

## MASS SPECTROMETRY OF OXAZOLES

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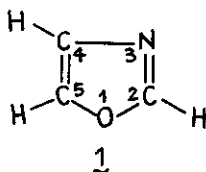
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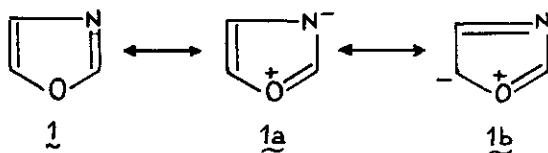
**Abstract** - The mass spectral behaviour of oxazole and its derivatives represents quite a particular aspect of the chemistry of these heterocyclic compounds but is of paramount importance for the understanding of their structures. This review is an attempt to rationalize and discuss the major advances reported since pioneer studies.

## INTRODUCTION

Oxazoles belong to a class of five-membered ring heteroaromatic compounds. The oxazole ring system (1) has an oxygen atom and a pyridine-type nitrogen atom at the 1- and 3-positions of the ring.



The classical structure of oxazole is somewhat inconsistent with its aromatic character and small dipole moment, but a set of resonance structures involving dipolar forms (1a, 1b) appears to give a more accurate picture.



Due to the contribution of these ionic structures, the oxazole ring possesses a great reactivity towards electrophilic and nucleophilic reagents. The resistance towards ring scission by acids and alkali makes the oxazoles to behave in between furans and pyridines. The ease with which they undergo Diels-Alder reactions and singlet oxygen autooxidation clearly shows that oxazoles are not fully aromatic compounds.

It is not our intention to dwell on the chemical properties of oxazole and its derivatives because this aspect has been the subject of recent reviews covering the field of oxazole chemistry up to 1973<sup>1-4</sup>. A large emphasis has been placed in these monographs on the methods of synthesis and their reactions while only few accounts deal with the physicochemical and spectroscopic properties of oxazoles<sup>5,6</sup>.

Furthermore, the wide range of application of oxazole derivatives sets this class of heteroaromatic compounds beyond the synthetic interest of their preparations: in fact they find application as scintillants<sup>7-19</sup> (particularly the 2,5-diaryl derivatives owing to their fluorescence properties), as optical sensitizing dyes<sup>20-28</sup> in silver halide emulsion in photography (especially oxazole cyanine and mesocyanine dyes, 2-mercaptooxazoles and their silver salts), as pharmaceuticals (because of their antiinflammatory<sup>29-39</sup>, antibacterial, antimicrobial, antiviral, analgesic<sup>40-51</sup>, antitubercular<sup>52,53</sup>, hypnotic, anticonvulsant<sup>54,55</sup> and hypertensive<sup>56,57</sup> properties).

The aim of the present review is to survey the developments made in the field of the mass spectrometry of oxazoles, stressing what a useful analytical tool represents this technique in the chemistry of heterocyclic compounds.

Pioneering studies on the mass spectrometry of oxazoles are referred to an attempt of establishing the structure of a new oxazole alkaloid: halfordinol and its derivatives<sup>58</sup>. For this alkaloid previous chemical and analytical data<sup>59,60</sup> had proved the presence of an oxazolic ring doubly substituted with pyridyl and hydroxyphenyl groups whose relative positions were unknown. The comparison of the mass spectrum of halfordinol with the mass spectra of 2,4- and 4,5-diphenyloxazoles, synthesized on purpose as models, permitted to establish the exact structure of this alkaloid corresponding to 2-(3-pyridyl)-5-(p-hydroxyphenyl)oxazole.

In this contest the electron impact fragmentation patterns of oxazole and its derivatives will be rationalized and discussed in some details.

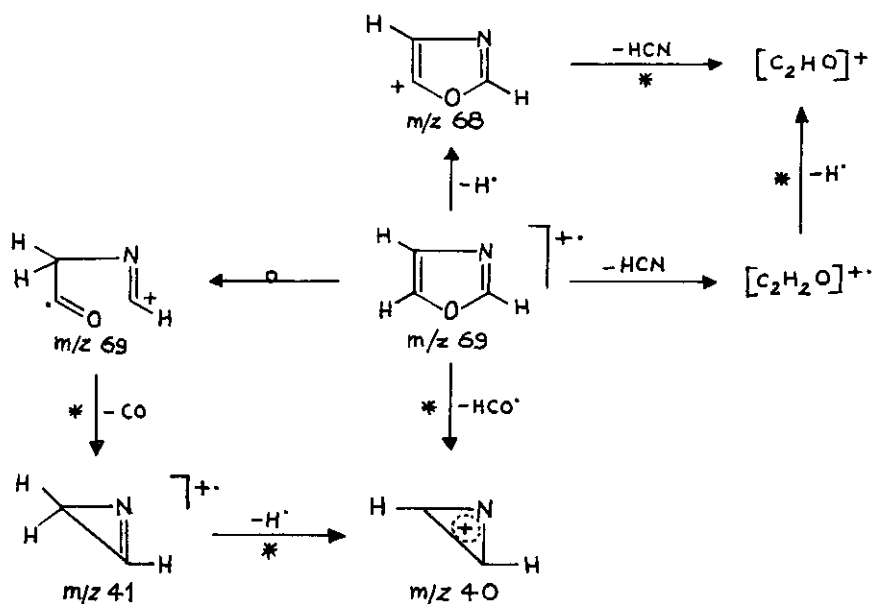
## OXAZOLE

The electron impact induced fragmentation mechanisms of oxazole (1) have been studied by H.-E. Audier et al.<sup>61</sup> using both experimental techniques (metastable ions studies, deuteration, IP-AP measurements) and M.O. calculation (Streitwieser, CNDO/2 and "ab initio" methods).

