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Electron impact mass spectrometry of some 1- and 2-benzimidazole derivatives

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Abstract. In the present investigation, a study of the electron-impact mass spectrometry data is reported for fifteen compounds of a series of 1- and 2-benzimidazole derivatives previously synthesized. Possible fragmentation routes of this class of compounds under electron-impact are outlined.

1. Introduction

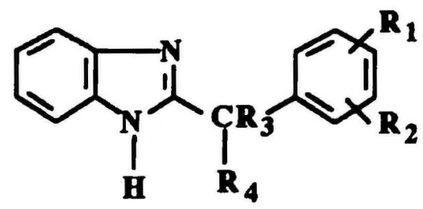
Inhibitors of aromatase have demonstrated therapeutic utility in oestrogen-dependent metastatic breast cancer [1]. Synthesis of the compounds discussed herein have been described previously [2]. This report is concerned with the mass spectra of the imidazole and benzimidazole derivatives (**I-XV**), which are recorded in Tables 1 and 2.

2. Results and discussion

The compositions of ions determined by exact mass measurements are listed in Tables 1 and 2. The main features of the spectra of **I-VII** are summarized in Scheme I. The preferred fragmentation of the methylenic carbon and nitrogen atom in the imidazole ring giving the A base peak is checked. Different fragmentation substituents are observed depending of the nature of R_1 and R_2. The ion B (m/z = 206) in **II** and **III** derivatives is formed by the loss of a halogen ion in the para position of phenyl compounds followed by an associated cycle rearrangement [3]. A similar behaviour is present in the other cases with a weak intensity. The fragmentations of ions B and C lead only to one fragment (m/z = 102) which gives m/z = 103 or 106 by protons capture in the case of ion C.

The presence of ion m/z = 90 results from the loss of a methyl radical and the ring formation due to rearrangement. The loss of a nitrogen atom or a CN leads to a common peak (m/z = 77) for all studied compounds having a mass corresponding to $C_6H_5^{+\cdot}$. Other processes observed are the direct cleavage M - C_2H_2 giving m/z = 51 or a process involving the intermediate m/z = 63. The isotopic fragments [M + 2] and [M + 4] denote the presence of bromine and chlorine ions, and are in agreement with the proposed structure. Imidazole ring seems to be stable enough since it is found unbroken at first (m/z = 68), then there is elimination of ion HCN leading to the ion m/z = 40 [3, 4].

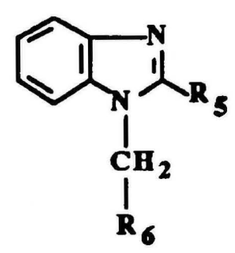
Table 1
2-Benzimidazole derivatives



Compounds	R_1	R_2	R_3	R_4	Formula	M
I	H	H	H	$C_3H_3N_2$(a)	$C_{17}H_{14}N_4$	272
II	H	4'-Cl	H	$C_3H_3N_2$	$C_{17}H_{13}ClN_4$	308
III	H	4'-F	H	$C_3H_3N_2$	$C_{17}H_{13}FN_4$	292
IV	H	4'-Br	H	$C_3H_3N_2$	$C_{17}H_{13}BrN_4$	352
V	H	2'-F	H	$C_3H_3N_2$	$C_{17}H_{13}FN_4$	292
VI	2'-Cl	4'-Cl	H	$C_3H_3N_2$	$C_{17}H_{12}Cl_2N_4$	342
VII	3'-Cl	4'-Cl	H	$C_3H_3N_2$	$C_{17}H_{12}Cl_2N_4$	342
VIII	H	H	C_6H_5	$C_4H_5N_2O$(b)	$C_{24}H_{20}N_4O$	380
IX	H	4'-Cl	H	$C_4H_5N_2O$	$C_{18}H_{15}ClN_4O$	338
X	H	H	H	$C_4H_5N_2O$	$C_{18}H_{15}ClN_4O$	338
XI	2'-Cl	4'-Cl	H	$C_4H_5N_2O$	$C_{18}H_{14}Cl_2N_4O$	372

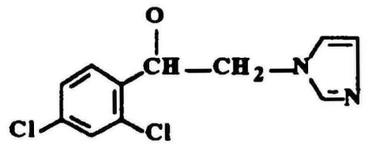
(a): $C_3H_3N_2$: imidazole ring; (b): $C_4H_5N_2O$: 1H-methoxy-imidazole ring

