley, S.G., presented at ASTM Committee E-14 Conference on Mass Spectrometry, May, 1963, San Fransisco, California.

21. Widmer, H. and Gaumann, T., Helv. Chim. Acta , 1962, 45, 2175.

22. Teranishi, R., Buttery, R.G., McFadden, W.H., Mon, T.R. and Wasserman, J., Analyt. Chem., 1964, 36, 1509.

23. Holmes, J.C. and Morell, F.A., Appl. Spectrosc., 1957, 11, 86.

24. Gohlke, R.S., Analyt. Chem., 1959, 31, 535.

25. Sweeley, C.C., Elliott, W.H., Fires, I. and Ryhage, R., Analyt Chem 1966, 38, 1549.

26. Hammar, C.G. and Holmstedt, B., Analyt. Biochem., 1968, 25, 532.

27. Borga, O., Palmer, L., Linnarsson, A. and Holmstedt, B., Anal. Lett., 1971, 4, 837.

28. Bertilsson, L., Atkinson, A.J. Jnr., Althaws, J.R., Harfast, A., Lindgren, J.E. and Holmstedt, B., Analyt. Chem., 1972, 44, 1434.

29. Millard, B.J., "Quantitative Mass Spectrometry," Heyden, London, 1978.

30. Harrison, R.G., Jolley, M.R.J., Neville, M.C., Ross, W.J., Todd, A., Verge, J.P., Dawson, W. and Sweatman, W.J.F., in press.

31. Rebuck, A.S., Drugs, 1974, 37, 344.

32. Ryhage, R., Analyt. Chem., 1964, 36, 759.

33. Bowie, J.H., Donaghue, P.F., Rodda, H.J., Cooks, R.G. and Williams, D.H., Org. Mass Spectrometry, 1968, 1, 13.

34. Audier, H., Fetizon, M., Henry, Y. and Prange, T., Org. Mass Spectrometry, 1976, 11, 1047.

35. Clarke, G.M., Grigg, R. and Williams, D.H., J. Chem. Soc. B., 1966, 339.

36. Biemann, K., Mass Spectrometry, McGraw-Hill, New York, 1962, p. 135.

37. Spiteller, G., "Mass Spectrometry of Heterocyclic Compounds" in Advances in Heterocyclic Chemistry, Vol. 7 (A.R. Katritzky, Ed.) Academic Press, New York, p. 318.

38. Beynon, J.H., Mass Spectrometry and its Applications to Organic Chemistry, Elsevier, Amsterdam, 1960, p. 403.

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

40. Zerilli, L.F., Tuan, G., Tarzia, G. and Gallo, G.G., Proceedings of the International Symposium of Gas-Chromatography Mass Spectrometry, 1972, 231.

41. Crow, W.D., Hodgkin, J.H. and Shannon, J.H., Aust. J. Chem., 1965, 18, 1433.

42. Bowie, J.H., Donaghue, H.E., Rodda, H.J. and Simons, H.K., Tetrahedron, 1968, 24, 3965.

43. McLafferty, F.W., Analyt Chem., 1959, 31, 477.

44. Jaffé, M.H., Chem. Rev., 1953, 53, 191.

45. McLafferty, F.W., Analyt. Chem., 1959, 31, 477.

46. Bursey, M.M. and McLafferty, F.W., J. Amer. Chem. Soc., 1966, 88, 529.

47. McLafferty, F.W. and Bursey, M.M., J. Amer. Chem. Soc., 1968, 90, 5299.

48. Brown, P., J. Amer. Chem. Soc., 1968, 90, 4459.

49. Bursey, M.M. and Kissinger, P.T., Org. Mass Spectrometry, 1970, 3, 395.

50. Brown, P. and Djerassi, C., J. Amer. Chem. Soc., 1967, 89, 2711.

51. Chin, S.M. and Harrison, A.G., Org. Mass Spectrometry, 1969, 2, 1073.

52. Bursey, M.M., Org. Mass Spectrometry, 1968, 1, 31.

53. American Petroleum Institute, Research Project 44, Spectrum 545.

54. Williams, D.H., Cooks, R.G., Ronayne, J. and Tan, S.W., Tetrahedron Letters, 1968, 1777.

55. Heyns, K., Stute, R. and Scharmann, H., Tetrahedron, 1966, 22, 2223.

56. Budzikiewicz, H., Djerassi, C. and Williams, D.H., Mass Spectrometry of Organic Compounds, Holden-Day, San Fransisco, 1967, p. 616.

57. Chang, S.S., Smouse, T.H., Krishnamurthy, R.G., Mookertee, B.P. and Reddy, R.B., Chem. and Ind., (London) 1966, 1926.

58. Burdon, J., Tatlow, J.C. and Thomas, D.F., J. C. S. Chem. Comm., 1966, 48.

59. Budzikiewicz, H., Djerassi, C. and Williams, D.H., Interpretation of Mass Spectra of Organic Compounds, Holden-Day, San Fransisco, 1964, p. 231-235.

60. Kinney, I.W. and Cook, G.L., Analyt. Chem., 1952, 24, 1391.

61. Hanus, V. and Cermak, V., Collect. Czech. Chem. Comm., 1959, 24, 1602.

62. Nishiwaki, T., Tetrahedron, 1967, 23, 2979.

63. Budzidiewicz, H., Djerassi, C., Jackson, A.H., Kenner, G.W., Newman, D.J. and Wilson, J.M., J. Chem. Soc., 1964, 1949.

64. Buttery, R.G., Ling, L.C. and Lundin, R.E., J. Agr. Food Chem., 1973, 21, 488.

65. Entenmann, G., Org. Mass Spectrometry, 1975, 10, 831.

66. Bowie, J.H., Cooks, R.G., Lawesson, S.O. and Schroll, G., Aust. J. Chem., 1967, 20, 1613.

67. Nishiwaki, T., J. Chem. Soc. B., 1967, 885.

68. Van Thuijl, J., Klebe, K.J. and Van Houle, J.H., Org. Mass Spectrometry, 1970, 3, 1549.

69. Hodges, R. and Grimmett, M.R., Aust. J. Chem., 1968, 21, 1085.

70. Van Thuijh, J., Klebe, K.J. and Van Houte, J.J., Org. Mass Spectrometry, 1971, 5, 1101.

71. Van Thuijh, J., Klebe, K.J. and Van Houte, J.J. Org. Mass Spectrometry, 1973, 7, 1165.

72. El Khadem, H., Foltz, R.L. and Horton, D., J. Heterocyclic Chem., 1974, 11, 575.

73. Zeller, K.P., Meier, H. and Muller, E., Org. Mass Spectrometry, 1971, 5, 373.

74. Ainsworth, C., J. Amer. Chem. Soc., 1965, 87, 5800.

75. Cotter, J.L., J. Chem. Soc., 1964, 5491.

76. Westphal, G. and Schmidt, R., Org. Mass Spectrometry, 1976, 11, 304,

77. Cotter, J.L., J. Chem. Soc., 1965, 6842.

78. Selva, A. and Zerilli, L.F., Org. Mass Spectrometry, 1976, 11, 2.

79. Selva, A., Zerilli, L.F, Cavalleri, B. and Gallo, G.G., Org. Mass Spectrometry, 1974, 9, 558.

80. Selva, A., Zerilli, L.F., Cavelleri, B. and Gallo, G.G., Org. Mass Spectrometry, 1972, 6, 1347.

FIGURES

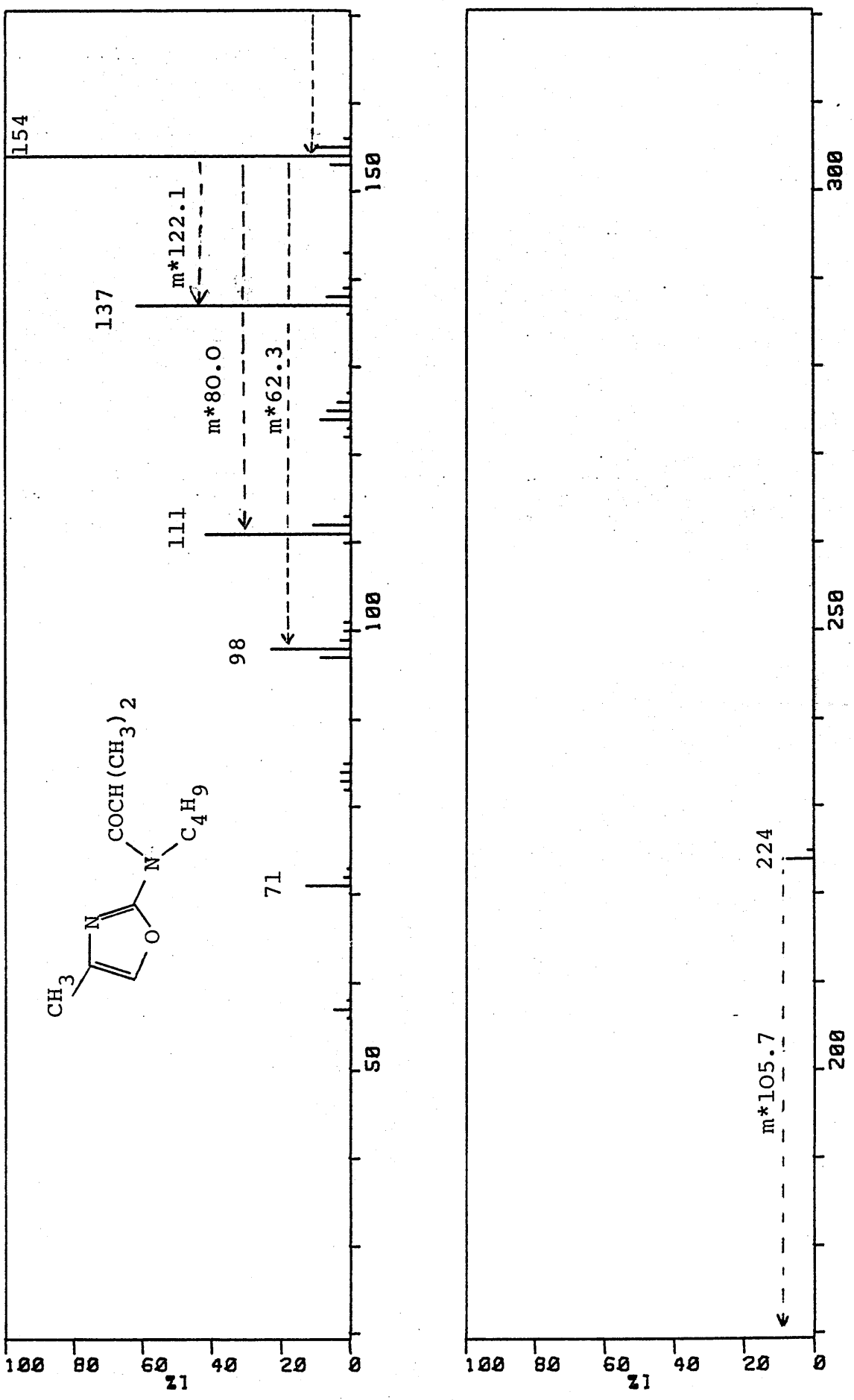


FIGURE 1: Mass spectrum of 2-methyl-N-butyl-N-(4-methyloxazol-2-yl)propanamide.

FIGURE 2: Mass spectrum of 2-methyl-N-d_9-butyl-N-(4-methyloxazol-2-yl)propanamide.

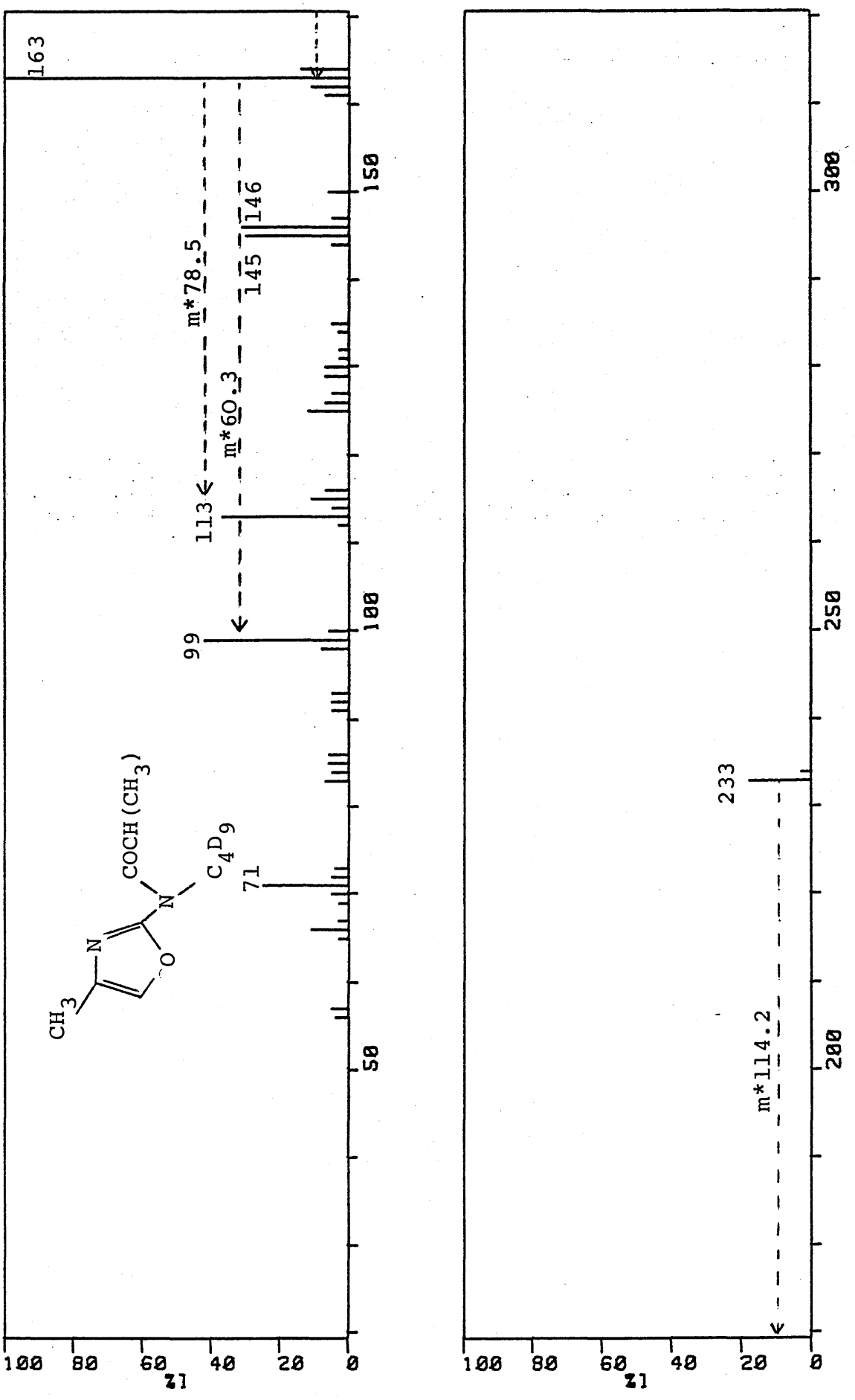


FIGURE 3: Elimination of the hydroxyl radical as shown by the spectra of compounds 26a and 26b.

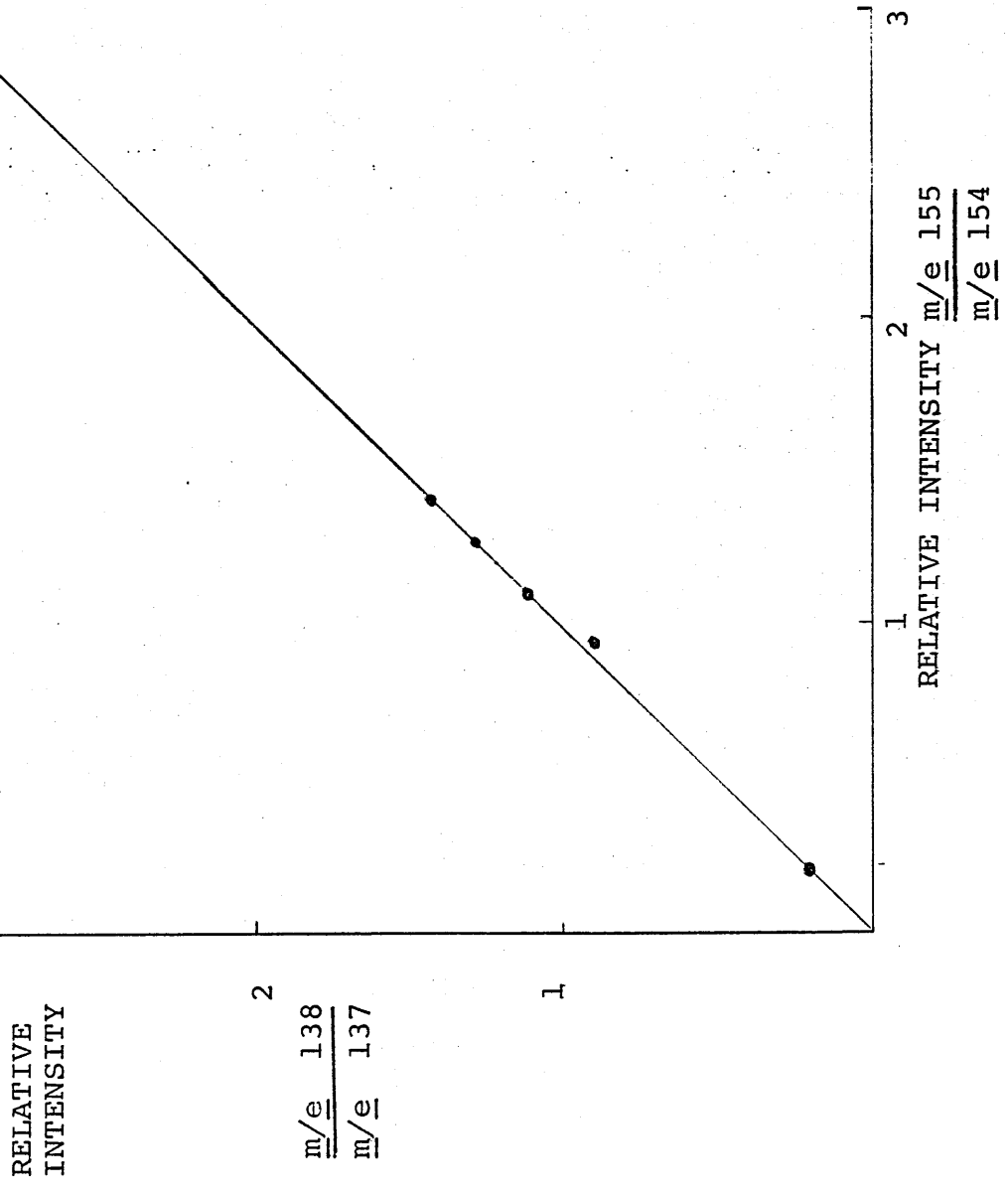


FIGURE 4: Mass spectrum of N-(4-methyloxazol-2-yl)-N-(trimethylsilyl)butylamine.