The 70 eV mass spectrum of oxazole appears lacking of peaks, as it was expected. The base peak corresponds to the molecular ion ( $m/z$  69), which decomposes in four fragments at  $m/z$  68 ( $[M-H]^+$ ),  $m/z$  42 ( $[M-HCN]^+$ ),  $m/z$  41 ( $[M-CO]^+$  and  $[M-CH_2N]^+$ ) and  $m/z$  40 ( $[M-HCO]^+$ ).

By means of accurate metastable measurements on oxazole itself and by studying 2-d<sub>1</sub>-oxazole mass spectrum the following fragmentation pattern was established:

Scheme 1



The mass spectrum of 2-d<sub>1</sub>-oxazole makes it also possible to clarify the fragmentation pathways, indicating which atoms are involved:

- i)  $[\text{M}-\text{H}]^+$  ions correspond to the loss of H atom at position 5,
- ii)  $[\text{M}-\text{HCO}]^+$  ions correspond to the loss of oxygen, C atom at position 5 and its H atom,
- iii)  $[\text{M}-\text{HCN}]^{++}$  ions correspond to the loss of nitrogen, C atom at position 2 and its H atom.

Appearance potentials (AP) values were determined for all the ions reported in Scheme 1 by using the Lossing's semilogarithmic plot method ( see Table 1 ).

Table 1 - Appearance Potentials (AP) and Activation Energies (AE) of oxazole ions.

Ions	AP (eV)	AE = AP - IP (eV)
$[\text{M}]^{++}$	9.60	-
$[\text{M}-\text{CO}]^{++}$	11.00	1.40
$[\text{M}-\text{H}]^+$	12.70	3.10
$[\text{M}-\text{HCN}]^{++}$	12.15	2.55
$[\text{M}-\text{HCO}]^+$	14.10	4.50

Activation energies (AE) for the formation process of these ions, calculated as difference between the APs and the Ionization potential (IP) of oxazole itself, are also given in Table 1.

AP values for m/z 40 and m/z 41 species should be regarded with particular care being these

ions originated through different pathways.

A theoretical approach was done with the extent to clarify the heterocyclic ring clavages, using CNDO/2 and "ab initio" calculations. The bond orders for the neutral molecule and the molecular ion (considering the latter having the same structure as the former), shown in Table 2, indicate the 1-2 bond as the weakest in both the calculation methods.

Table 2 - Bond orders of  $[M]$  and  $[M]^{++}$  of oxazole calculated by CNDO/2 and "ab initio" methods.

calculation methods	bonds					
		1-2	2-3	3-4	4-5	5-6
CNDO/2	M	0.422	0.861	0.403	0.881	0.354
	$M^{++}$	0.389	0.660	0.603	0.570	0.420
"ab initio"	M	0.317	0.491	0.388	0.562	0.319
	$M^{++}$	0.298	0.448	0.404	0.451	0.331

Therefore 1-2 bond cleavage can be assumed as the more probable process for the molecular ion.

The likely initial rupture of 1-2 bond is also confirmed by the stability of the possible different open structures of  $M^{++}$ . MO calculations show that an increase of the bond length causes a decrease of the corresponding bond order.

The energies of three hypothetical ion structures, obtained increasing of 0.4 Å the 1-2, 1-5 and 3-4 bond lengths and calculated by optimization, are reported in Table 3.

Table 3 - Total energies (a.u.) of ion structures by lengthening of 0.4 Å the 1-2, 1-5 and 3-4 bonds of oxazole.

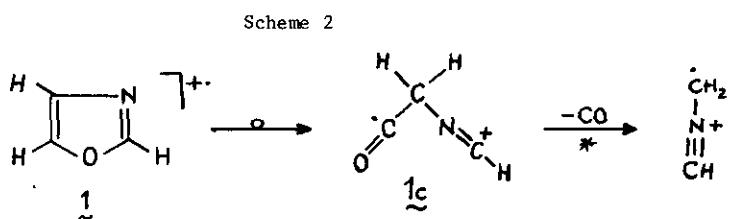
Bonds	Total energies (a.u.) by CNDO/2 method	Total energies (a.u.) by ab initio method
1-2	- 52.9479	- 241.2273
1-5	- 52.9044	- 241.1878
3-4	- 52.9080	- 241.1775

From Table 3 it can be observed that the most stable ion structure is the one corresponding to 1-2 bond lengthening.

These results bear evidence that the initial rupture of 1-2 bond leads to different transition states corresponding to different  $M^{++}$  oxazole fragmentations but they are not sufficient enough to gain insight into either the concerted character of these fragmentations or the intermediate nature of the originated ions.

Increasing the length  $d_{1-2}$  of the 1-2 bond, an increase of the 4-5 bond order is observed: these calculations indicate that elimination of  $\text{HCO}^\cdot$  cannot be the result of subsequent cleavages of 1-2 and 4-5 bonds of the heterocyclic ring. Then the mechanism of this fragmentation must be assumed as a concerted one.

Assuming  $\underline{1c}$  (Scheme 2) to be the open structure of the molecular ion, in which classic linear geometries of CO, HCN and ketene are postulated, the more stable final configuration is consistent with CO elimination.