Table 2
1-Benzimidazole derivatives



Compounds	R_5	R_6	Formula	M
XII	H	$C_3H_3N_2$	$C_{11}H_{10}N_4$	292
XIII	CH_3	$C_3H_3N_2$	$C_{12}H_{12}N_4$	342
XIV	H	$C_{11}H_9Cl_2N_2O$	$C_{19}H_{16}Cl_2N_4O$	342
XV	CH_3	$C_{11}H_9Cl_2N_2O$	$C_{20}H_{18}Cl_2N_4O$	380

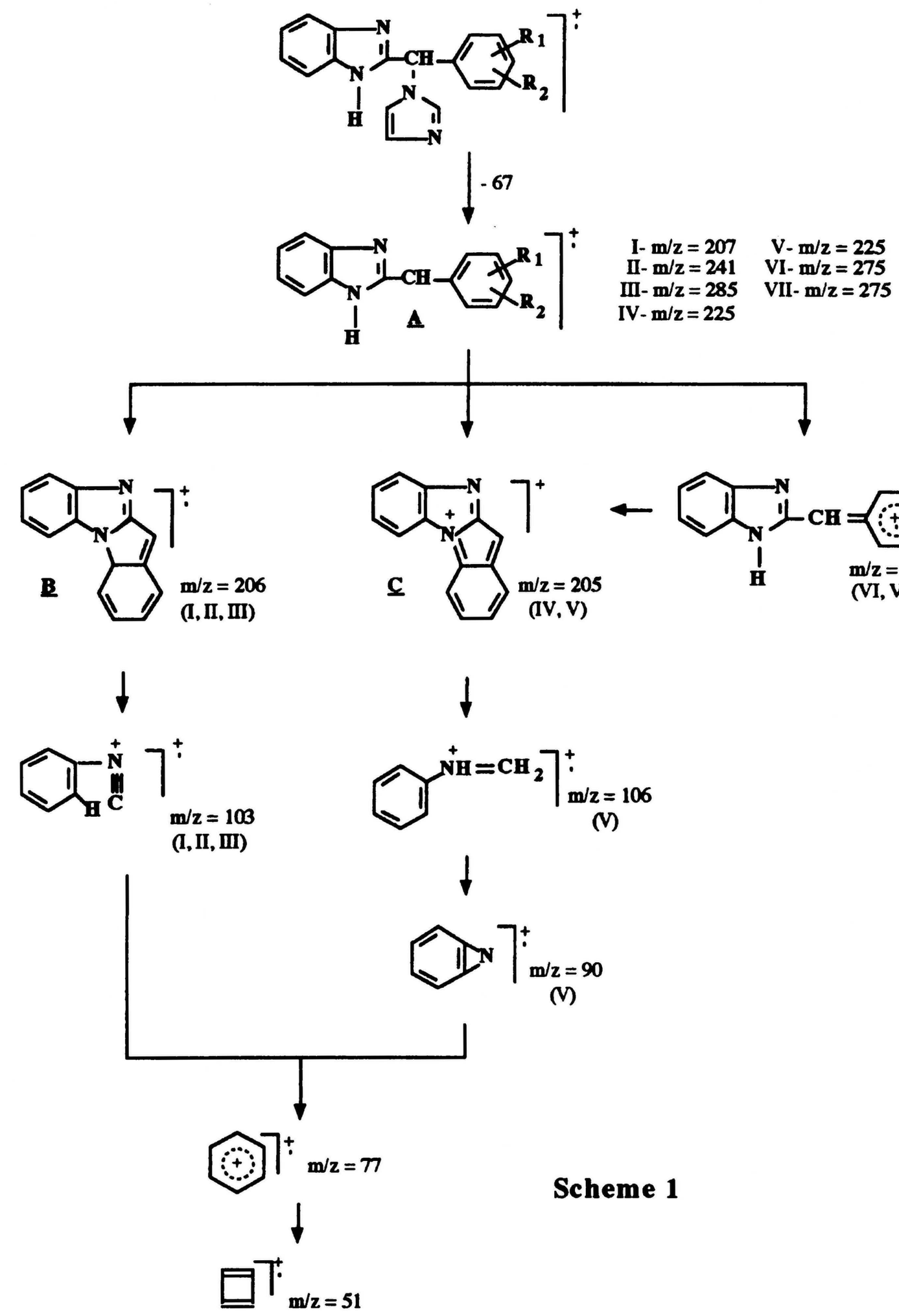
$C_3H_3N_2$



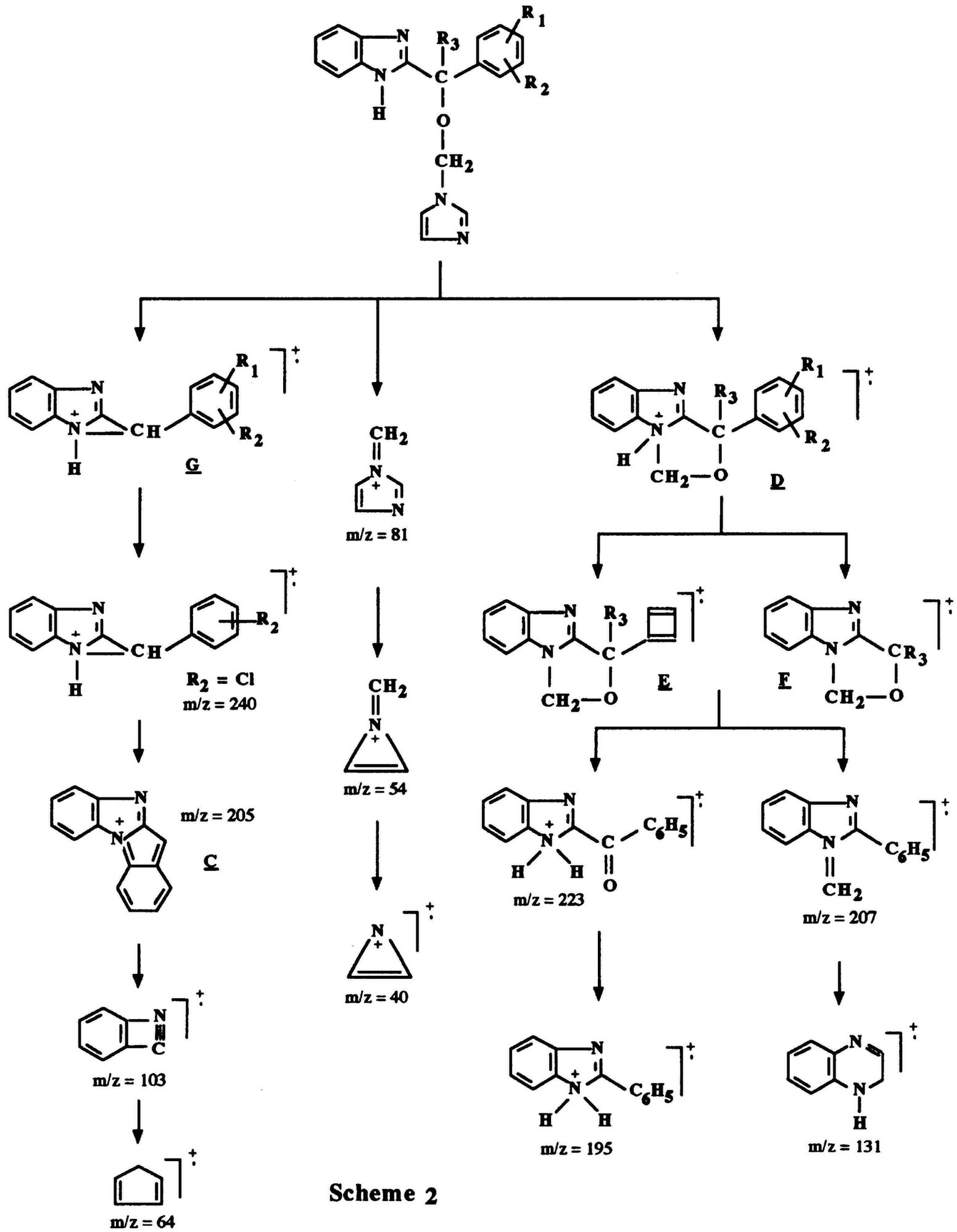
$C_{11}H_9Cl_2N_2O$

Table 3
Principal fragmentations and intensities of benzimidazole and imidazole derivatives