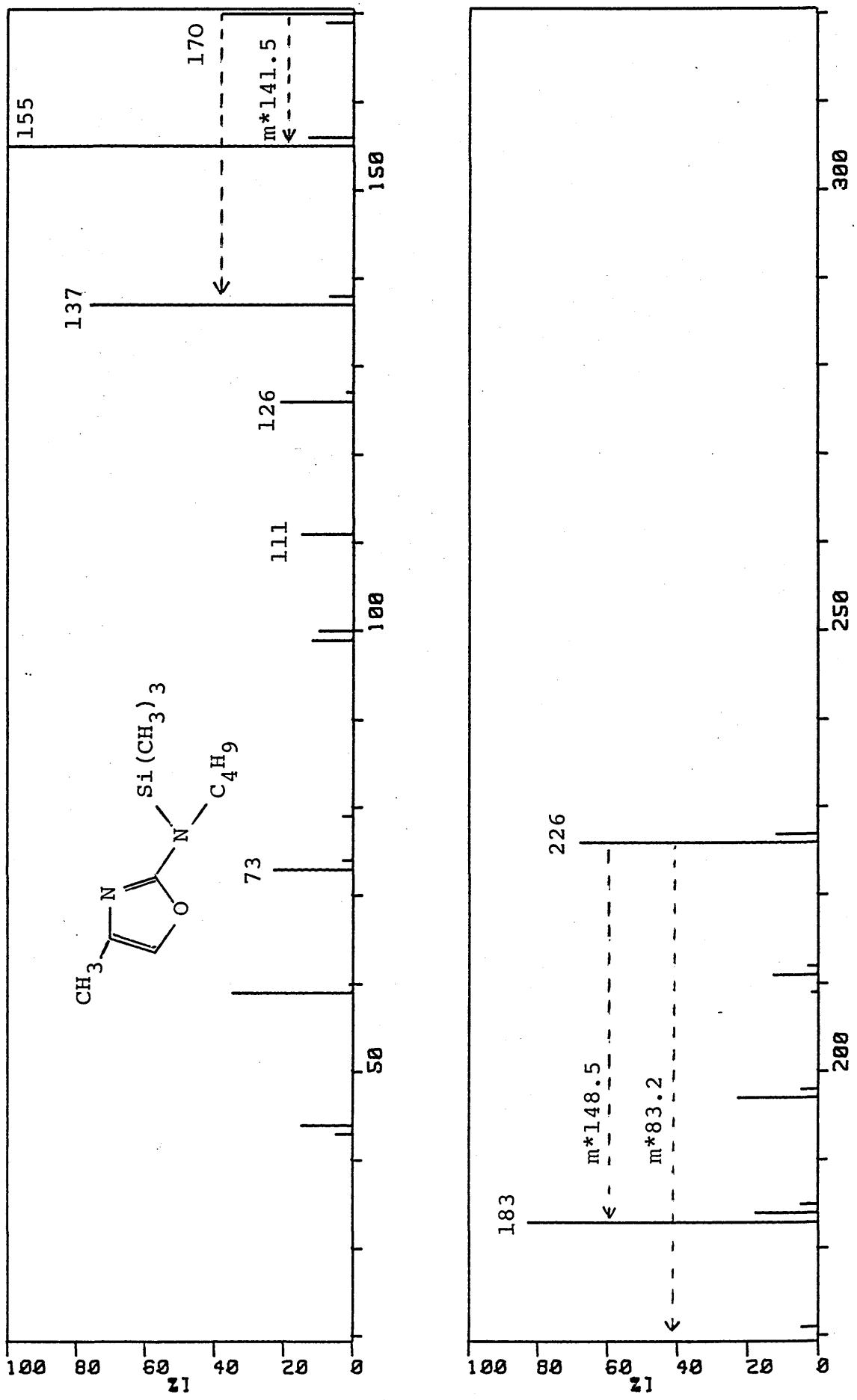
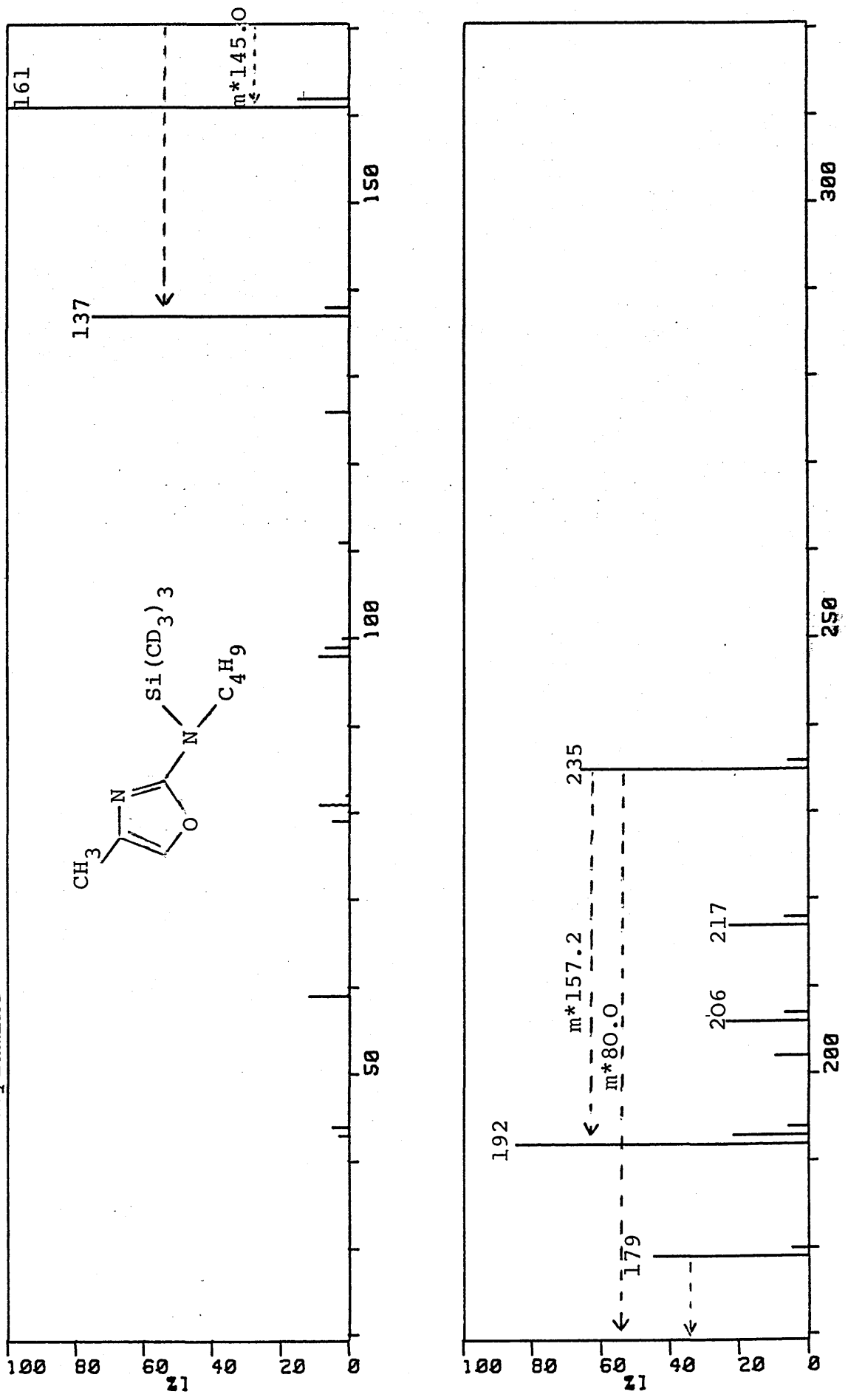


FIGURE 5: Mass spectrum of N-(4-methyloxazol-2-yl)-N-(d_9-trimethylsilyl)-butylamine



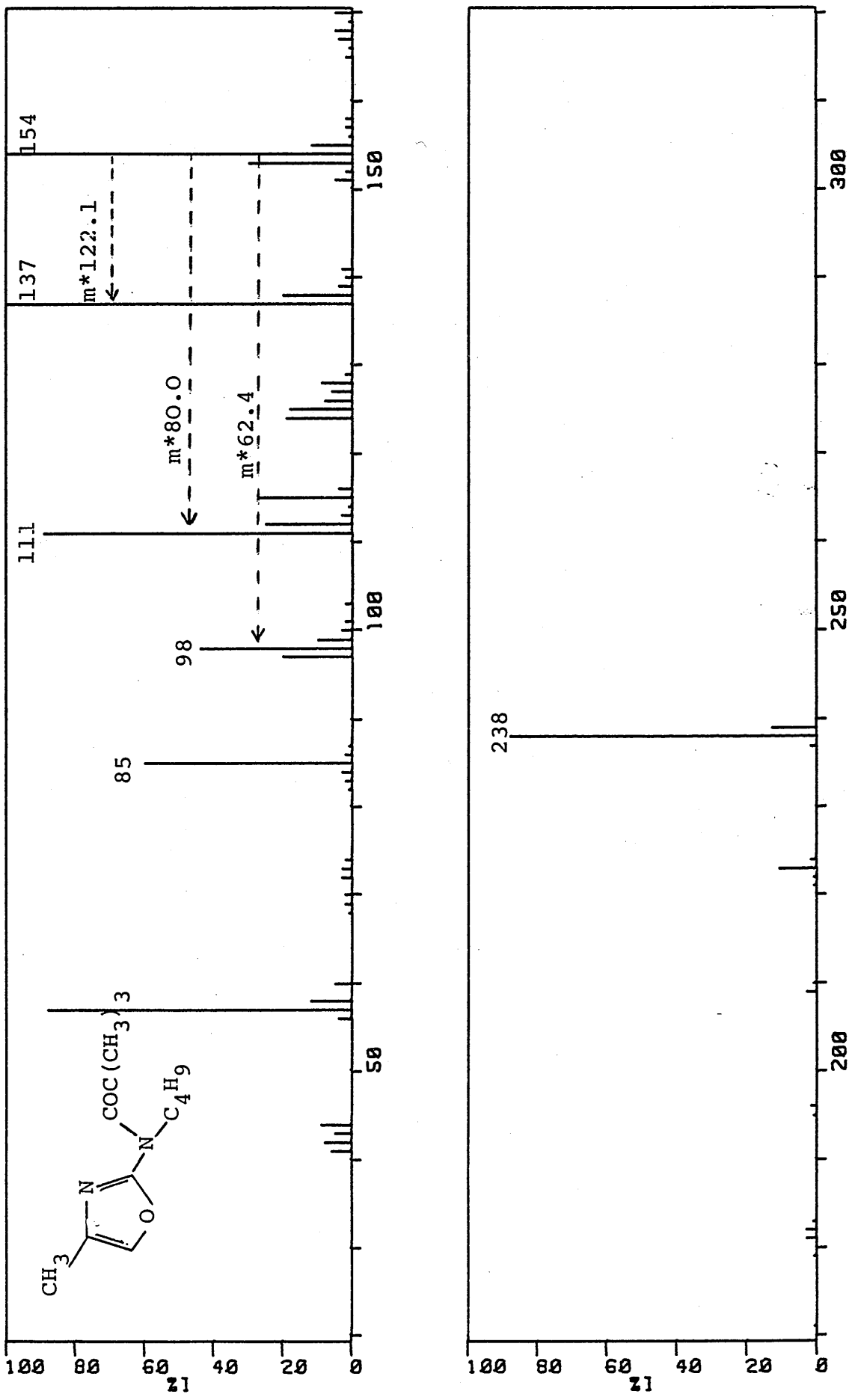
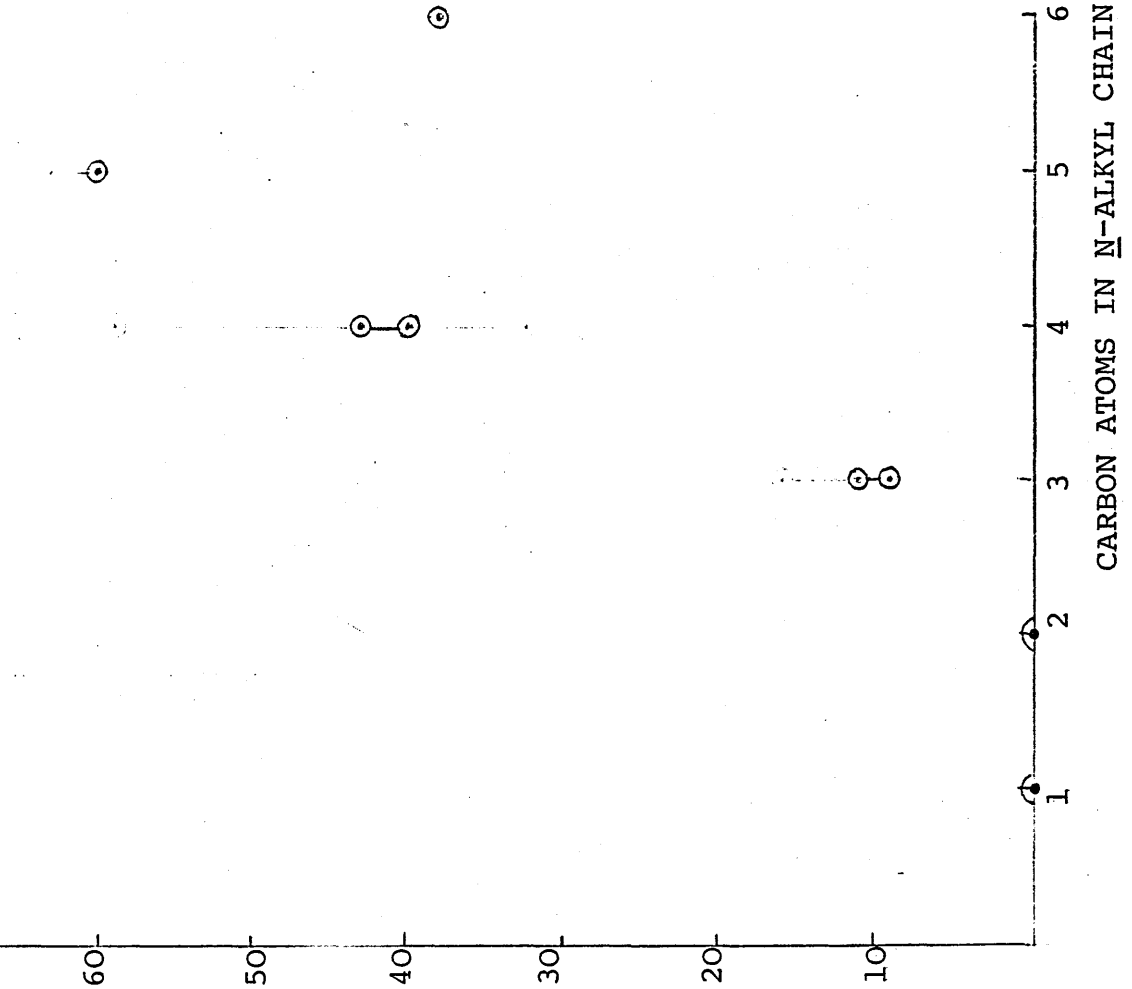


FIGURE 6: Mass spectrum of 2,2-dimethyl-N-butyl-N-(4-methyloxazol-2-yl) propanamide.

FIGURE 7: Dependence of hydroxyl radical elimination on the N-alkyl substituent in the mass spectra of 2[acyl(alkyl)amino]oxazoles.



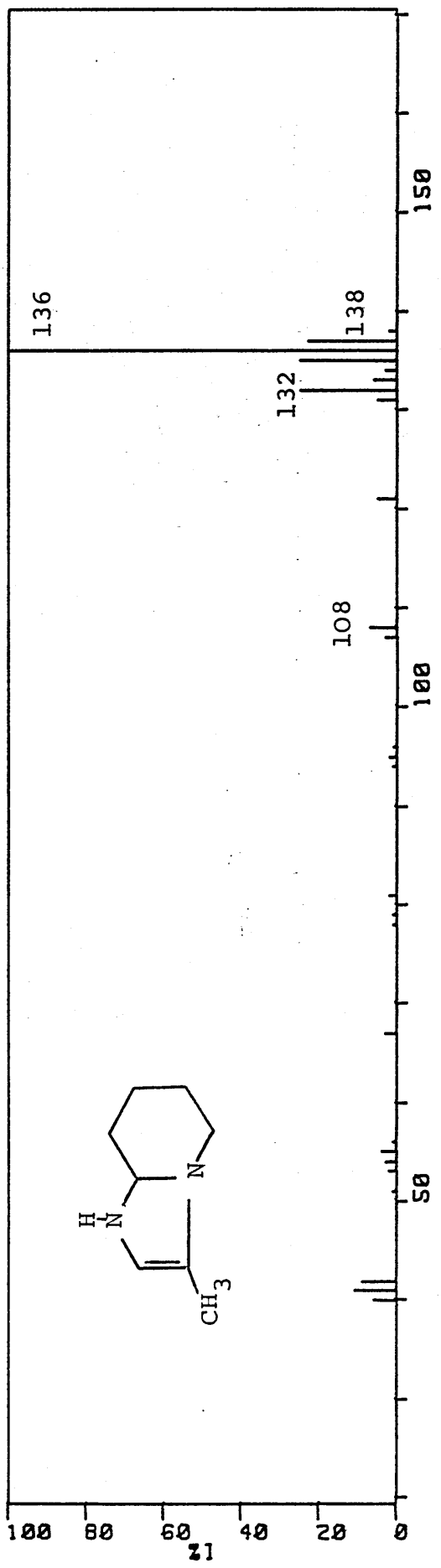


FIGURE 8: Mass spectrum of 3-methyl-1,5,6,7,8,8a-hexahydroimidazolo[1,2-a]pyridine