For the HCN elimination various mechanisms are possible, the more reasonable of which are:

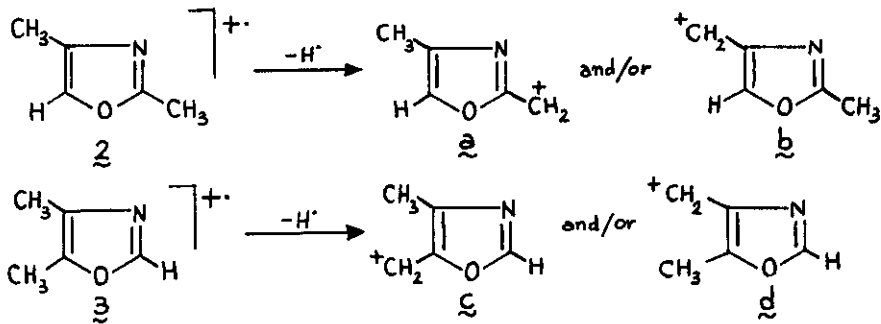
- i) loss of HCN from an open, and not transposed, configuration of  $\text{M}^{+\cdot}$ , i.e. from successive cleavages of 1-2 and 3-4 bonds. Actually CNDO/2 calculations indicate that the progressive opening of the heterocyclic ring (increasing  $d_{1-2}$ ) is followed by a weakening of 3-4 bond and a strengthening of 2-3, 4-5 and 5-1 bonds;
- ii) loss of HCN from  $\text{M}^{+\cdot}$  by means of a concerted mechanism, i.e. a simultaneous increasing of  $d_{1-2}$  and  $d_{3-4}$ .

The comparison between the calculations related to these two mechanisms indicates the concerted mechanism as the most likely to happen, but it does not rule out the participation of the former. Then HCN loss probably results from both mechanisms.

#### METHYL SUBSTITUTED OXAZOLES<sup>62</sup>

2,4- and 4,5-dimethyloxazoles (compounds 2 and 3 respectively) are markedly unlike in their mass spectrometric behaviour. According to mass spectrometry of alkylpyridines<sup>63</sup>,  $[\text{M}-\text{H}]^+$  ions are more abundant for 3 which may give rise to c and d species (Scheme 3), certainly more stable than a and b species originating from 2.

Scheme 3



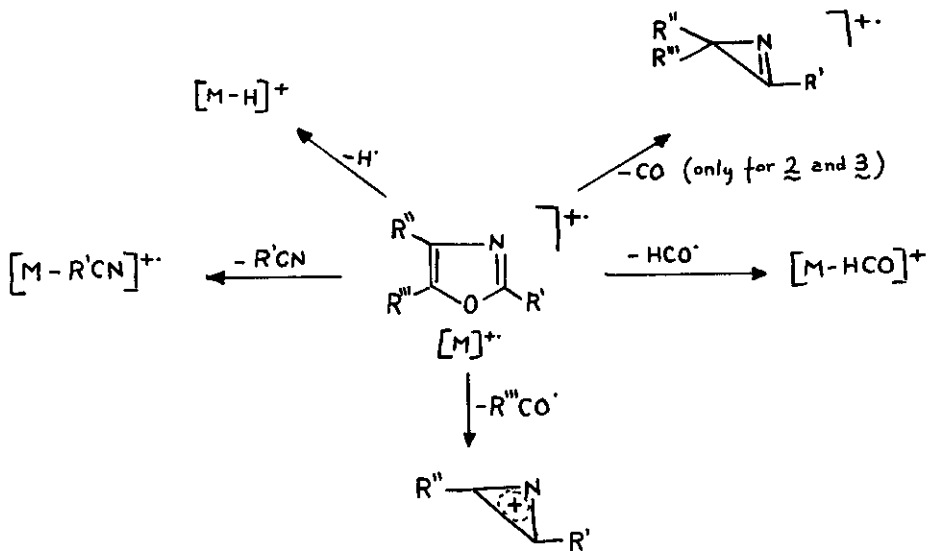
Primary losses of  $\text{CH}_3^\cdot$  and  $\text{HCN}$  from  $\text{M}^{+\cdot}$  are distinctive features of compound 3; no peaks corresponding to these fragmentations are present in the mass spectrum of 2. Also the fragments  $[\text{CH}_3\text{CO}]^+$  and their complementary species  $[\text{M}-\text{CH}_3\text{CO}]^+$  are very abundant only for compound 2.

As far as 2,3,4-trimethyloxazole (4) and (2) are concerned loss of  $\text{CH}_3\text{CN}$  is observed.

Again, less abundant peaks are present in the mass spectra of 2, 3 and 4 due to primary losses of  $\text{HCO}^\cdot$  and of  $\text{CO}$  (only for 2 and 3) from  $\text{M}^{+\cdot}$ , indicating the presence of wide skeletal rearrangements of  $\text{M}^{+\cdot}$ .

It is then possible to depict the following fragmentation pattern for methyl substituted oxazoles:

Scheme 4



2:  $\text{R}'=\text{R}''=\text{CH}_3$ ,  $\text{R}'''=\text{H}$

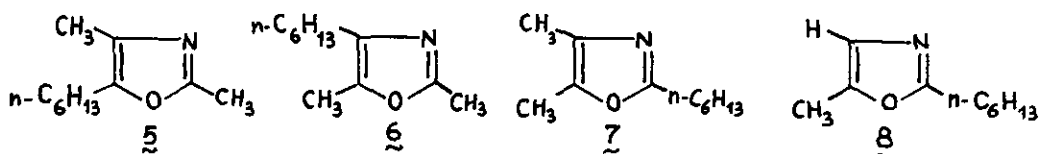
3:  $\text{R}'=\text{H}$ ,  $\text{R}''=\text{R}'''=\text{CH}_3$