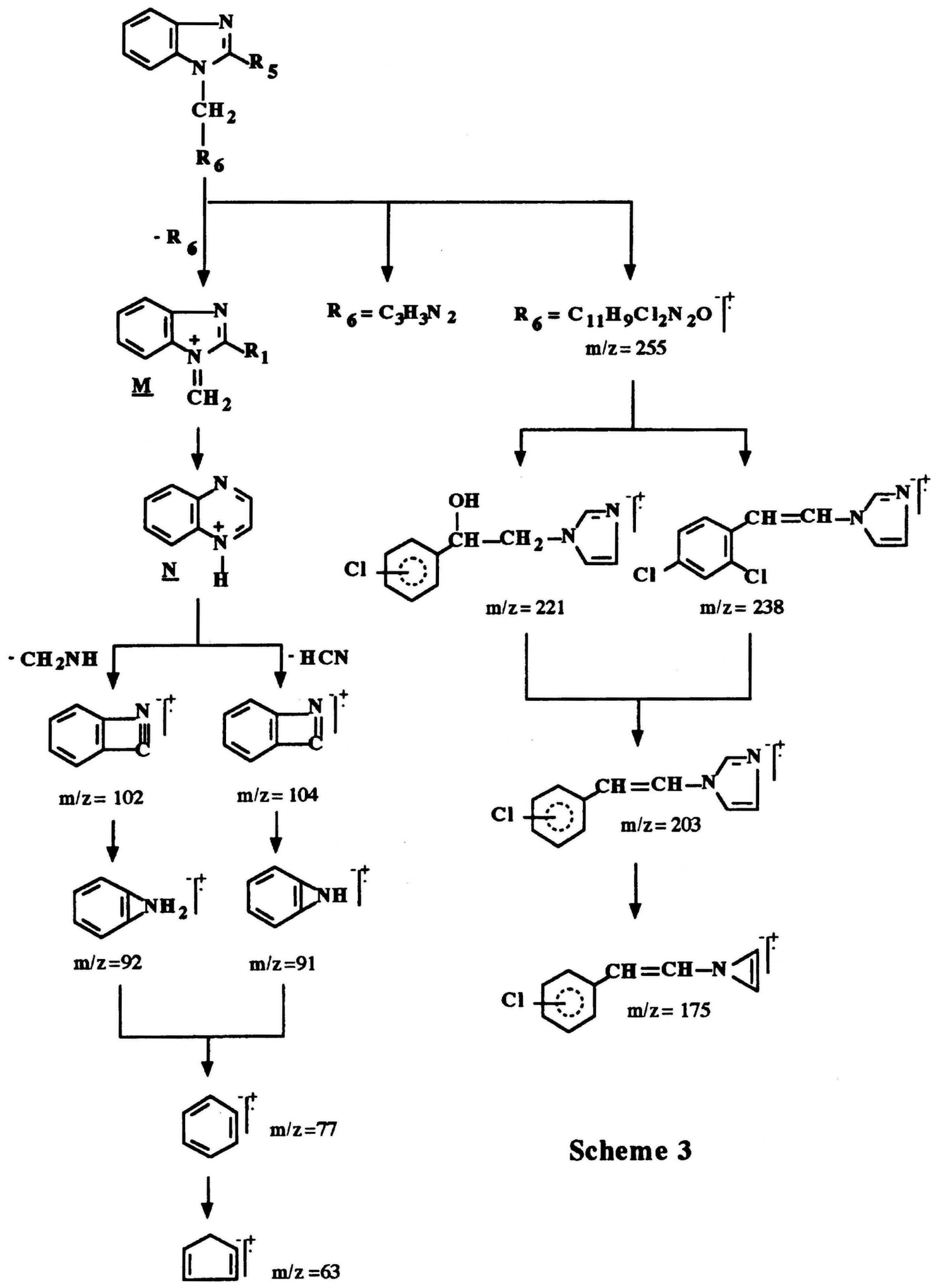
			Fragments (m/z %)							
Cpds.	**M^+**	**A**	**205 ± 1**	**103 ±1**	**91 ±1**	**77**	**68**	**63 ±2**	**51**	**40**
I	274 (15.0)	207 (100)		5.5		3.3		2.7	2.3	2.8
II	308 (24.8)	241 (68.3)	100	27.7			70.7	4		2.2
III	292 (13.2)	225 (100)	3	1.5	1.1	4.2	3.6	6.1	4.5	6.7
IV	354 (15.1)	285 (11.1)	100	20	8	36.1	39.4	19.4	16.7	38.9
V	292 (17.2)	225 (51.1)	4.4	14.4	8.3	100	28.9	25	31.4	5.9
VI	342 (32.9)	275 (42.7)	36.1	16.5	6.4	18.4	25.5	13.7	11.9	37.3
VII	342 (62.3)	275 (55.2)	65.4	26.1	19.4	54.4	48.9	40	24.3	
VIII	380 (72.0)	81 (73.0)	30.6	13.4		68.8		10.9	19.5	7.9
IX	338 (11.2)	81 (61.6)	100	63.5				7.9	2.4	18.6
X	338 (13.6)	81 (6.4)	100	13.5		1.1		2.1	0.7	2.3
XI	372 (12.7)	81 (89.0)	48.7	23.8				7.2		37
XII	198 (36.3)	131 (100)		12.4	2.3			2.8	1.9	4.3
XIII	212 (97.0)	145 (100)		1.6	6.8	9.4		1.6	5.5	3.9
XIV	386 (10.5)	131 (100)		11.9	4.6	20.3		3.6	7	1.6
XV	400 (1.7)	145 (100)		4.4	12.5	17.2		4.7	10.2	5.4