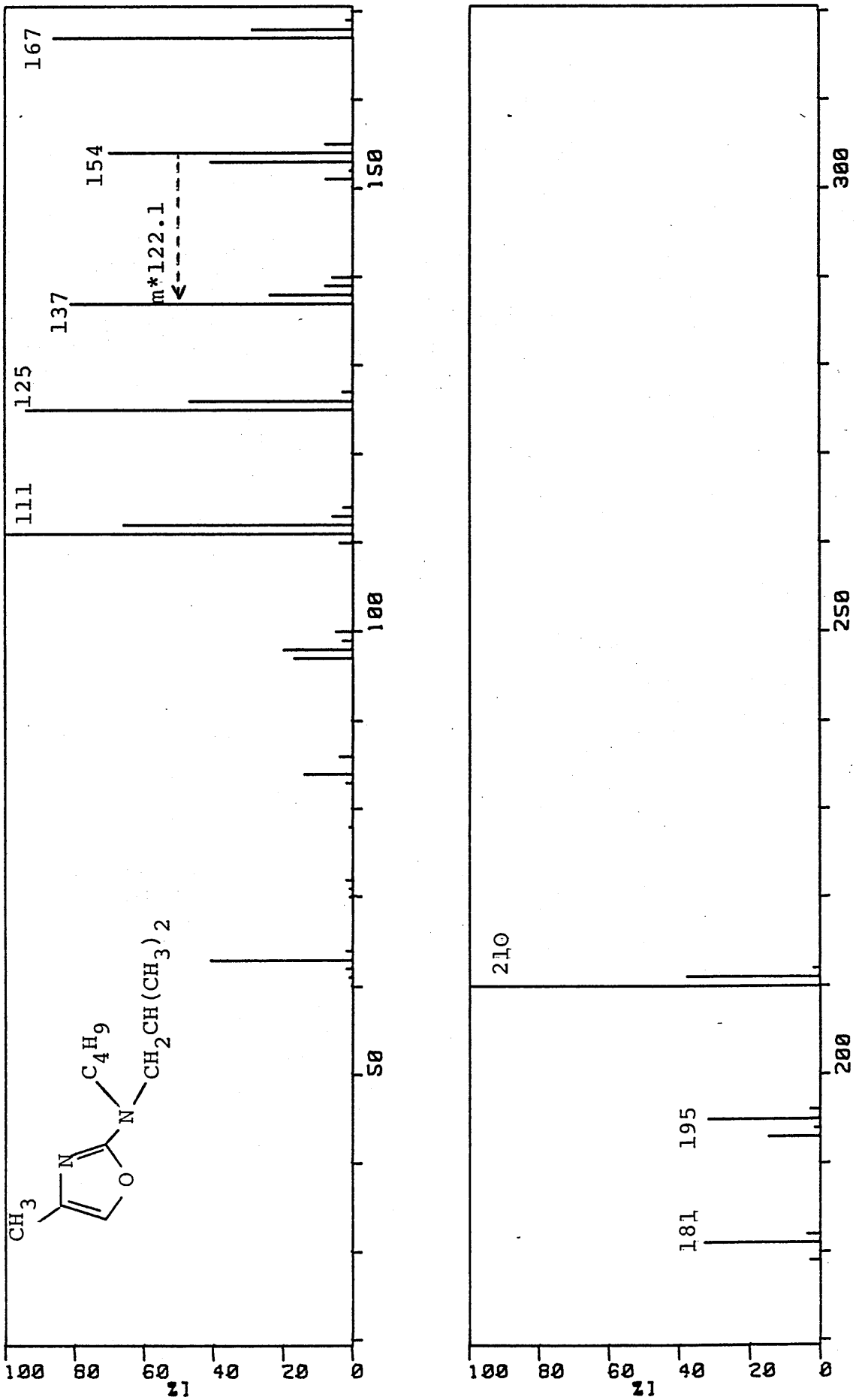


FIGURE 9: Mass spectrum of N-butyl-N-s-butyl(4-methyloxazol-2-yl)amine

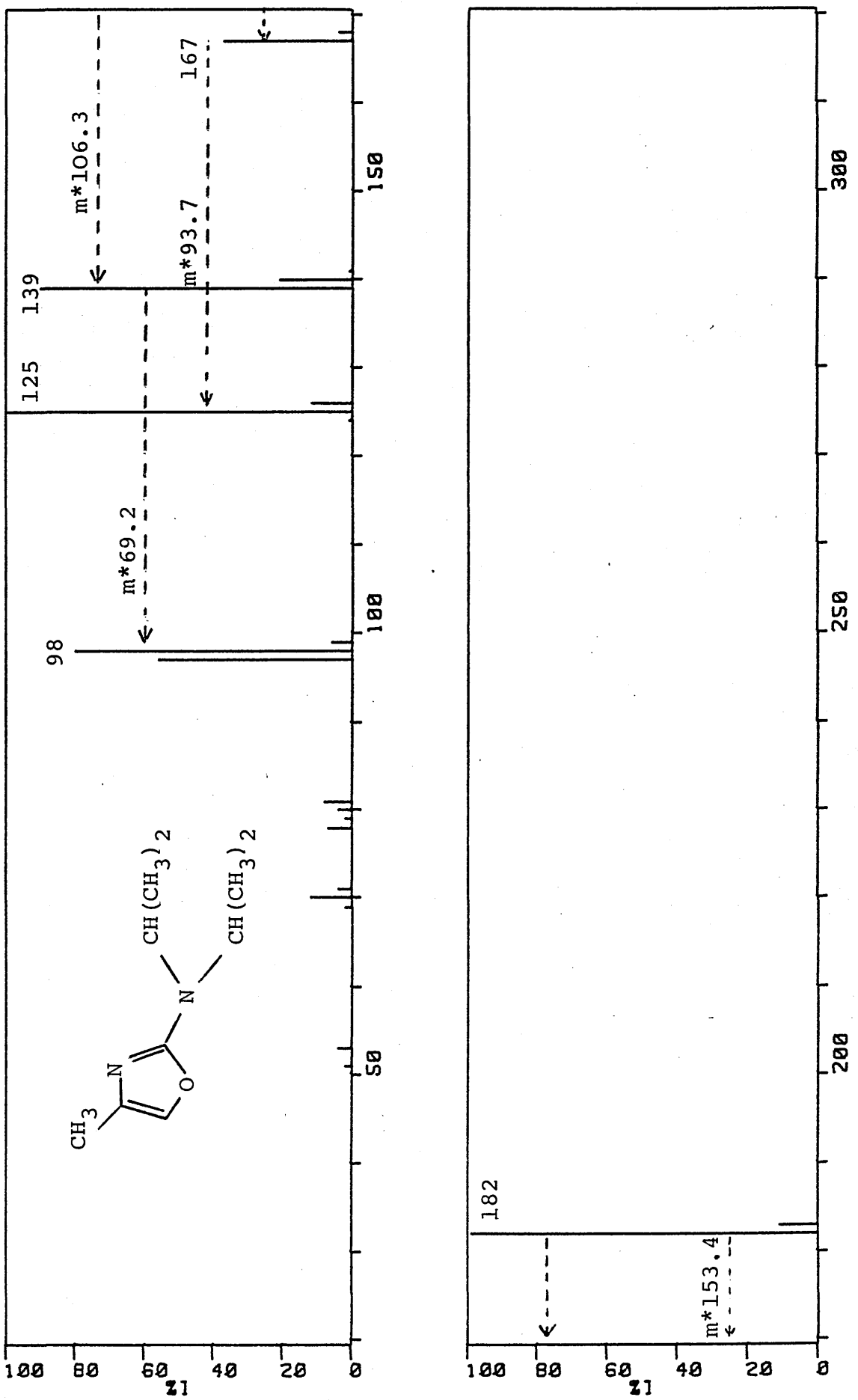


FIGURE 10: Mass spectrum of NN-di-isopropyl(4-methyloxazol-2-yl)amine.

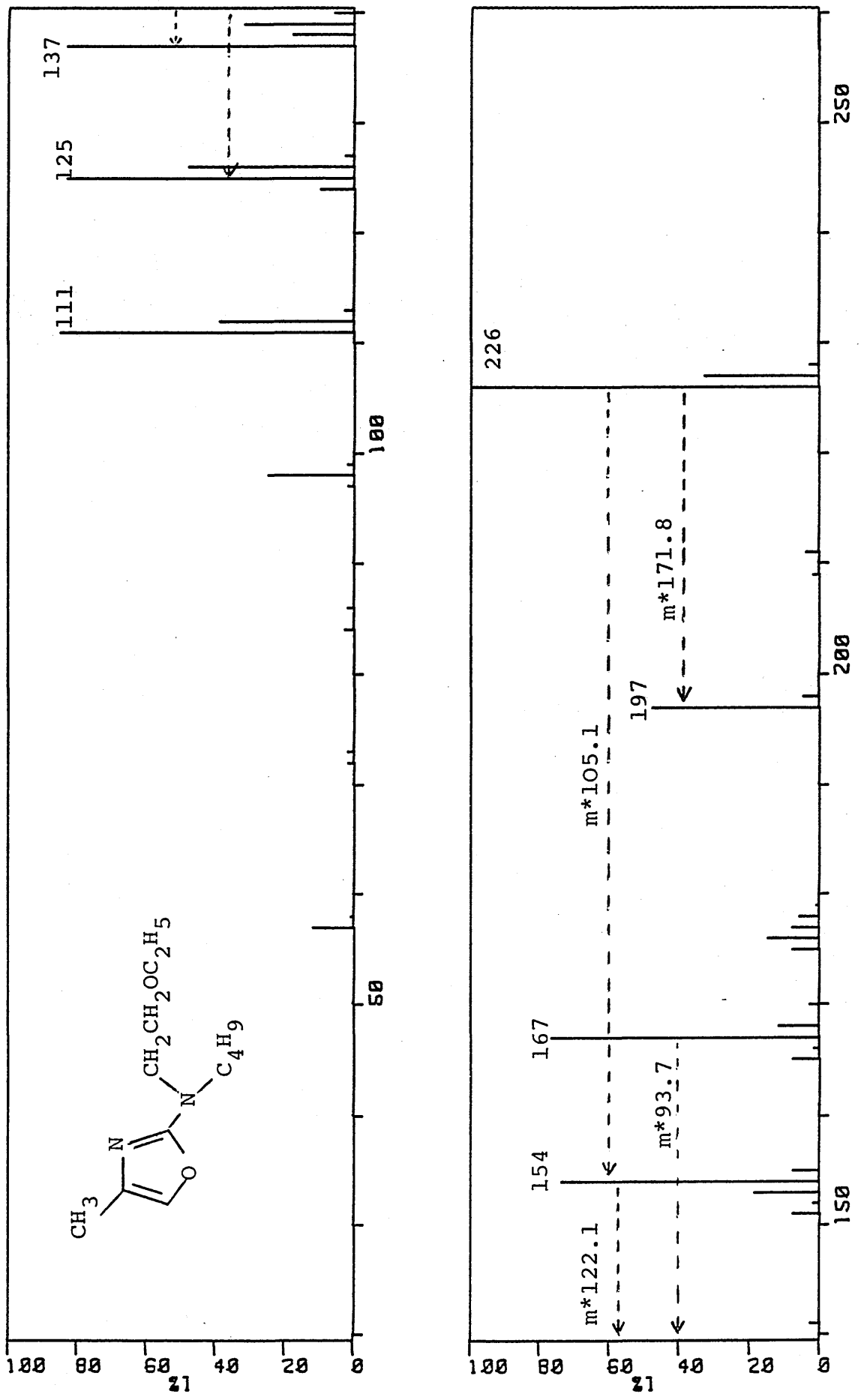


FIGURE 11. Mass spectrum of N-butyl-N-(2-ethoxyethyl)(4-methyloxazol-2-yl)amine.

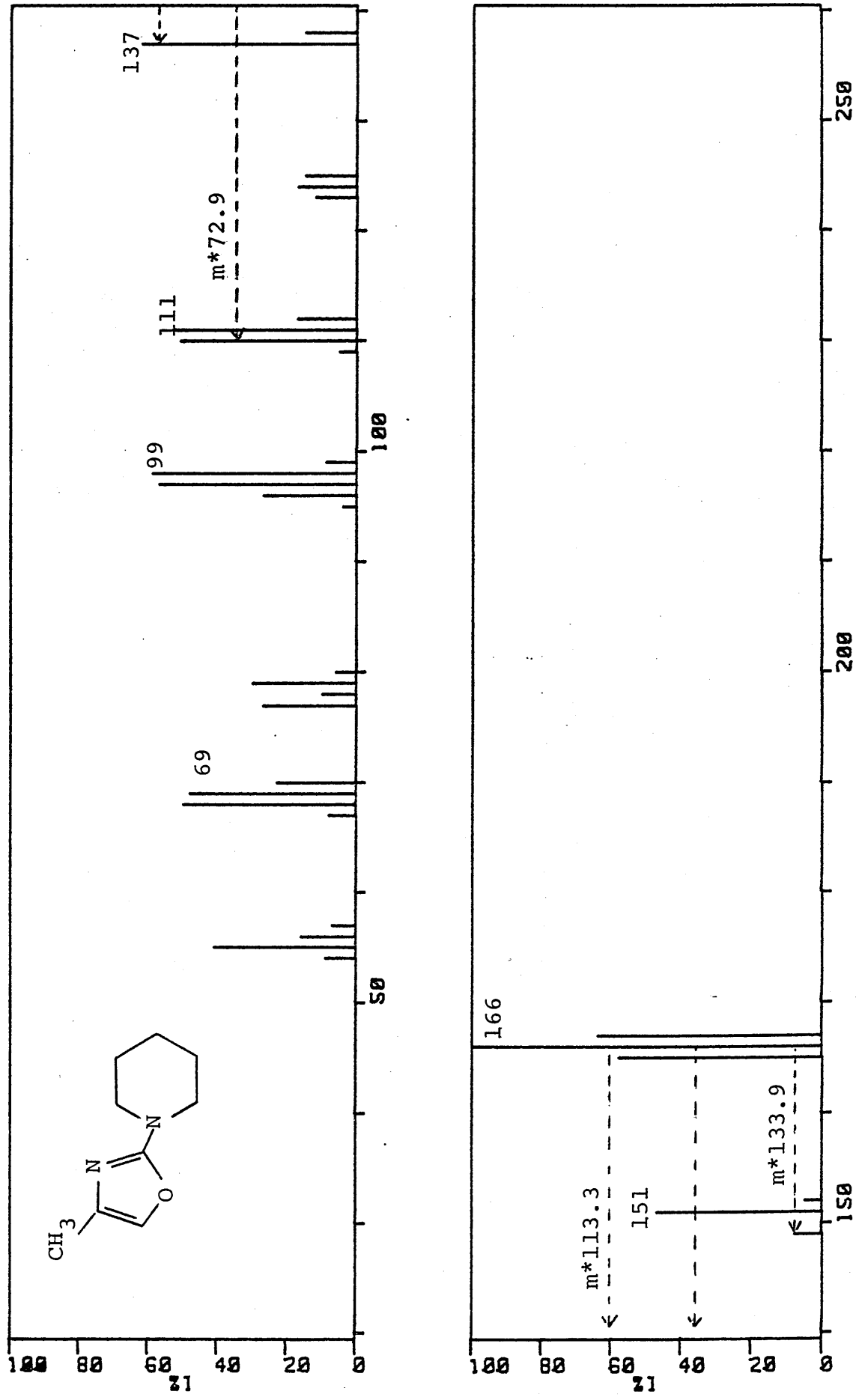


FIGURE 12. Mass spectrum of N-(4-methyloxazol-2-yl)piperidine.

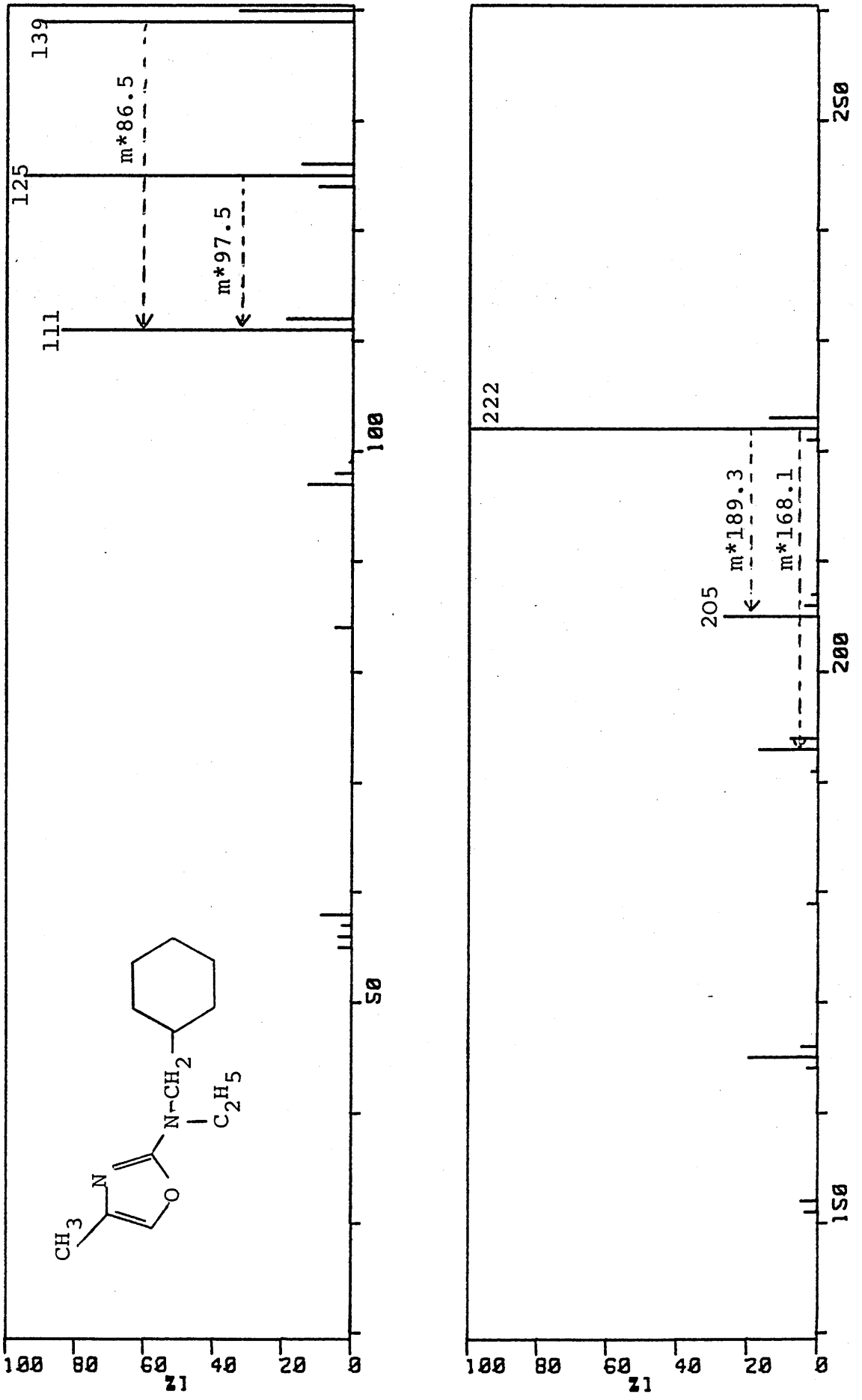


FIGURE 13: Mass spectrum of N-cyclohexylmethyl-N-ethyl(4-methyloxazol-2-yl) amine.