4:  $\text{R}'=\text{R}''=\text{R}'''=\text{CH}_3$

ALIPHATIC LONG CHAIN SUBSTITUTED OXAZOLES<sup>62</sup>

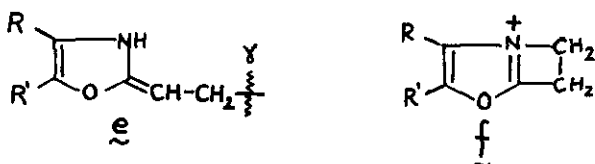
The introduction of an aliphatic long chain group in the free position of dimethyl substituted oxazoles gives rise to a typical set of ionic species due to the fragmentation of the chain. Furthermore the heterocyclic ring cleavages described in Scheme 4 seem to be depressed: as particular case no loss of R'CN is observed.

Most attention was paid in order to rationalize the mass spectrometric behaviour of these compounds with respect to the long chain group positions: for such a reason the mass spectra of compounds 5 to 8 were compared.



The  $\beta$ -scission results to be a more favourable process for compounds 5 and 6, according to the larger stability of the product ions, which are practically identical to c and d species (Scheme 3). The  $\beta$ -cleavage with H rearrangement ( $[M-C_5H_{10}]^{+}$ ) is also current in all these compounds and results to be especially favourite for compound 6.

On the contrary the  $\gamma$ -scission results to be enhanced in compounds 7 and 8, probably because of the possibility of an allylic cleavage in the tautomeric form e and/or the formation of a stabilized ion f.

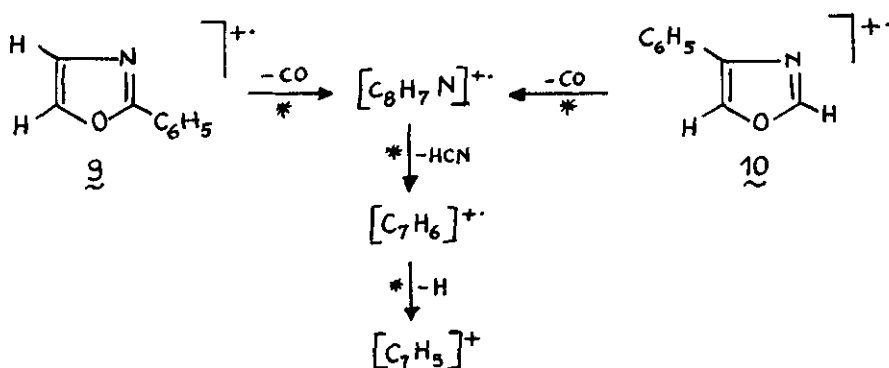


## PHENYL SUBSTITUTED OXAZOLES

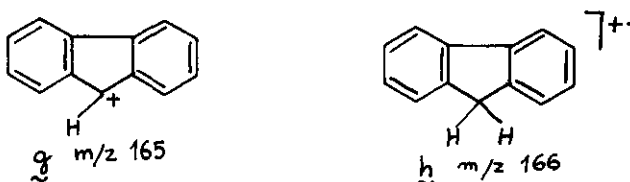
Consecutive losses of CO, HCN and H<sup>+</sup> were stressed on as a particular behaviour of 2-phenyloxazole (9) and 4-phenyloxazole (10) (Scheme 5).

Labelling experiments on compound 10 (deuteration at 2-position) have proved the secondary loss of HCN to involve C(2), its H atom and N atom. Then, after the primary loss of CO, no randomization occurs between H atoms of the heterocyclic ring.

Scheme 5



One of the most intriguing features of diphenyl (11, 12 and 13) and triphenyl (14) substituted oxazoles mass spectra is the presence of peaks at  $m/z$  165 ( $\text{C}_{13}\text{H}_9$ ) and  $m/z$  166 ( $\text{C}_{13}\text{H}_{10}$ ) (see Table 4) which most likely correspond to the fluorene cation (g) and the fluorene radical ion (h)<sup>63</sup> respectively. The former has been observed for other several diphenyl substituted compounds<sup>63-68</sup>.

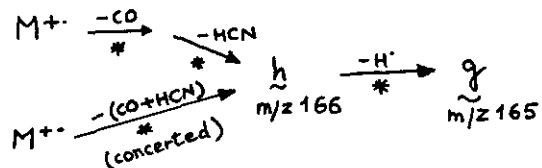
Table 4 - Relative abundances of  $m/z$  165 and  $m/z$  166 on the mass spectra of di- and triphenyl oxazoles.

Compounds	Relative abundances	
	$m/z$ 165	$m/z$ 166
4,5-diphenyloxazole (11)	76	16
2,5-diphenyloxazole (12)	55	48
2,4-diphenyloxazole (13)	4	2
2,4,5-triphenyloxazole (14)	79	46

For phenyloxazole derivatives, the fragmentation pathways leading to these species is reported in Scheme 6.



Scheme 6

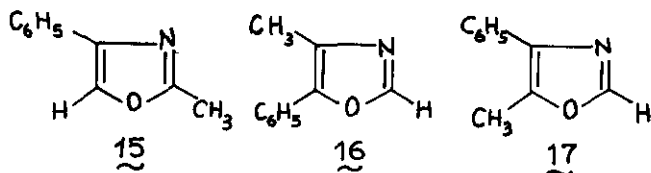


Both g and h species require skeletal rearrangements with phenyl migration. The mechanism of their formation has been studied by means of accurate deuterium labelling experiments<sup>63</sup> which proved that these ions may originate through two different routes depending on the phenyl position in the heterocyclic ring. Again, the secondary loss of HCN involves the H atom of the heterocyclic ring in compounds 11 and 12, confirming that no randomization occurs between this H atom and the H atoms of the phenyl groups.