- 67
A
I- m/z = 207
II- m/z = 241
III- m/z = 285
IV- m/z = 225
V- m/z = 225
VI- m/z = 275
VII- m/z = 275
B
m/z = 206
(I, II, III)
C
m/z = 205
(IV, V)
m/z = 240
(VI, VII)
m/z = 103
(I, II, III)
m/z = 106
(V)
m/z = 90
(V)
m/z = 77
m/z = 51

Scheme 1


G
m/z = 81
D
R2 = Cl
m/z = 240
E
F
m/z = 54
m/z = 205
C
m/z = 223
m/z = 207
m/z = 103
m/z = 40
m/z = 195
m/z = 131
m/z = 64

Scheme 2


R6 = C3H3N2
R6 = C11H9Cl2N2O
m/z = 255
M
N
m/z = 221
m/z = 238
m/z = 203
m/z = 175
m/z = 102
m/z = 104
m/z = 92
m/z = 91
m/z = 77
m/z = 63

Scheme 3

In the spectra of **VIII** to **XI**, it is probable that the observed principal fragmentation processes are similar to those observed in 2-[(1H-imidazolyl)benzyl]benzimidazole derivatives **I** to **VII**. The base peak (m/z = 81) seems to come from the scission of the β-bond in the imidazole ring. This fragment can eliminate one molecule of HCN leading to the ion m/z = 54. The spectra of the decomposition of the imidazole ring exhibit an ion (m/z = 40) which corresponds to the loss of a methyl group (Scheme 2).

The D ion takes place from the α-cleavage of the imidazole ring bond and leads by fragmentation to:

- the ion E by elimination of C_2H_3 (**VIII**),
- the ion F at m/z = 235 by elimination of $C_6H_5^+$, this ion F can fragment and lead to the peak m/z = 207 by rearrangement then elimination of one mole of carbon monoxide [2]. The fragment m/z = 131 is then formed by cleavage of the aromatic ring bond and by the capture of an hydrogen radical.
- the loss of HCN then CH_2NH fragments leads to the ions m/z = 104 and 77 respectively.
- the ion m/z = 223 by loss of one methyl radical and the capture of two hydrogen radicals.

For **IX**, **X** and **XI**, the ion G is the resulted product of the β-cleavage of the benzimidazole ring (Scheme 2). This ion leads to a fragment m/z = 240 by loss of a chlorine radical. It can give another fragment at m/z = 205 or 206 (ion C) according to R_1 or R_2 by a second elimination of a chlorine atom.

The main cleavages of these compounds occur according to Mathias *et al.* [6] for analogous series.

The fragmentation pathways of **XII** to **XV** are in agreement with the usual fragmentation of benzimidazole and imidazole compounds.

The base peak M is formed by cleavage of 1-methyl benzimidazole-R_2 bond and can give the ion N by elimination of CH_2 (**XIII** and **XV**) (Scheme 3). According to R_1, N can fragment at m/z = 104 (**XII**, **XIV**) and m/z = 102 (**XIII**, **XV**) by respective loss of HCN and -CH_2NH.

The cleavage of the R_6-α bond leads to the peak M. This ion (**XIV** or **XV**) fragments and leads to:

- ion m/z = 238 by capture of a hydrogen atom then loss of a mole of water,
- ion m/z = 221 by elimination of a chlorine atom. The loss of a mole of water leads to ion m/z = 203.

The cleavage of the benzimidazole ring α-bond gives the ion m/z = 81 then m/z = 40 by loss of a mole of HCN and CH_2.

3. Experimental section

Mass spectra were recorded in electron-impact mode from the Centre d'Étude et de Recherche sur les Macromolécules Végétales (CERMAV, C.N.R.S., Université de Grenoble I). The data processing is carried out by a Delsi-Nermag R-1010 spectrometer.

4. Conclusion

According to the literature data, it appears that the following generalisations can be made. The fragmentation pathways for 1- or 2-substituted benzimidazoles are very similar. The mass spectra exhibit the molecular ion as the base peak. They also indicate an ensuing sequential loss of two molecules of hydrogen cyanide and one proton. The ion m/z = 40 is finally obtained by loss of H^+ and HCN from the molecular ion.

5. References

[1] J. O. Johnston and B. W. Metcalf, Aromatase: A target enzyme in breast cancer, in *Novel Approaches to Cancer Chemotherapy*, (Sunkara, Ed.), Academic Press, New York (1984) pp. 307.
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