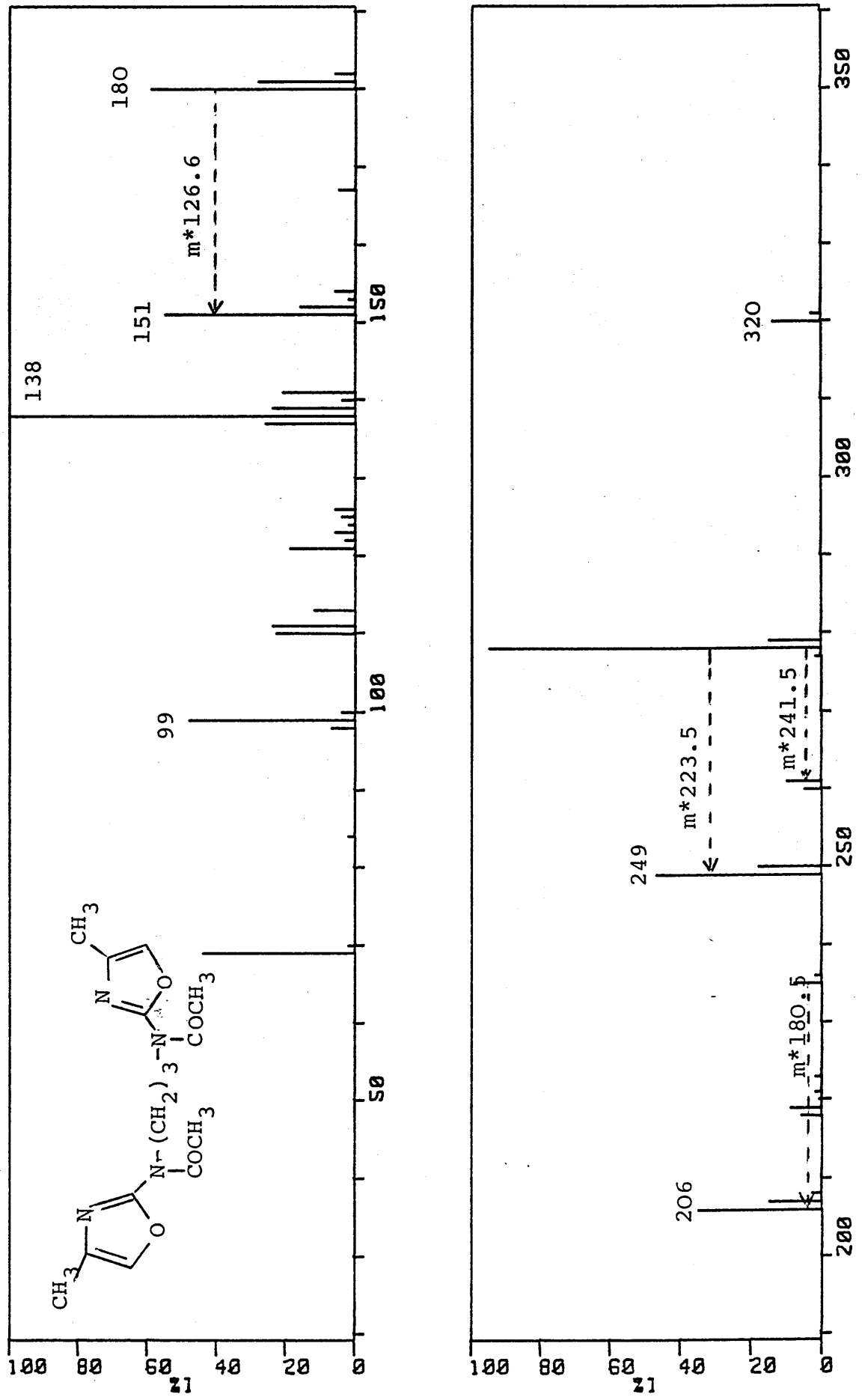
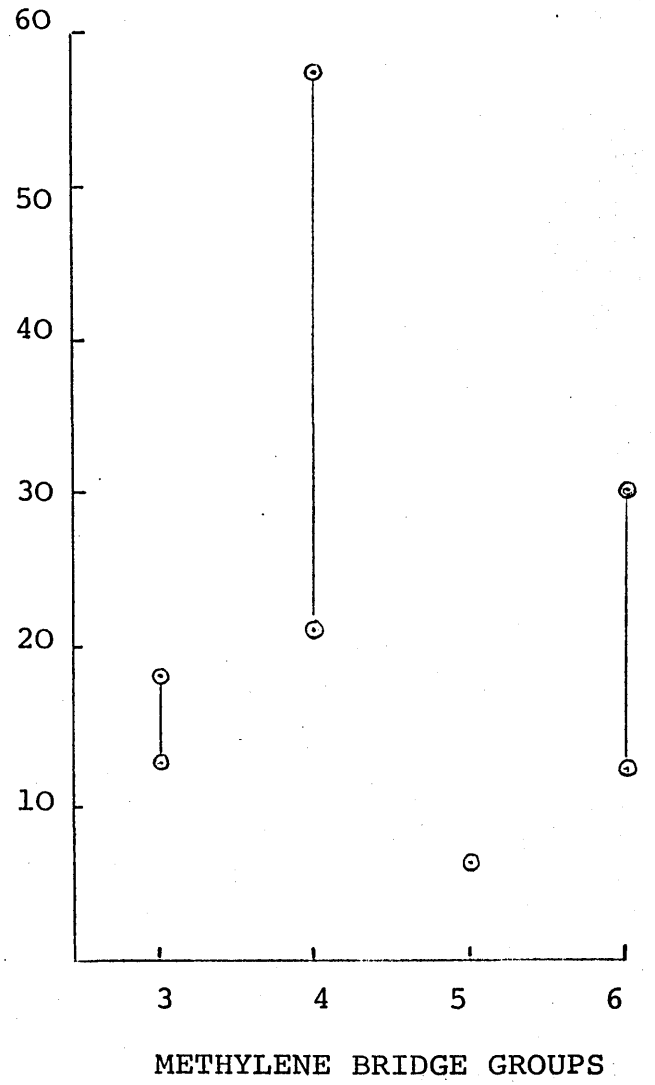


FIGURE 14: Mass spectrum of 1,3-bis-[N-acetyl-N-(4-methyloxazol-2-yl)-amino]propane.

FIGURE 15. Dependence of relative abundance of $[M-(COR-1)-17]^+$ ion on length of methylene bridge in the mass spectra of α,ω-bis-[N-acyl-N--(4-methyloxazol-2-yl)amino]alkanes.



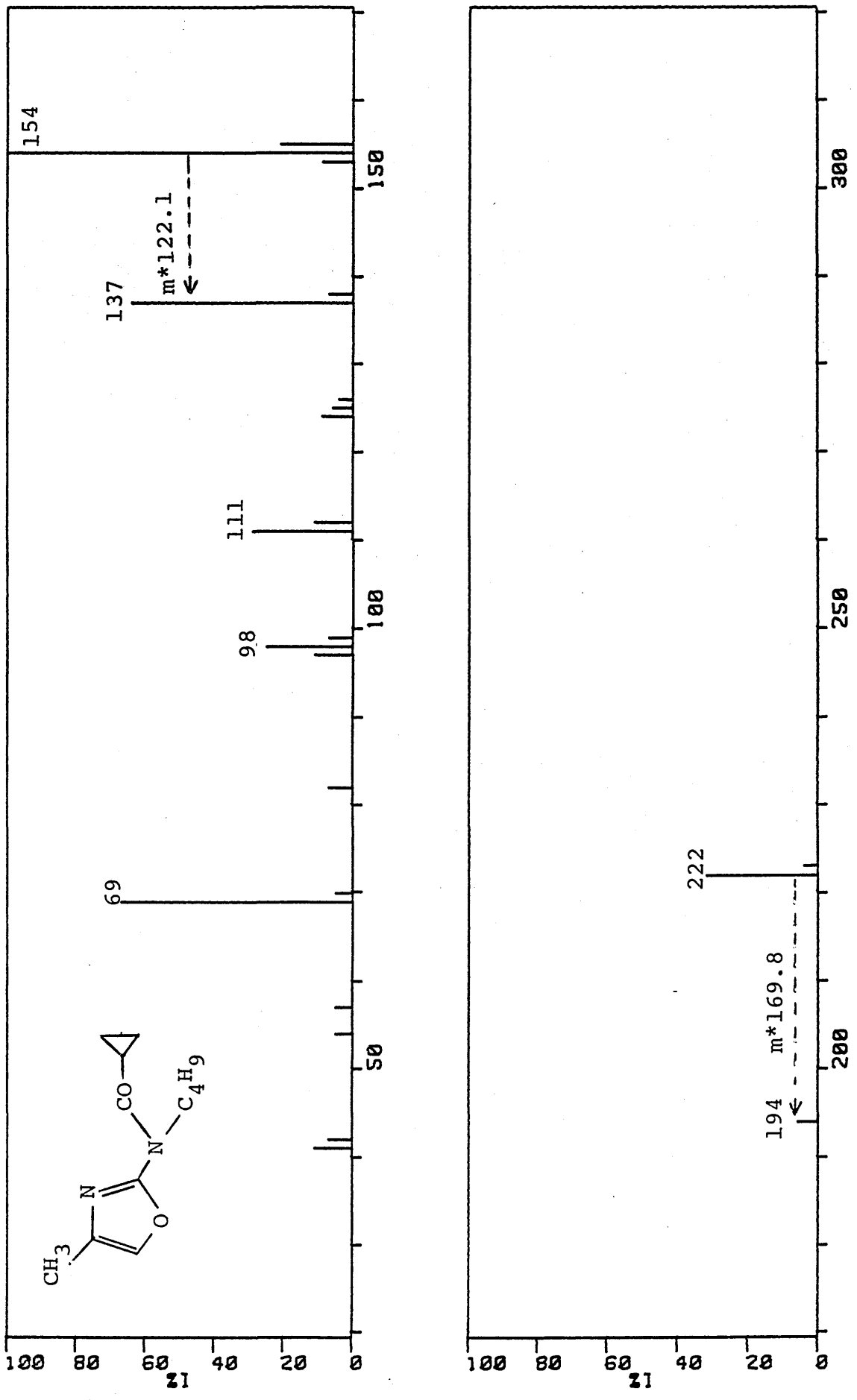


FIGURE 16: Mass spectrum of N-butyl-N-(4-methyloxazol-2-yl)cyclopropanecarboxamide.

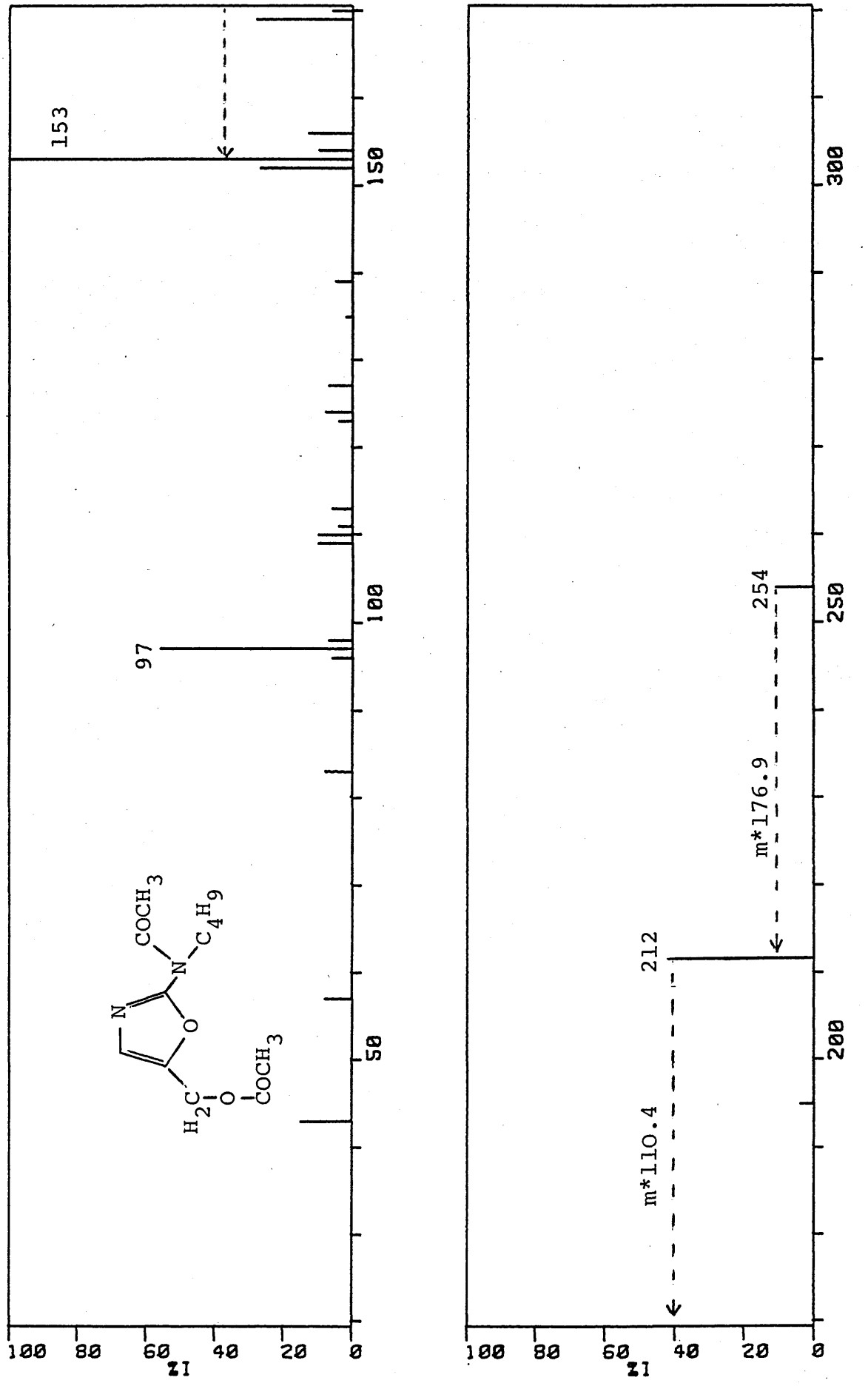


FIGURE 17. Mass spectrum of N-butyl-N-(5-acetoxymethyloxazol-2-yl)acetamide.

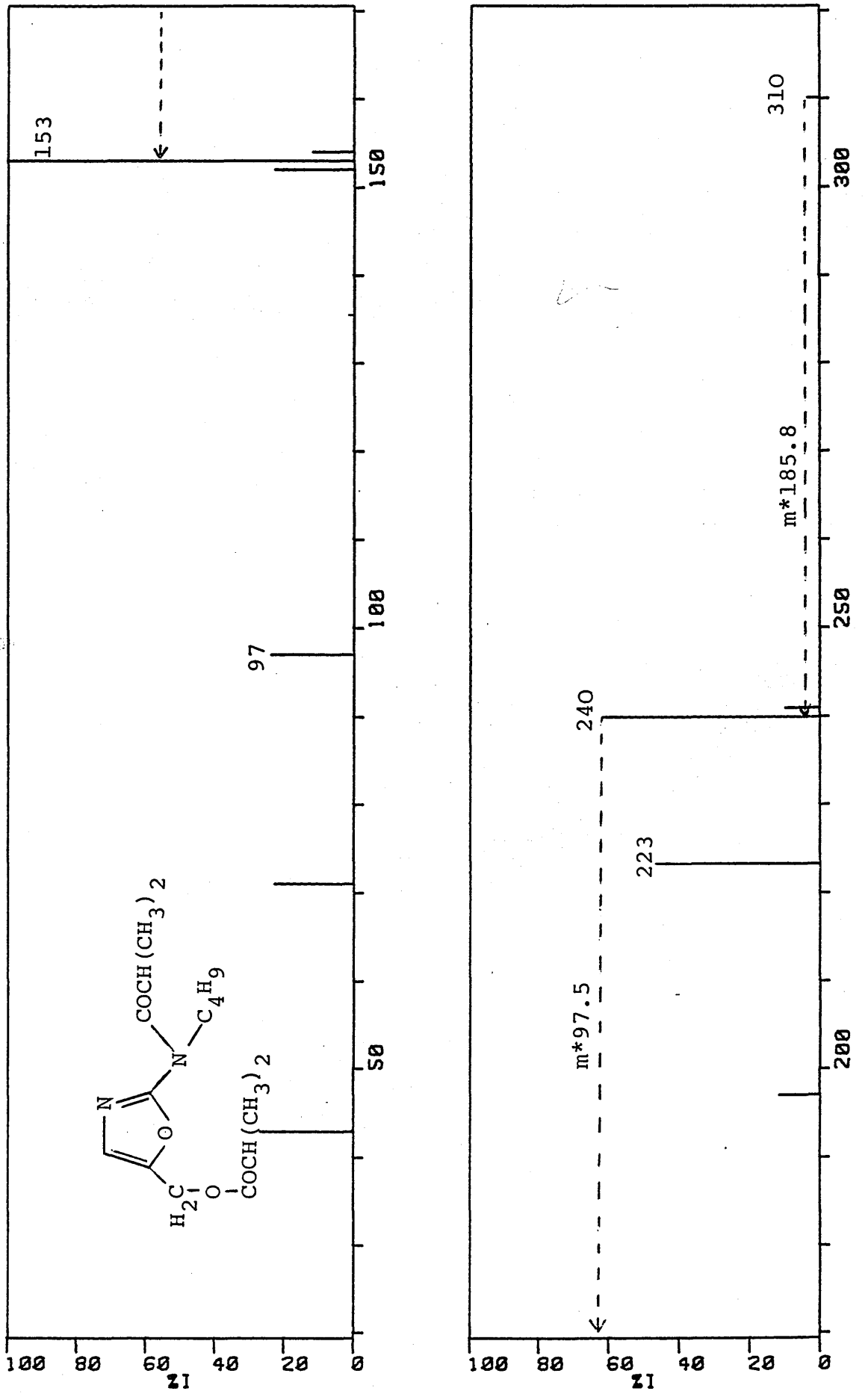


FIGURE 18: Mass spectrum of N-butyl-N-(5-isobutyroxymethyloxazol-2-yl)isobutyramide.