Deuterium labelling has also proved that compound 14 leads to g ions through different pathways: the first (60%) involves 4,5-phenyl groups while the second (40%) involves 2,5-phenyl groups (very scarce contribution was observed from 2,4-phenyl groups).

### PHENYLMETHYL SUBSTITUTED OXAZOLES<sup>62</sup>

One of the most typical fragmentations of several substituted oxazoles is the consecutive loss of CO and H<sup>•</sup> from M<sup>+</sup>. The relative abundances of the ions originated from these fragmentations are reported in Table 5 for phenylmethyl oxazoles (compounds 15, 16 and 17):



and their labelled derivatives (compounds 18, 19, 20 and 21):

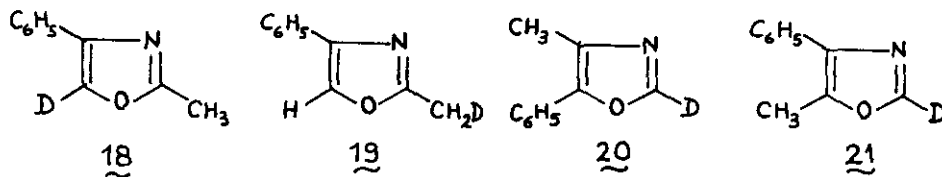


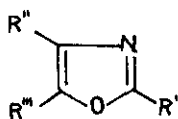
Table 5 - Relative abundances of M-CO (m/z 131) and M-CO-H (m/z 130) fragment ions on the mass spectra of phenylmethyl oxazoles and their labelled derivatives.

Compounds \ I%	m/z 132	m/z 131	m/z 130
15		52	37
16		32	65
17		5	15
18	45	34	8
19	36	27	10
20	17	55	11
21	2	15	4

Furthermore, identities and relative abundances for M-28 moieties arising from a series of trisubstituted oxazoles (compounds 22 - 28) are reported in Table 6 and usefully contribute to clarify the mechanism of such a process.

Table 6 - Relative abundances and compositions of M-28 fragment ions of some trisubstituted oxazoles.

Compounds	R'	R''	R'''	I% M-28	Composition
22	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	-	-
23	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	Br	78	M-CO
24	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	27	M-CO
25	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	2	M-CO
26	n-C <sub>3</sub> H <sub>7</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	72	M-C <sub>2</sub> H <sub>4</sub>
27	n-C <sub>5</sub> H <sub>11</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	6	M-C <sub>2</sub> H <sub>4</sub>
28	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	23	M-CO



From these data it is possible to achieve the following conclusions: since the CO loss is a process involving the C(5) atom, the nature of the substituent at this position, whose migration at C(4) atom is implied, plays a fundamental role. In fact, as it can be observed from Table 5 and 6, the M-CO fragment is abundant when the C(5) substituents are H, phenyl or Br whereas it is extremely reduced or completely absent in the case of methyl and other alkyl substituents. Besides the competitive C<sub>2</sub>H<sub>4</sub> loss (due to the peculiar cleavage from the alkyl chain regardless the substituent position) greatly contributes to minimize the M-CO fragmentation.

The secondary loss of H' seems to be strongly influenced by the presence of a methyl group at 2- and 4- positions, being the contribution of the heterocyclic ring hydrogens very scarce.

As a matter of fact the relative abundances of the species  $M-CO$  and  $M-CO-H'$  for 4-phenyloxazole (10) are respectively 60% and 5% of the base peak, whereas compounds 15 and 16 lead to a very abundant  $m/z$  130 peak (see Table 5). Furthermore the data of Table 5 concerning the labelled derivatives 18 - 21 demonstrate the greater contribution of methyl hydrogens in comparison with the ring ones in the secondary loss of  $H'$ , owing to the higher stability of the product ions as it was already underlined in the case of methyl derivatives.

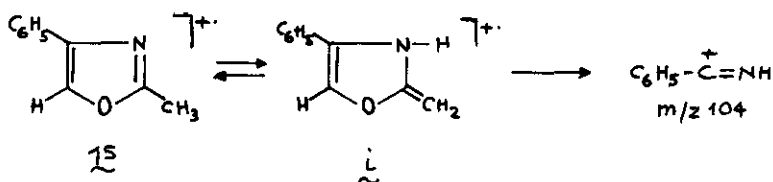
Other abundant peaks in the mass spectra of phenyl methyloxazole derivatives are  $m/z$  104 and  $m/z$  103.

Their compositions and relative abundances for compounds 15, 16, 17 and their deuterium labelled derivatives 18 to 21 are reported in Table 7.