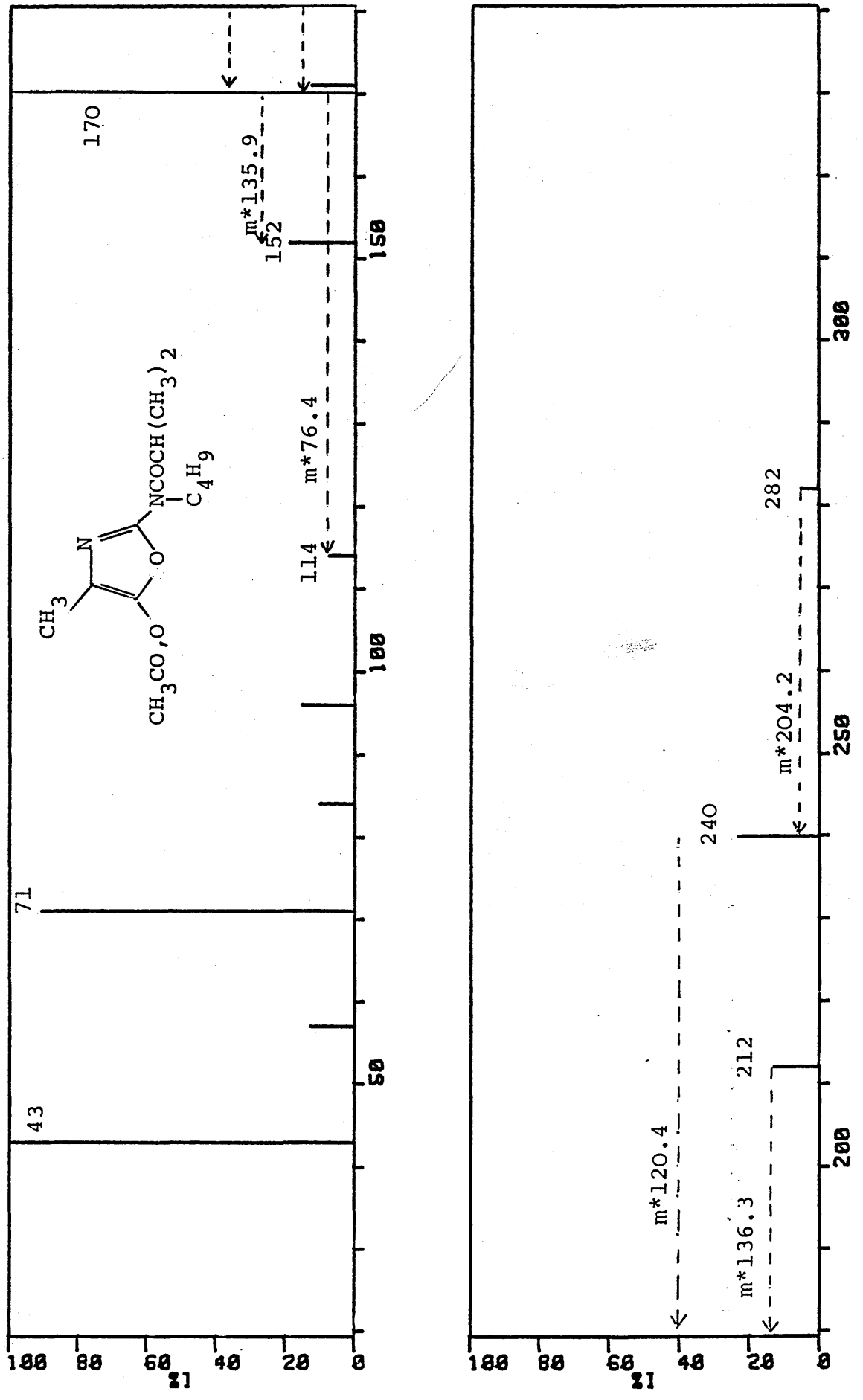


FIGURE 19: Mass spectrum of 2-methyl-N-(5-acetoxy-4-methyloxazol-2-yl)N-butyl-propanamide.

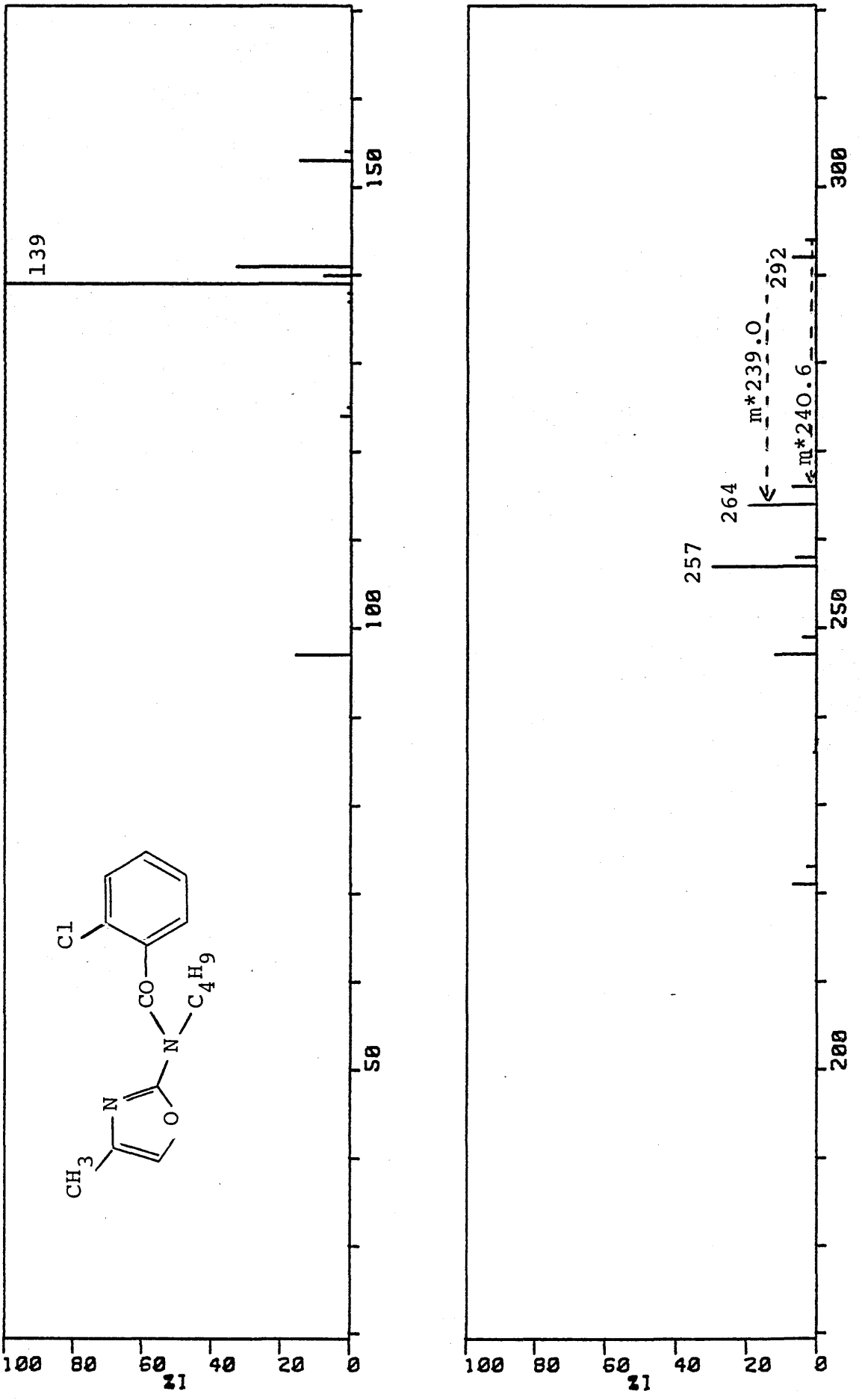


FIGURE 20: Mass spectrum of 2-chloro-N-butyl-N-(4-methyloxazol-2-yl)benzamide.

FIGURE 21: Mass spectrum of 2-methoxy-N-butyl-N-(4-methyloxazol-2-yl)benzamide.

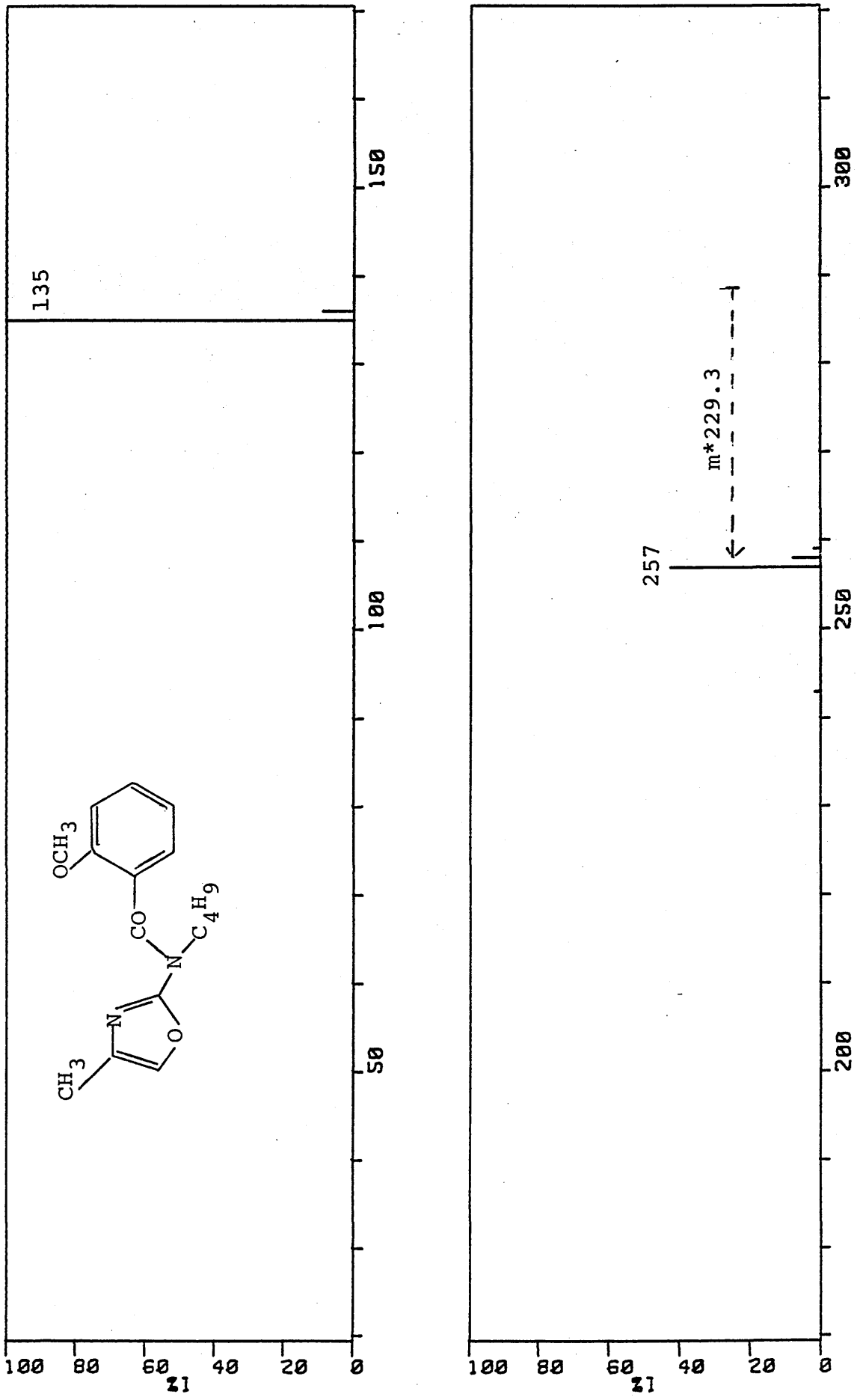


FIGURE 22a: Mass spectrum of 3-chloro-N-butyl-N-(4-methyloxazol-2-yl)-benzamide.

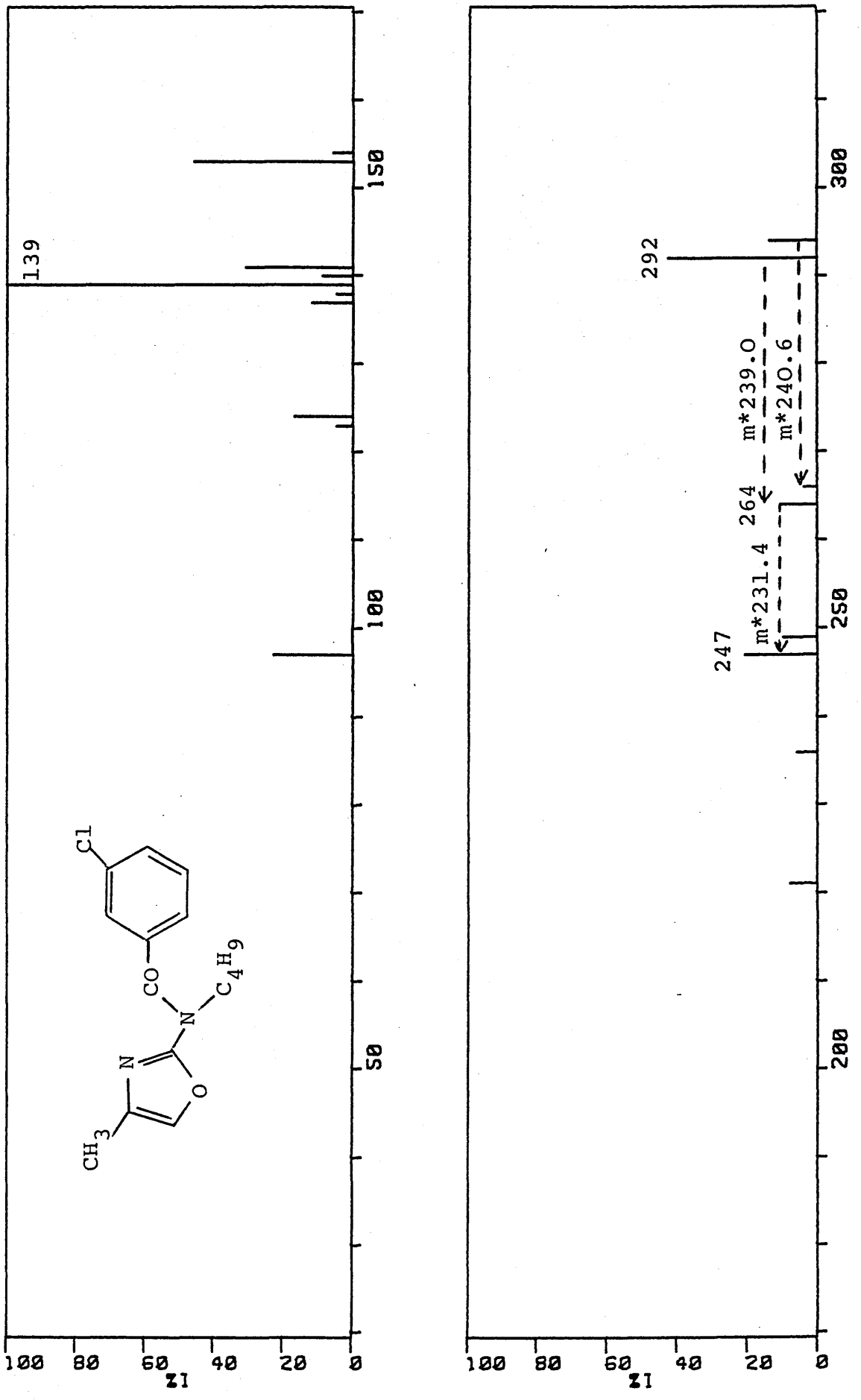


FIGURE 22b: Mass Spectrum of 4-chloro-N-butyl-N-(4-methyloxazol-2-yl)-benzamide.

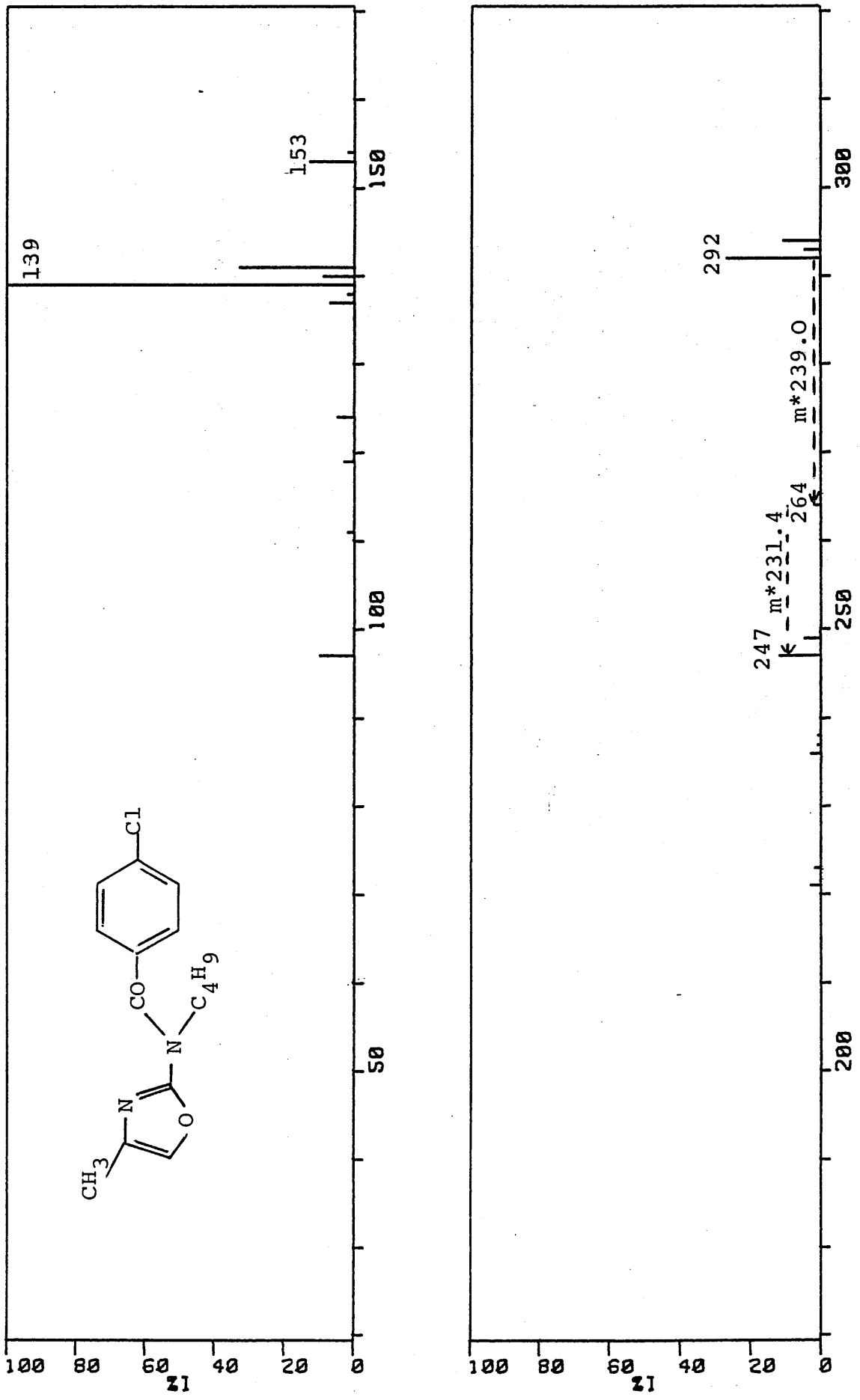
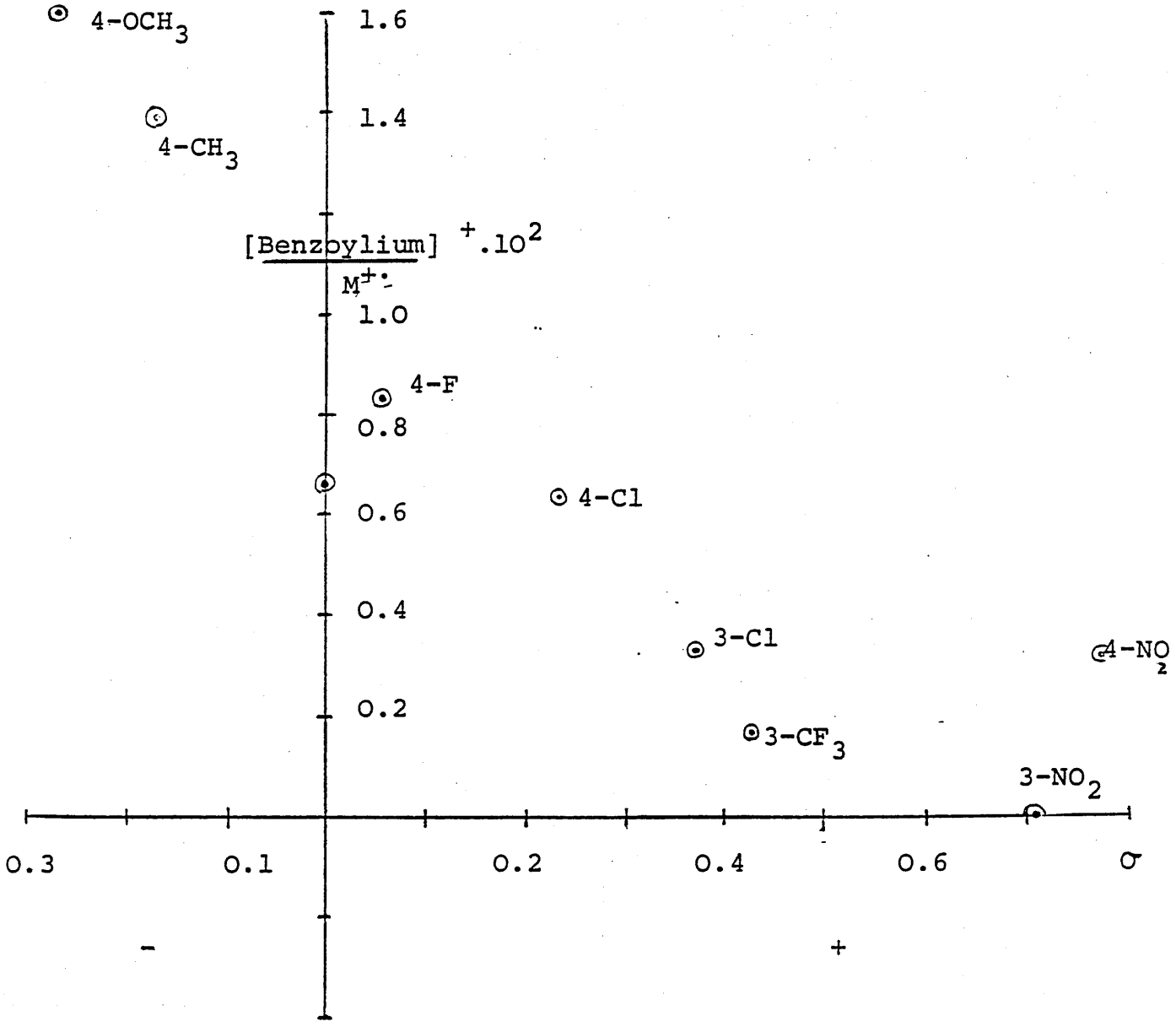


FIGURE 23: Correlation of ratio of benzoylium ion to molecular ion intensity in the mass spectra of N-butyl-N-(4-methyloxazol-2-yl)benzamides with Hammett σ Constants. (10 eV spectra)



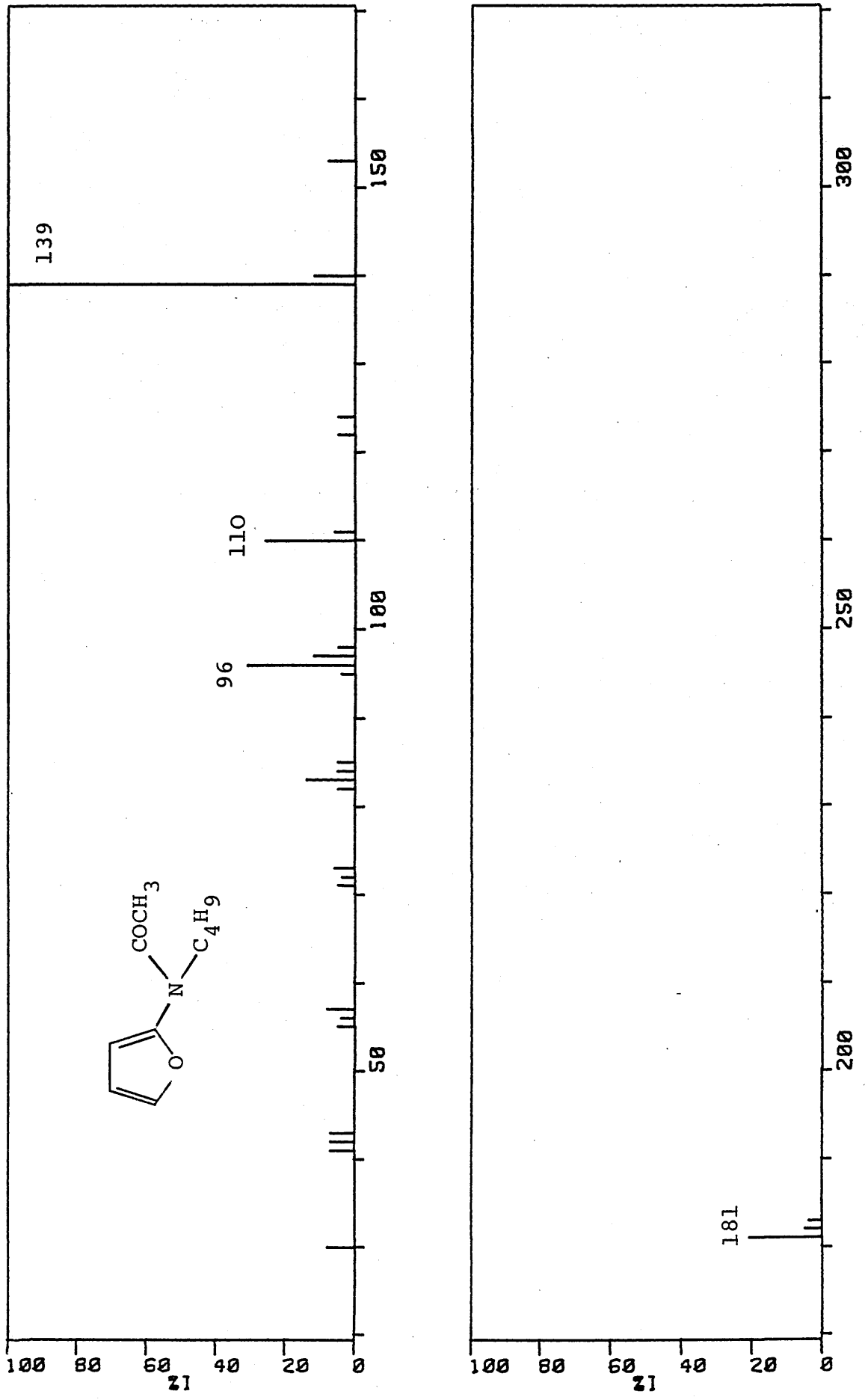
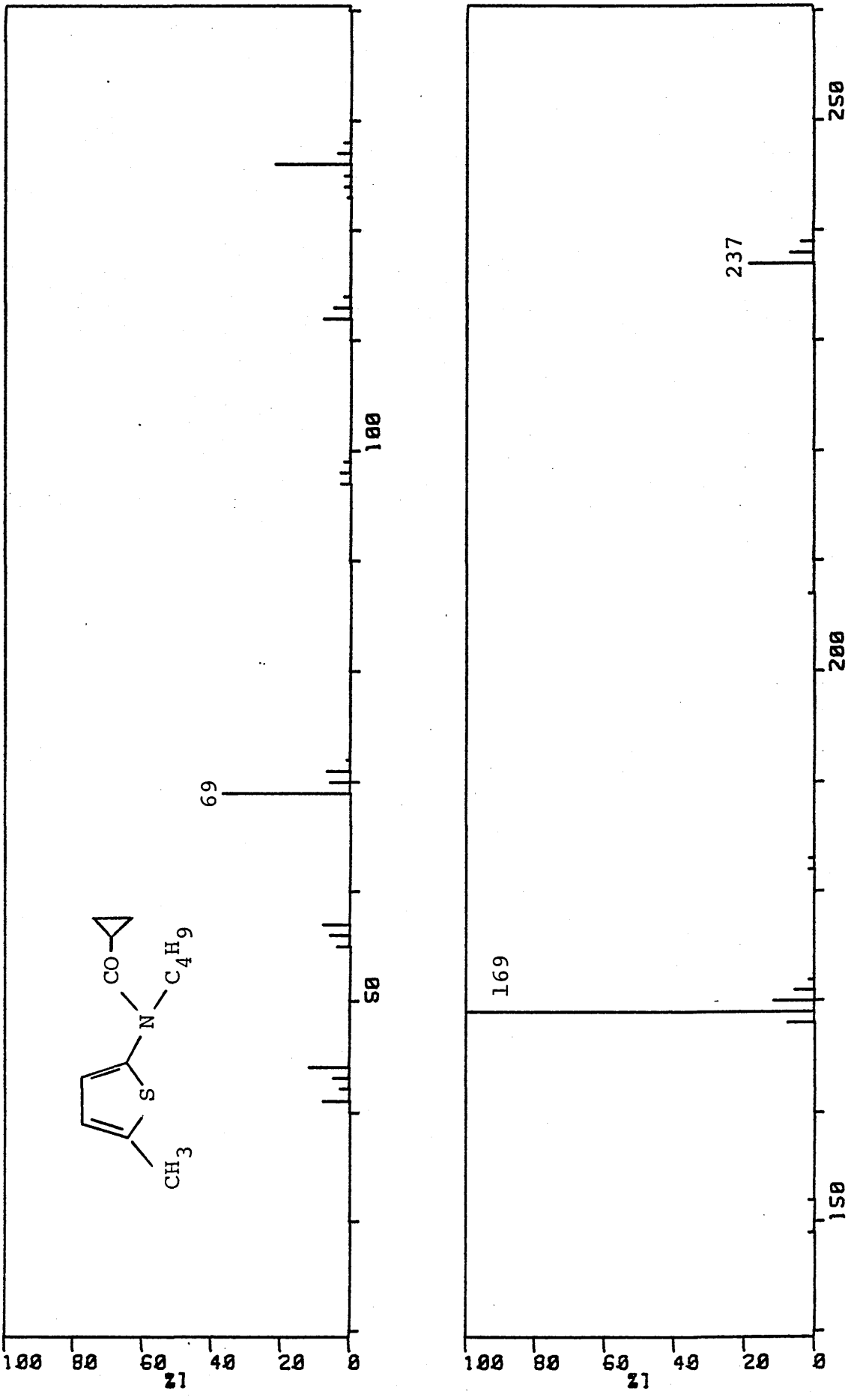


FIGURE 24: Mass spectrum of N-butyl-N-(fur-2-yl)acetamide.

FIGURE 25: Mass spectrum of N-butyl-N-(5-methylthien-2-yl)cyclopropanecarboxylic acid



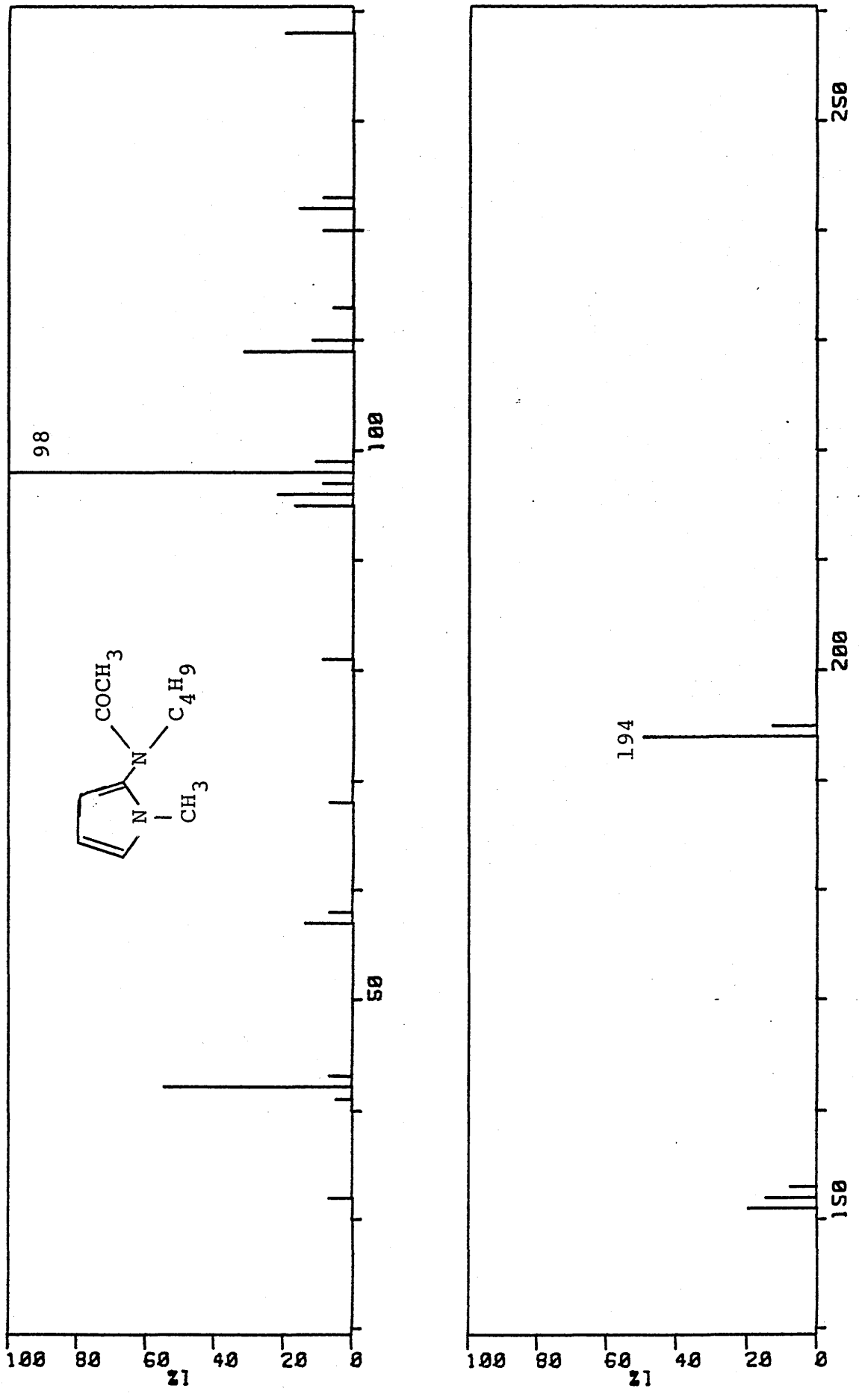


FIGURE 26: Mass spectrum of N-butyl-N-(1-methylpyrrol-2-yl)acetamide

FIGURE 27: Mass spectrum of N-butyl-N-(4-methylthiazol-2-yl)acetamide.

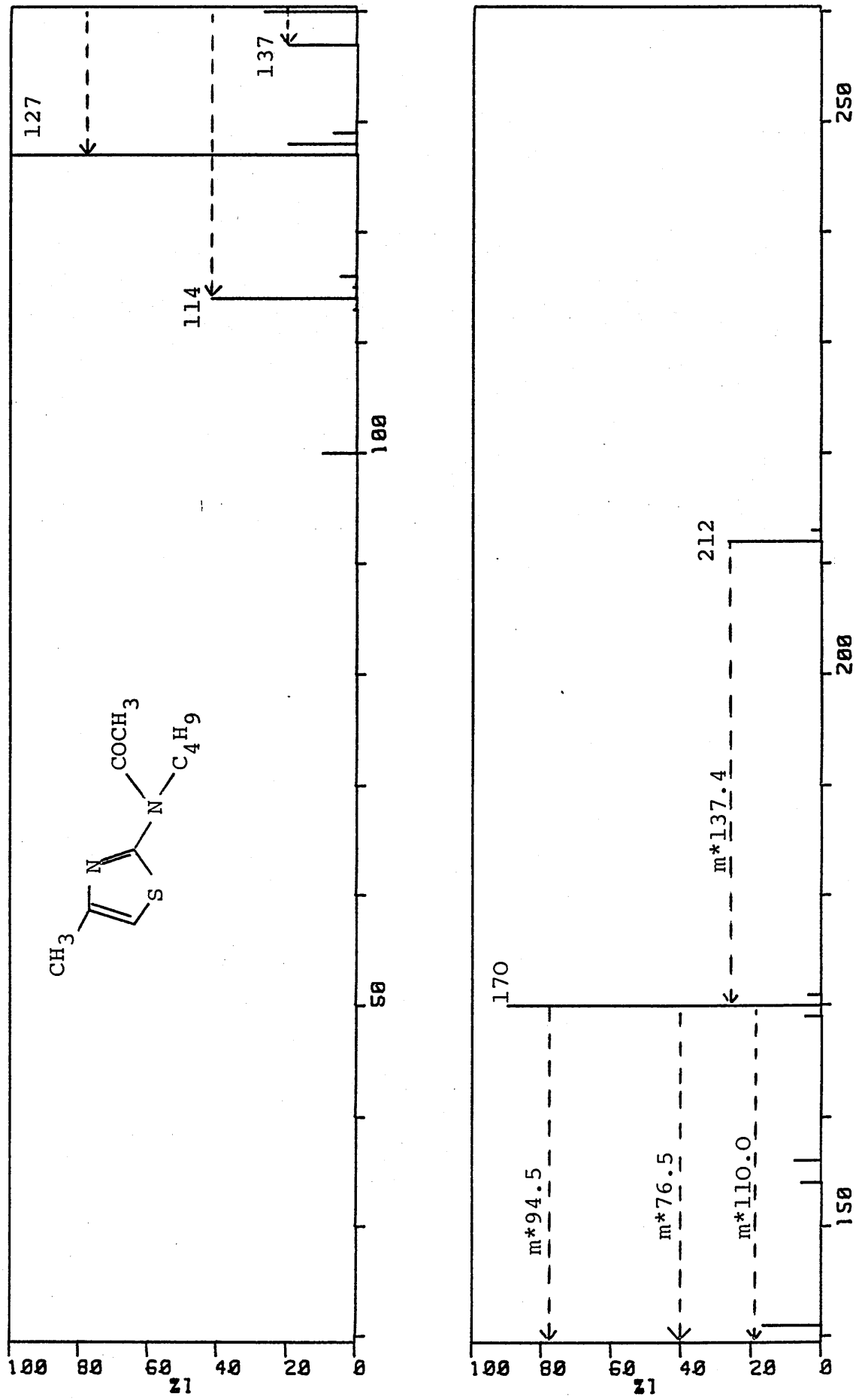
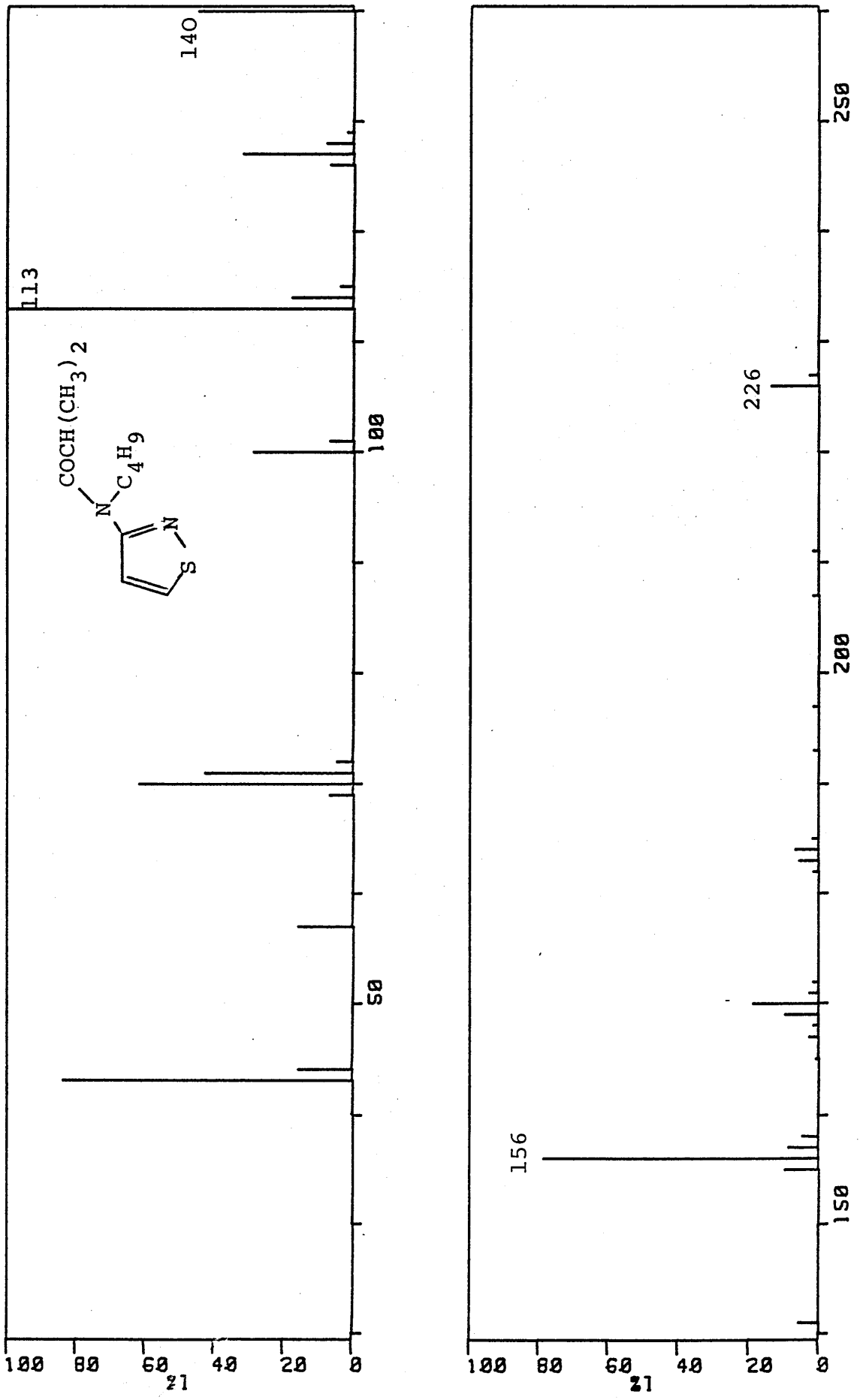