Table 7

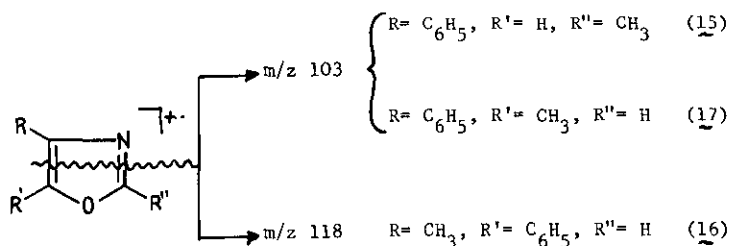
Ions Compounds	$m/z$ 105 I% Composition	$m/z$ 104 I% Composition	$m/z$ 103 I% Composition
<u>15</u>		(20) $\left\{ \begin{array}{l} C_8H_8 \text{ (40\%)} \\ C_7H_6N \text{ (60\%)} \end{array} \right.$	(30) $\left\{ \begin{array}{l} C_7H_5N \text{ (95\%)} \\ C_8H_7 \text{ (5\%)} \end{array} \right.$
<u>16</u>	(13) $C_7H_5$	(10) $C_8H_8$	(12) $C_8H_7$
<u>17</u>		(70) $C_7H_4O$	(35) $C_7H_5N$
<u>18</u>	(4)	(15)	(30)
<u>19</u>	(10)	(16)	(36)
<u>20</u>	(20)	(13)	(19)
<u>21</u>	(12)	(57)	(35)

The isomers 15, 16 and 17 show different compositions of the  $m/z$  104 peak. Specifically for 15 this peak is a doublet, while its labelled derivatives 18 and 19 show a deuterium distribution ( $m/z$  104 and 105) hard to rationalize. Anyway, the low abundance of the  $m/z$  105 peak in 18 and its increasing in 19, allow us to suppose that the main component of the  $m/z$  104 doublet ( $C_7H_6N$ ) in 15 brings in one of the methyl hydrogens via fragmentation of the prototropic form i of the molecular ion :



The formation of  $[C_7H_4O]^{+•}$  ions ( $m/z$  104) from 17 is of difficult explanation because it requires a complex rearrangement involving in part the hydrogen atom at C(2) position. Supporting evidence is given by the partial shift to  $m/z$  105 for 21. In the case of  $m/z$  104 ions of 16 we suggest that it could originate from a rearranged molecular ion in which methyl and phenyl groups are bonded to C(4) atom. However no experimental evidences confirm our hypothesis even though the lack of mass shift of the  $m/z$  104 and its correlated  $m/z$  103 peaks for 20 is in agreement with it. The cleavage of the bonds 2,3 and 4,5 is a process occurring in all the isomers 15, 16, 17 and leading to different ions. This is due to the strong localization of the positive charge on the moiety containing the phenyl group: the cleavage gives rise to benzonitrile ionic species ( $m/z$  103) for compounds 15 and 17 and  $[C_8H_6O]^{+•}$  ions for compound 16 (Scheme 7 and Table 7).

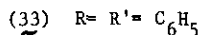
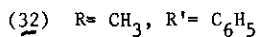
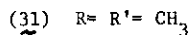
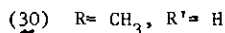
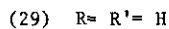
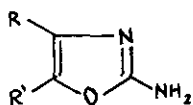
Scheme 7



The labelled derivatives confirm this interpretation because, as expected, both 18 and 19 produce no deuterated benzonitrile ions, while  $[C_8H_6O]^{+•}$  ( $m/z$  118) is completely shifted to  $m/z$  119 for compound 20.

## 2-AMINO OXAZOLES

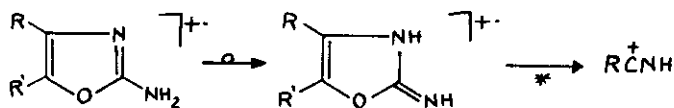
In a very recent paper<sup>69</sup> the electron impact mass spectra of 2-aminooxazole and some of its 4- and/or 5-substituted derivatives (29 - 33) were reported and discussed in detail with the aid of exact mass measurements, metastable ions studies and labelling experiments.



The mass spectrometric behaviour of 2-aminooxazoles clearly differs from that of other oxazole derivatives, being their fragmentations markedly influenced by the strong electron donating power of the amino group.

The most important primary fragmentation process leads to the abundant fragment ions (base peak for 29, 30 and 31) corresponding to  $R-\overset{\dagger}{C}NH$  moiety. This process, never described for other oxazole derivatives, involves H atom rearrangement of the amino group as proved by the shift of  $1\text{u}$  for 2-ND<sub>2</sub> derivatives (Scheme 8):

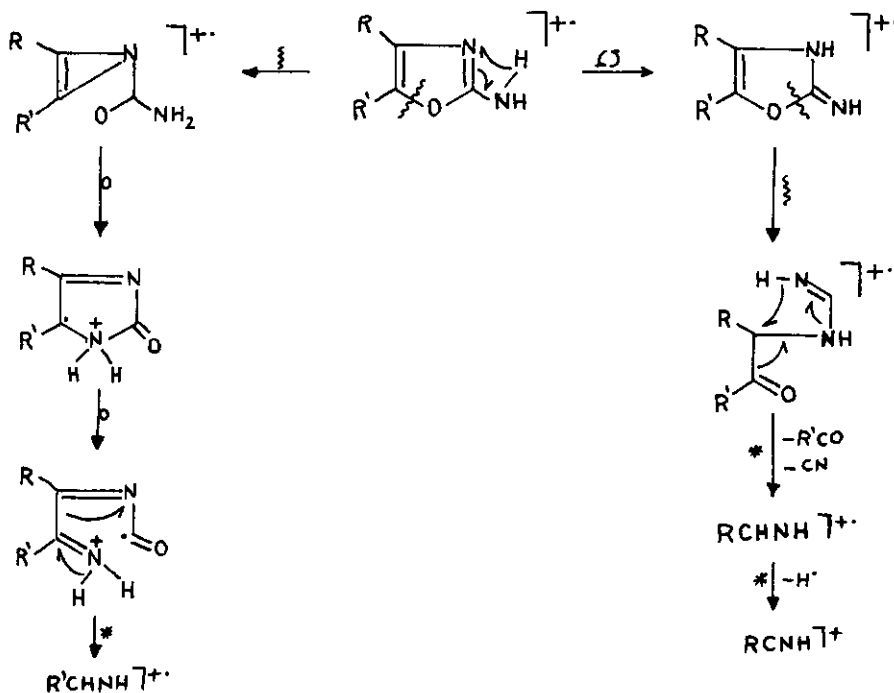
Scheme 8



Other significant fragments of 2-aminooxazoles, originated from  $M^{+\bullet}$  via metastable transition, are  $[R-CH=NH]^{\dagger+}$  and  $[R'-CH=NH]^{\dagger+}$ . These fragments, distinguishable only when  $R \neq R'$  (compounds 30 and 32), retain the H atoms of the amino group as proved by 2-ND<sub>2</sub> derivatives.

Their formation, though of difficult interpretation, was suggested to happen as indicated in Scheme 9:

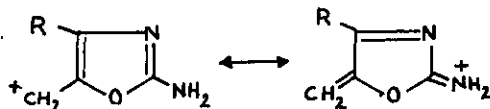
Scheme 9



Surprisingly the very strong peak at  $m/z$  105 in the mass spectra of 32 and 33 is solely due to  $[\text{C}_6\text{H}_5\text{-CH=NH}]^{++}$  moiety, being the  $[\text{C}_6\text{H}_5\text{-CO}]^+$  ion completely absent.

Again the primary loss of  $\text{H}^+$  involving the C(5) position of the oxazole<sup>61</sup> and the methyl group at C(4) of the substituted derivatives<sup>62</sup> is absent in compounds 29 and 30 and it is quite abundant (43%) only for 31.

This fact has been explained by the resonance stability of the product ions:



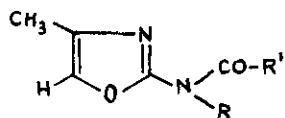
The spectrum of the 2-ND<sub>2</sub> derivatives show that the contribution of the amino hydrogen atoms is negligible.

#### MISCELLANEOUS

A mass spectral study of isamoxole (34): 2-methyl-N-butyl-N-(4-methyloxazol-2-yl)propanamide, a novel antiallergic drug, has been recently published<sup>70</sup>.

The more abundant peaks of the spectrum are due to the fragmentations of the substituent at 2-position of the ring (Scheme 10).

Particular attention has been given to the mechanism of loss of  $\text{OH}^+$  from the base peak (1 species in Scheme 10) originated via McLafferty rearrangement from the molecular ion. A series of labelled and differently N-alkylated and N-acylated derivatives were examined in order to locate which hydrogens contribute to this loss. In particular, the labelled derivative 35 show loss of  $\text{OH}^+$  and  $\text{OD}^+$  in the ratio 1 : 1 proving that the 50% of the hydrogens lost as  $\text{OH}^+$  in 34 comes from the N-alkyl chain (R)



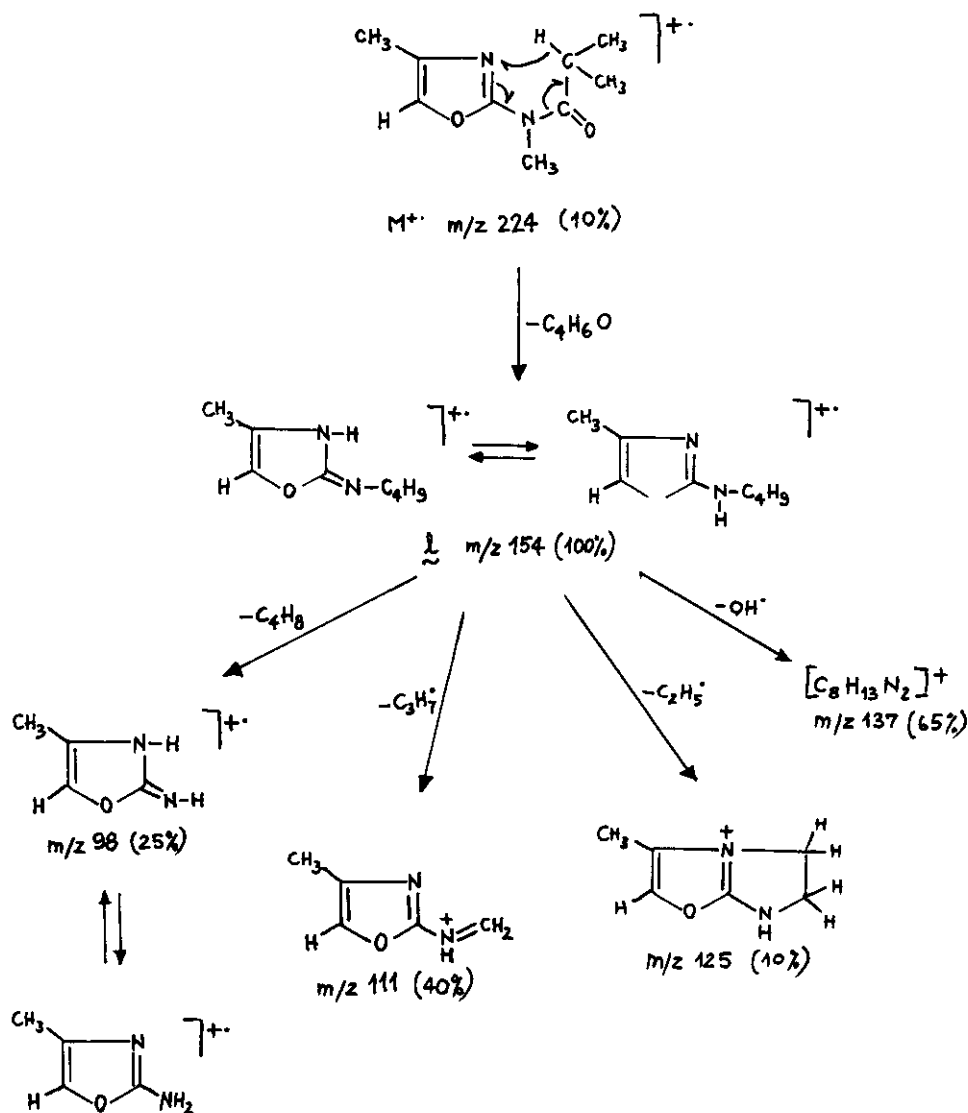
(35)  $\text{R}=\text{C}_4\text{D}_9$ ;  $\text{R}'=\text{CH}_3$