FIGURE 28: Mass spectrum of 2-methyl-N-butyl-N-(isothiazol-3-yl)propanamide.



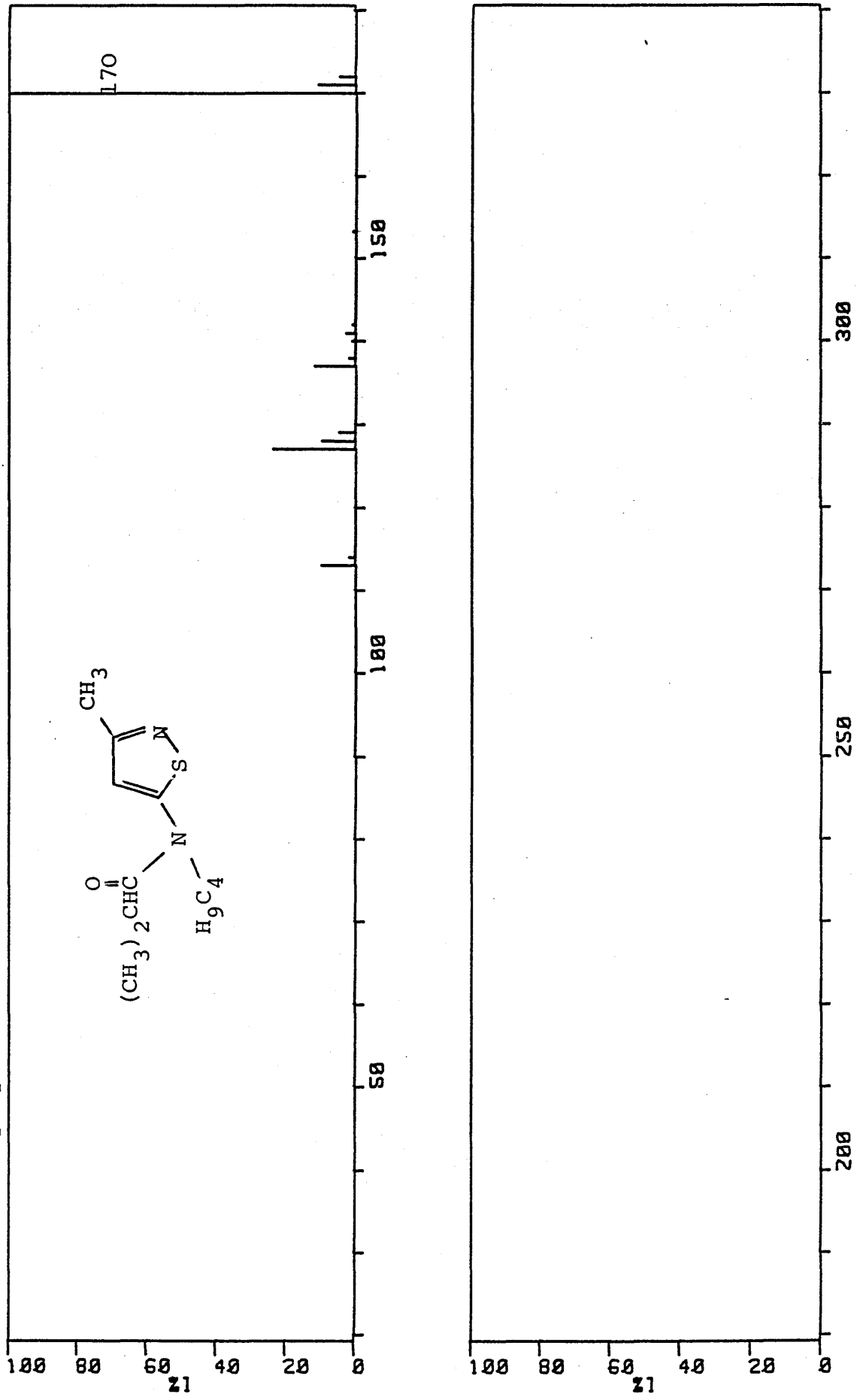


FIGURE 29: Mass spectrum of 2-methyl-N-butyl-N-(3-methylisothiazol-5-yl)-propanamide.

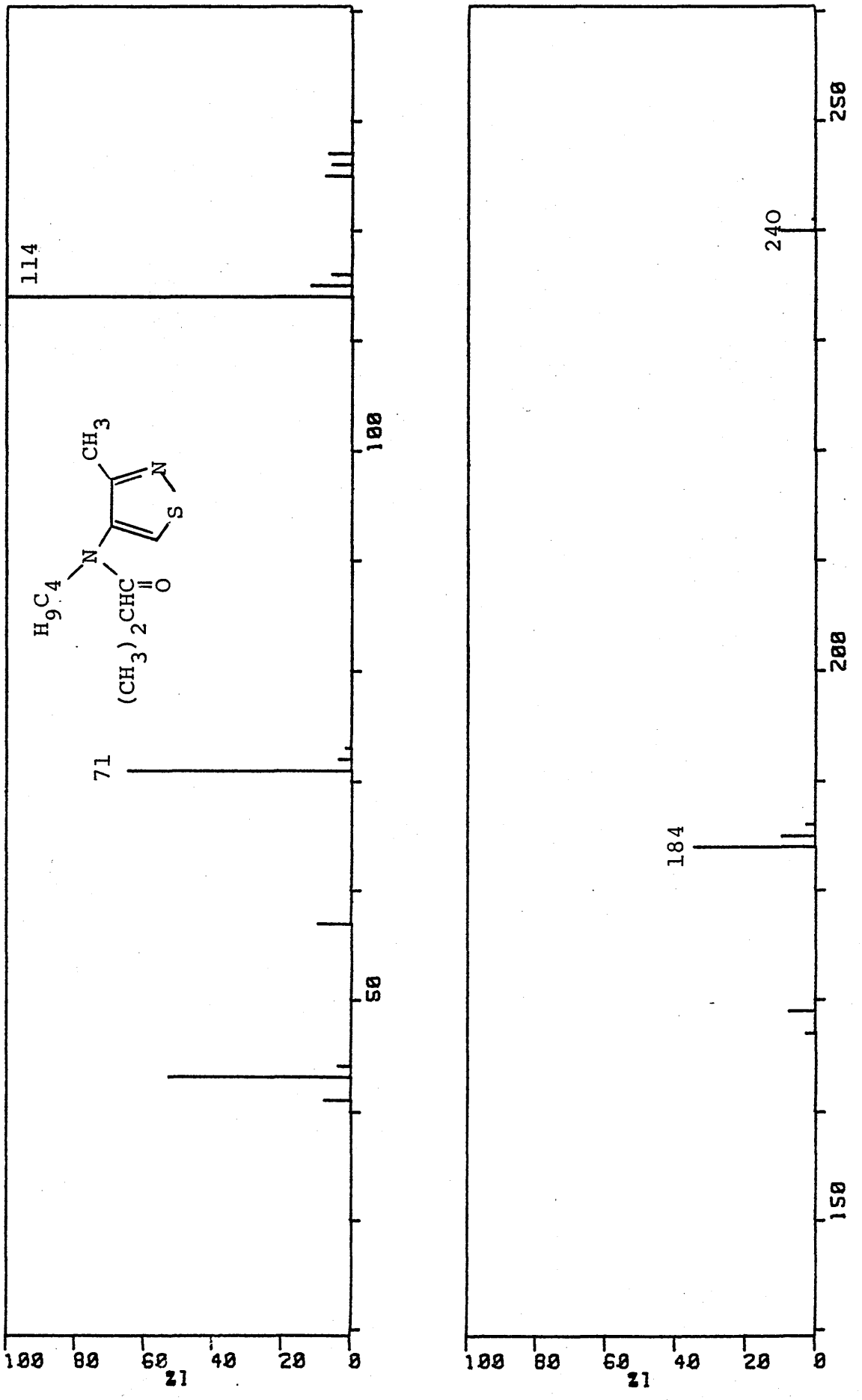


FIGURE 30: Mass spectrum of 2-methyl-N-butyl-N-3-(methylisothiazol-4-yl)-propanamide.

FIGURE 31: Mass spectrum of 2-methyl-N-butyl-N-(1-methylpyrazol-5-yl)propanamide

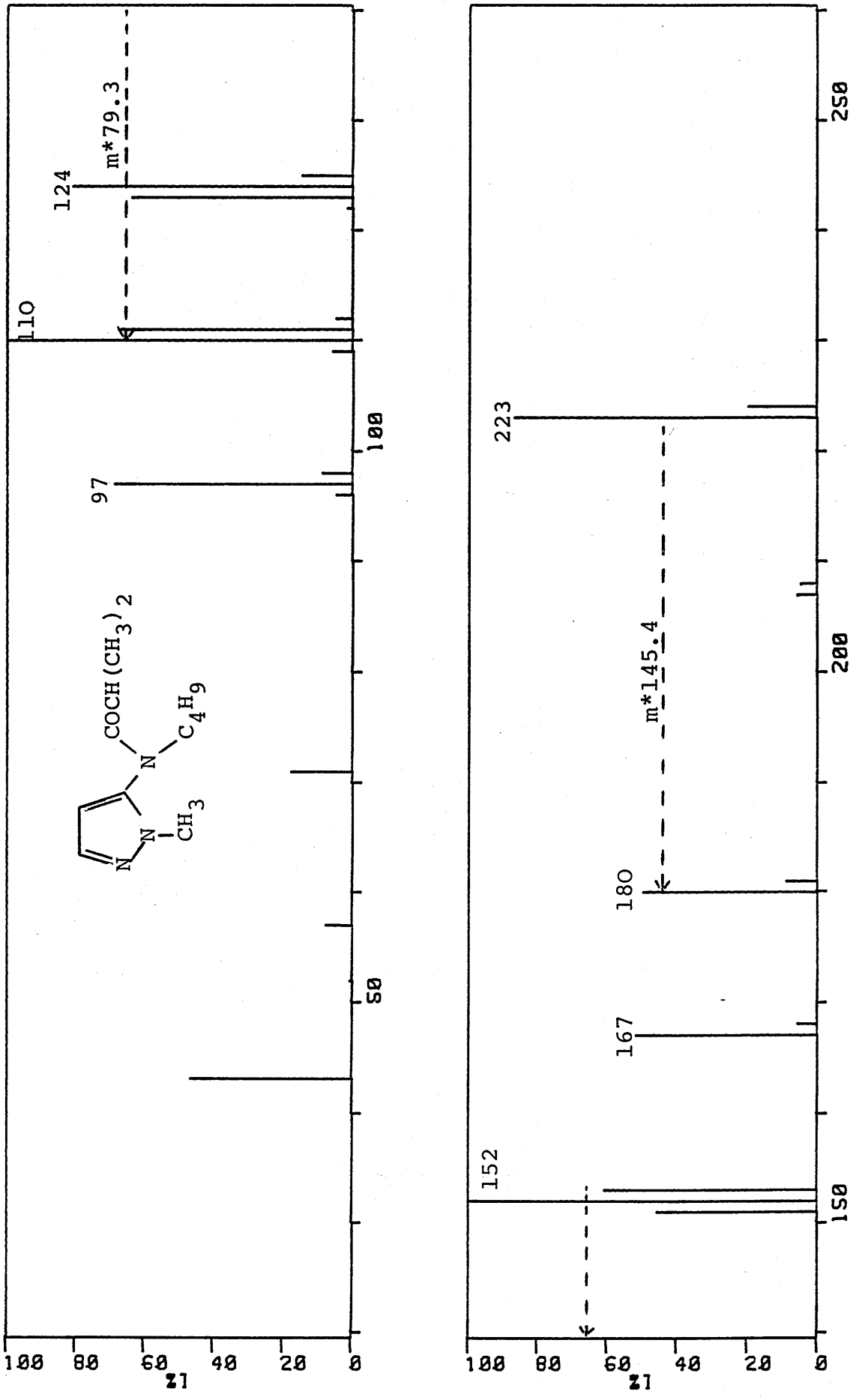
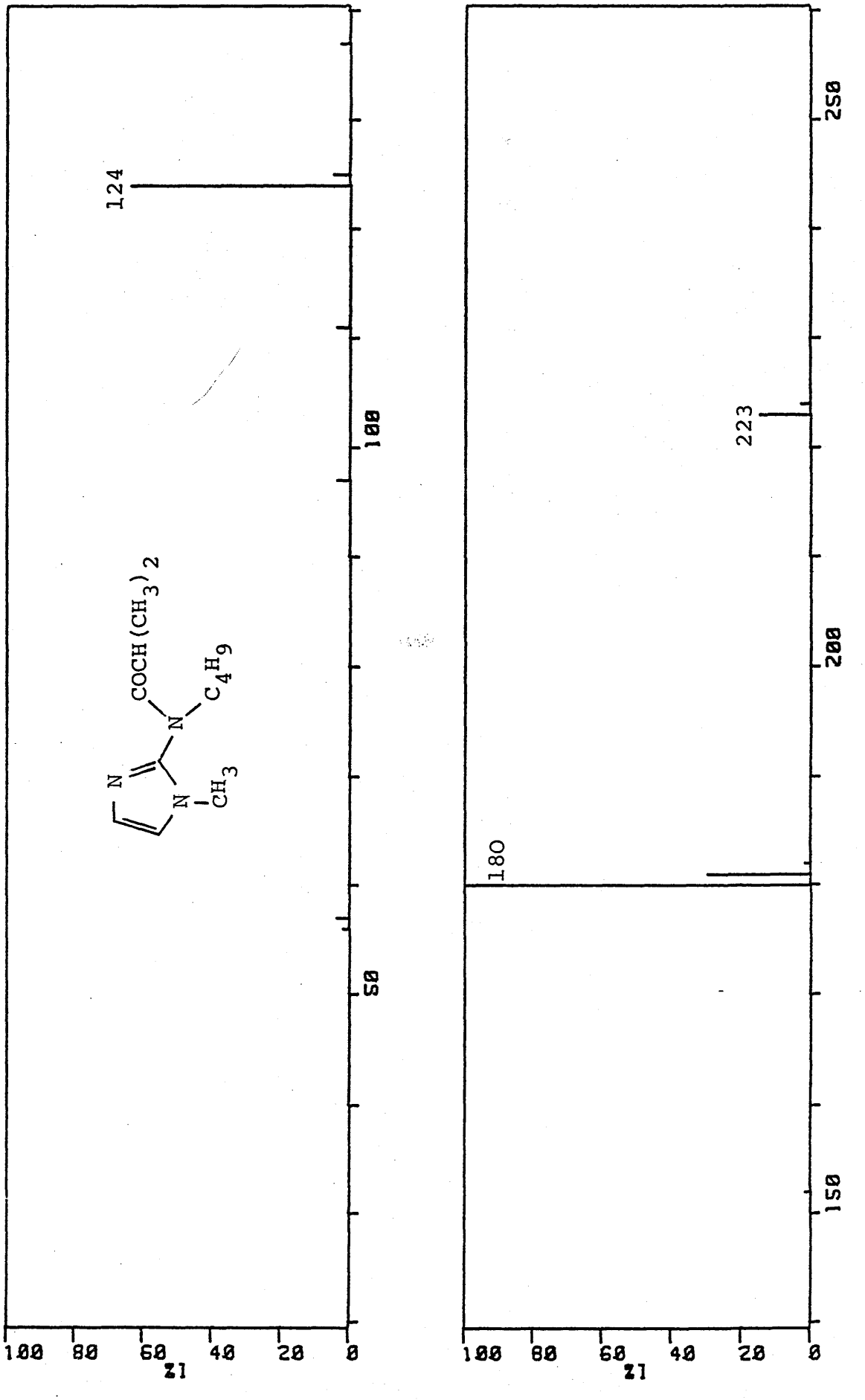