(36)  $\text{R}=\text{C}_4\text{H}_9$ ;  $\text{R}'=\text{CD}_3$

Besides, it was seen that the shortening of the R chain causes a marked decreasing of  $\text{OH}^+$  loss implying that the chain length clearly affects the elimination, which is optimum when the R chain is four or five units. Hence, in the specific case of isamoxole (34), the hydrogen which promotes

OH<sup>•</sup> loss is essentially the one at C(4) of the N-alkyl chain. By means of the derivative **36** it was also proved that the second hydrogen atom involved in OH<sup>•</sup> loss is the one next to the carbonyl.

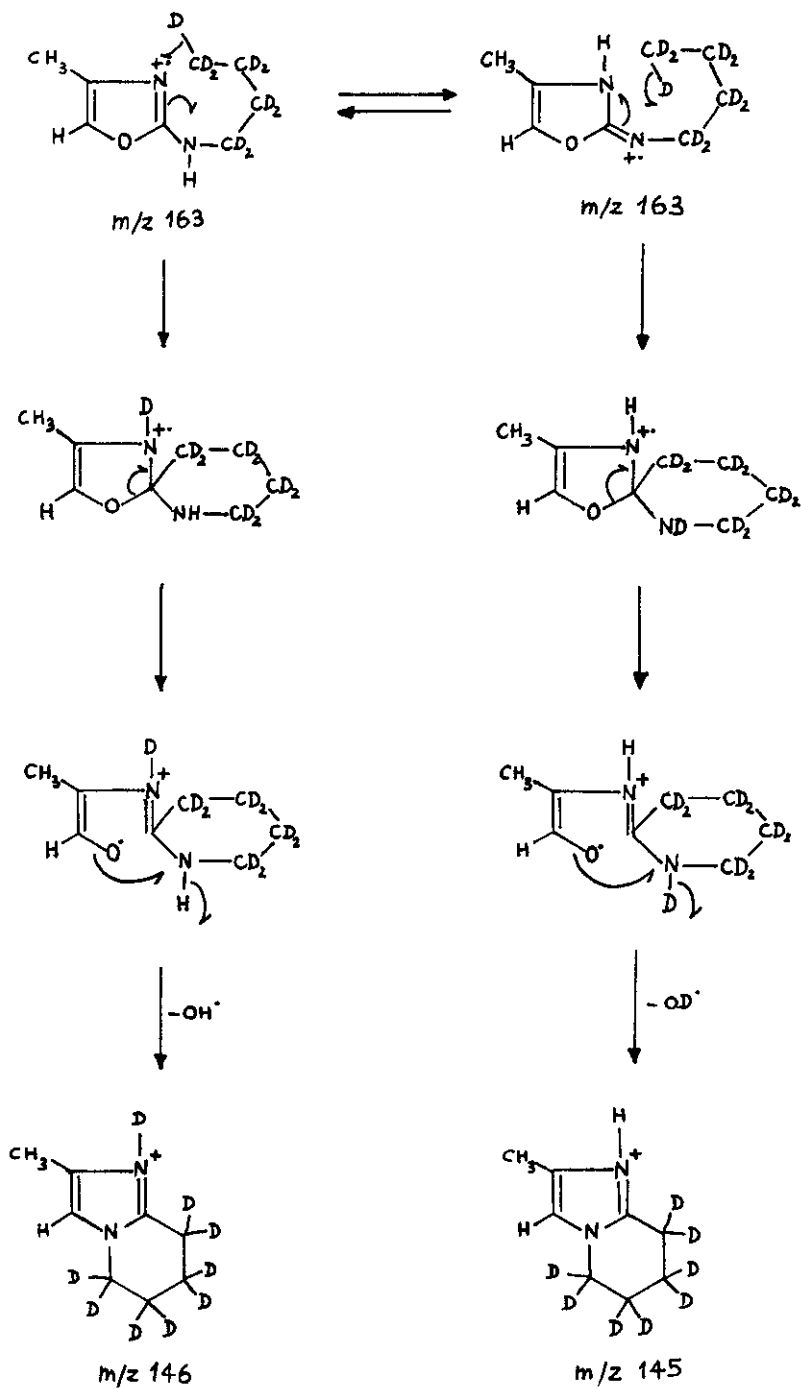
Scheme 10



These findings, along with other experimental evidences on different substituted derivatives, exclude any contribution to this process as due to the hydrogens at the C(4) and C(5) positions of the heterocyclic ring or other acyclic hydrogens.

In this view the mechanism results compatible with the sequence in Scheme 11.

Scheme 11





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