FIGURE 32: Mass spectrum of 2-methyl-N-butyl-N-(imidazol-2-yl)propanamide



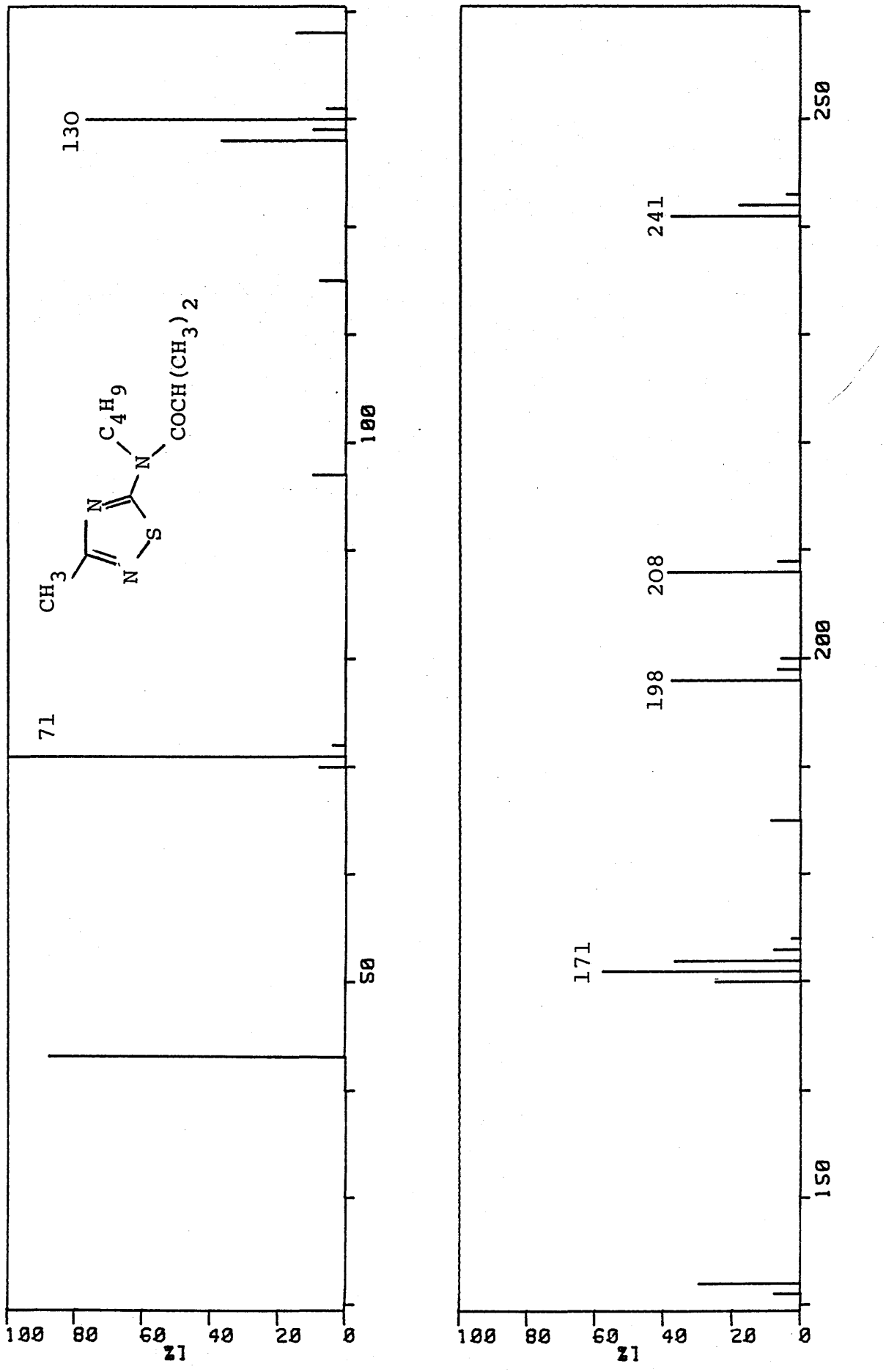


FIGURE 33: Mass spectrum of 2-methyl-N-butyl-N-(3-methyl-1,2,4-thiadiazol-5-yl)-propanamide.

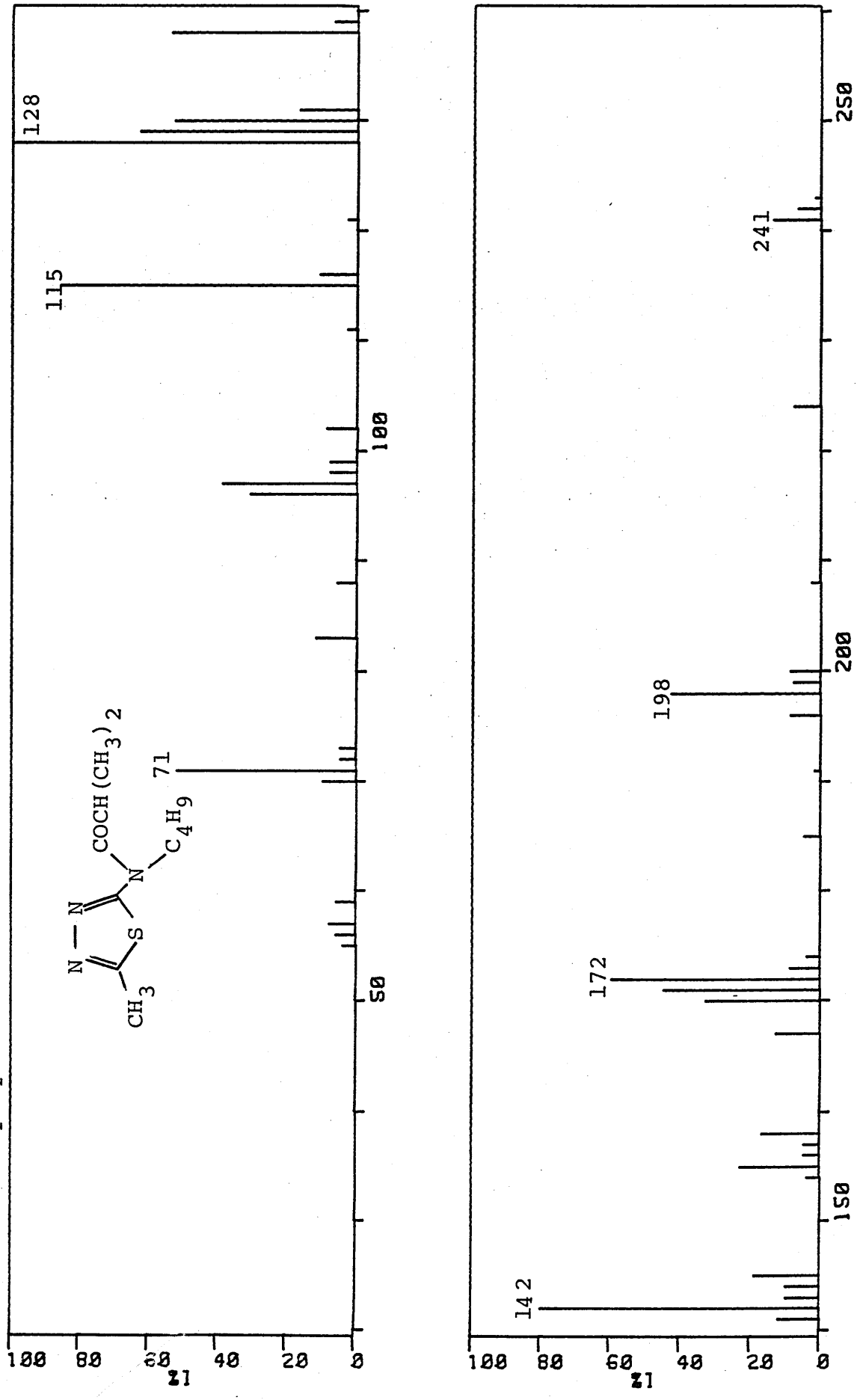


FIGURE 34: Mass spectrum of 2-methyl-N-butyl-N-(2-methyl-1,3,4-thiadiazol-5-yl)-propanamide.

FIGURE 35: Mass spectrum of 2-methyl-N-butyl-N-(2-methyl-1,3,4-oxadiazol-5-yl)-propanamide.

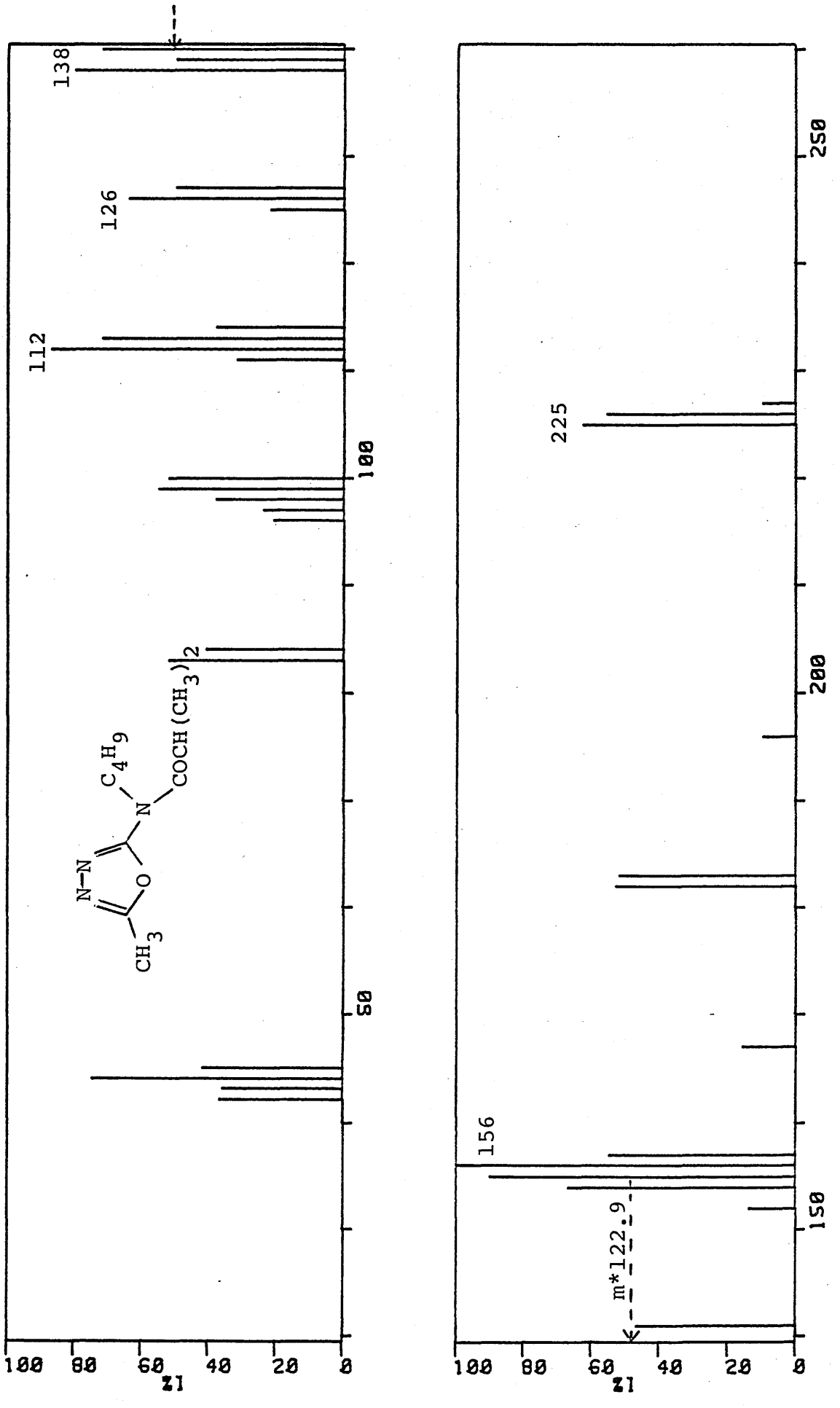
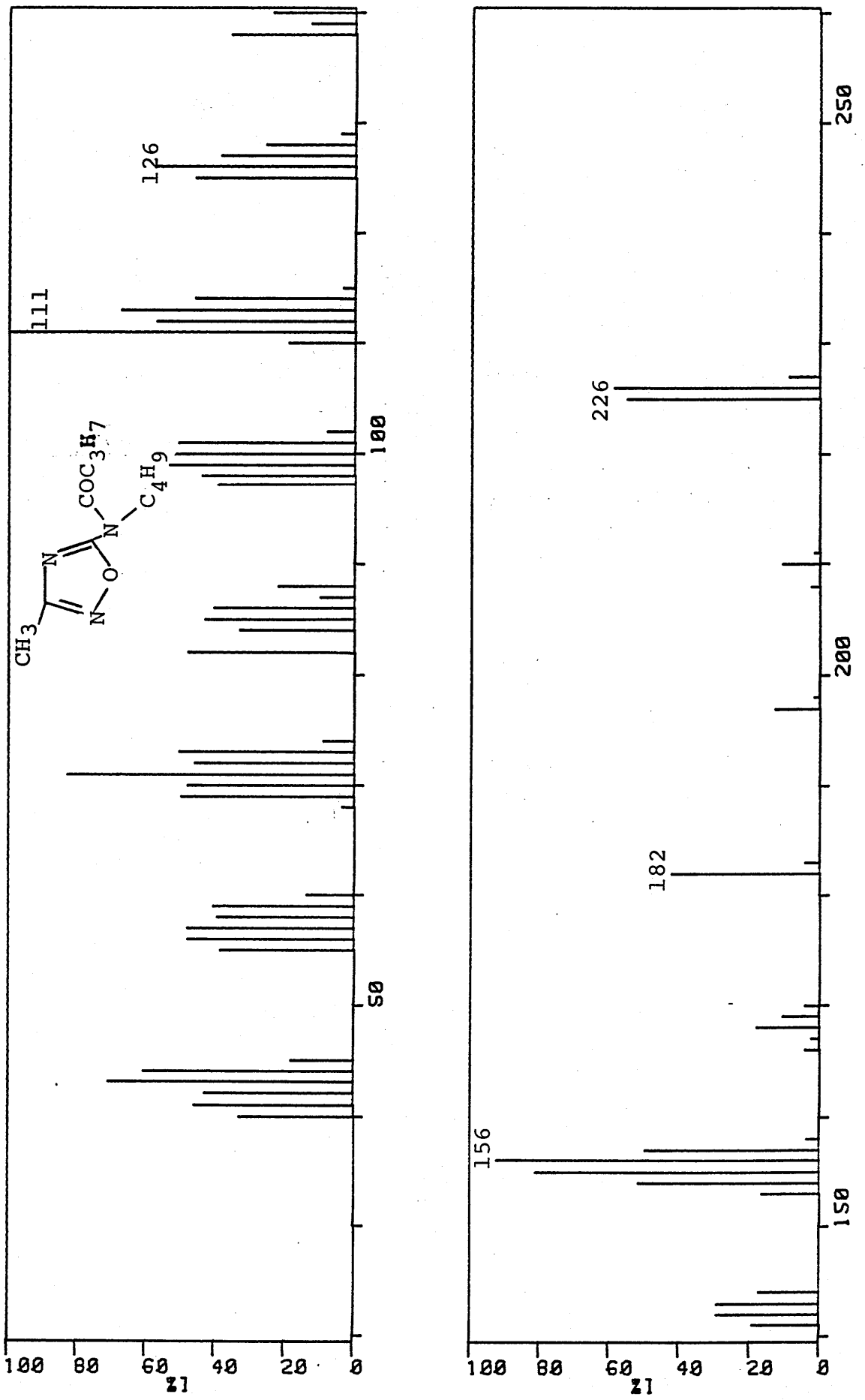


FIGURE 36: Mass spectrum of N-butyl-N-(3-methyl-1,2,4-oxadiazol-5-yl)-butanamide.



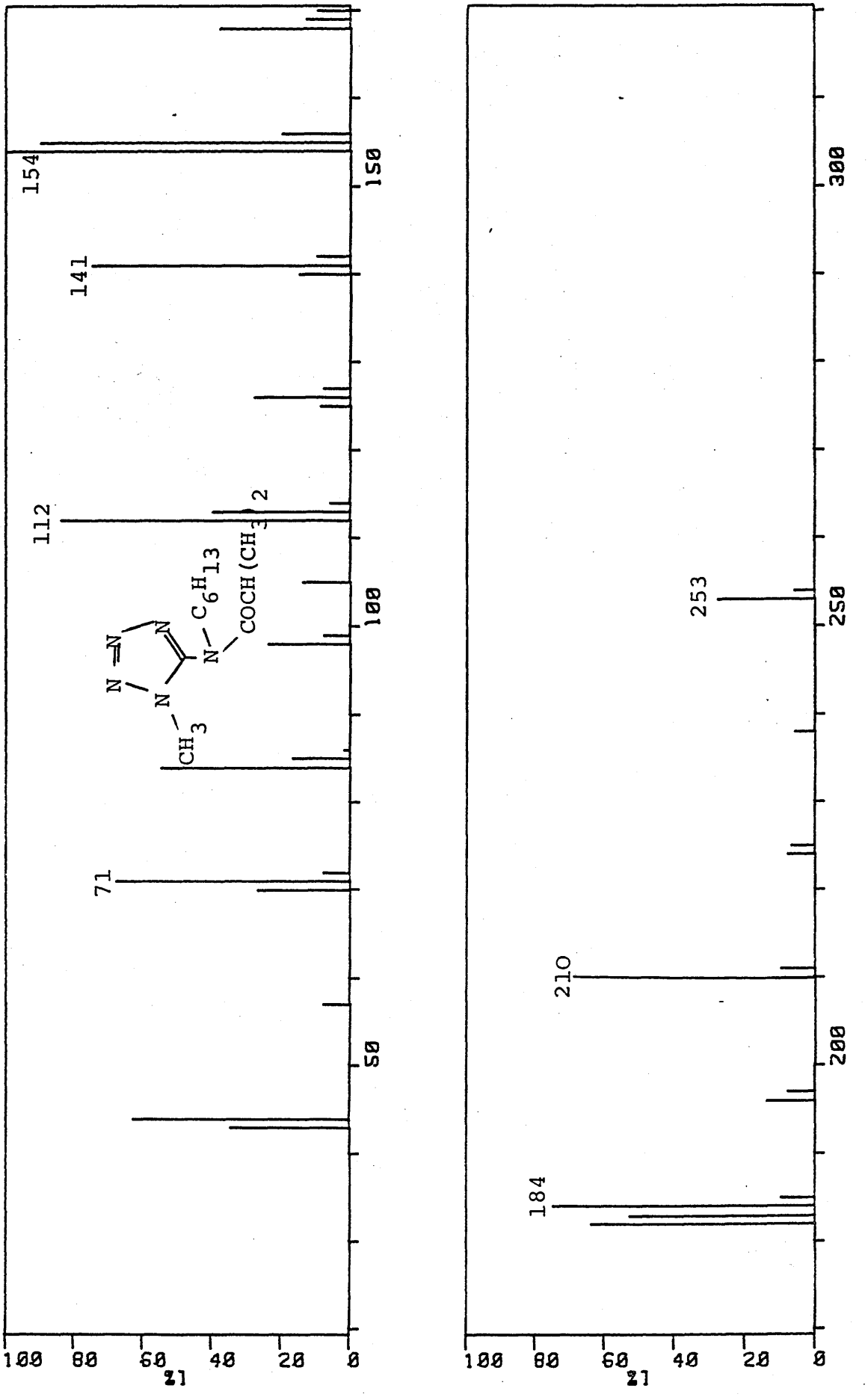


FIGURE 37: Mass spectrum of 2-methyl-N-hexyl-N-(1-methyltetrazol-5-yl)-propanamide.