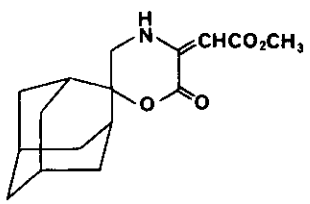
ELECTRON IMPACT MASS SPECTROMETRY OF SUBSTITUTED 3,4,5,6-TETRAHYDRO-1,4-OXAZIN-2-ONE DERIVATIVES

Vassil St. Georgiev*, David C. Coomber, and George B. Mullen

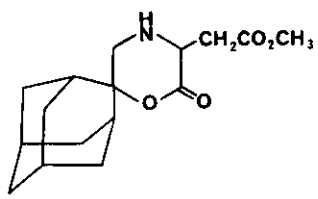
Departments of Organic and Analytical Chemistry, Pennwalt Corporation, Pharmaceutical Division, Rochester, New York 14623, U.S.A.

Abstract - The electron impact mass spectrometry of a series of novel and biologically active substituted 3,4,5,6-tetrahydro-1,4-oxazin-2-one derivatives is described. The mass spectral fragmentation pattern of spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (2), a novel adamantane-spiro-heterocyclic system has also been investigated. The fragmentation pattern of all compounds studied was found to be heavily influenced by the nature of their substituents.

Recently, we have reported the synthesis of a novel adamantane-spiro-heterocyclic system, the spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (1 and 2) [1]. When tested in the carrageenin-induced rat paw edema assay compound 1 showed anti-inflammatory activity. In addition, a series of novel substituted 3,4,5,6-tetrahydro-1,4-oxazin-2-one derivatives (3-9) were also prepared and tested for biological activity [2]. A number of them were found to exert a moderate to marked activity against Neisseria gonorrhoeae. The electron impact mass spectrometry of derivatives 1-9 (Table 1) was also investigated. The fragmentation pattern was found to be heavily influenced by the nature of the substituents on the 1,4-oxazine ring, thus allowing for their structural characterization by electron impact mass spectrometry. The mass spectral behavior of the title 1,4-oxazine derivatives not hitherto described in the literature is discussed in this communication.

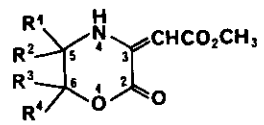


1



2

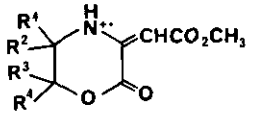
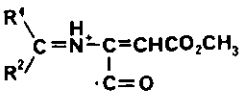
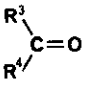
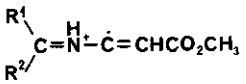
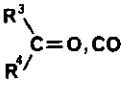
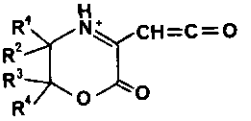
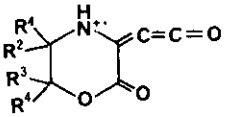
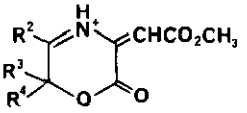
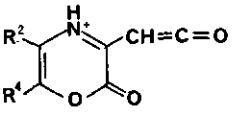
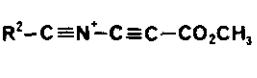
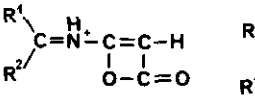
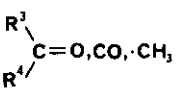
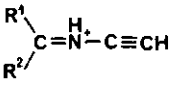
Table 1. Substituted 3,4,5,6-Tetrahydro-1,4-oxazin-2-one Derivatives (3-9)



Compd	R^1	R^2	R^3	R^4	MW	Compd	R^1	R^2	R^3	R^4	MW
3	H	H	H	H	171	7	C_2H_5	H	H	H	199
4	H	H	H	CH_3	185	8	$C_6H_5CH_2$	H	H	H	261
5	H	H	H	CH_2OH	201	9	CH_3	H	H	C_6H_5	261
6	CH_3	CH_3	H	H	199						

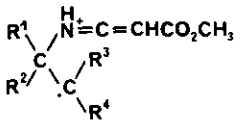
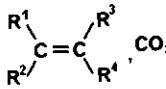
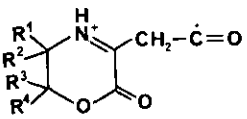
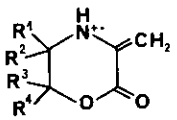
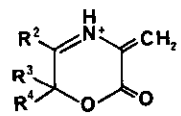
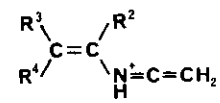
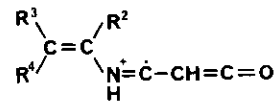
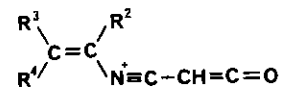
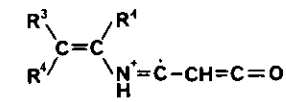
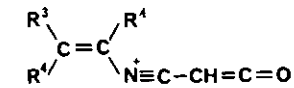
The mass spectral fragmentation data for compounds 1 and 3-9 are presented in Table 2.

Table 2. Relative Intensity(RI) of Fragmentation Ions of Substituted 3,4,5,6-Tetrahydro-1,4-oxazin-2-one Derivatives

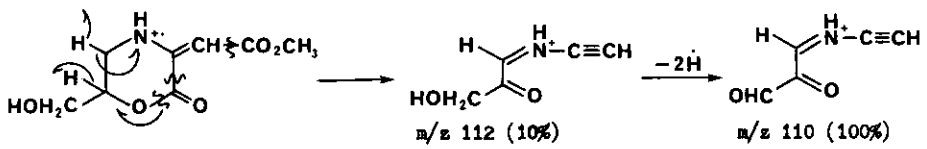
Ion	Suggested Structure	Mass Loss	Compounds							
			1	3	4	5	6	7	8	9
			m/z RI(%)	m/z RI(%)	m/z RI(%)	m/z RI(%)	m/z RI(%)	m/z RI(%)	m/z RI(%)	m/z RI(%)
M$^{+\cdot}$		—	291 39	171 69	185 100	201 96	199 34	199 25	261 10	261 7
A			141 61	141 10	141 22	141 27	169 9	169 8	231 -	155 100
B			113 100	113 34	113 49	113 47	141 19	141 10	203[a] - (201) 6	127 83
C		·OCH$_3$	260 8	140 75	154 71	170 64	168 23	168 17	230 6	230 3
D		·H, ·OCH$_3$	259 -	139 100	153 60	169 33	167[b] 4	167 -	229 -	229 -
E		·R^4	290 -	170 -	184 -	200 -	184 81	170 78	170 100	246 -
F		·R^4, ·R^3, ·OCH$_3$	258 -	138 1	152 2	168 3	152 100	138 100	138 91	214 -
G		·R^1, 2H, CO, 	110 -	110 8	110 16	110[c] 100	124 41	110 41	110 31	110 <1
H			98 3	98 8	98 26	98 49	126 18	126 19	188 2	112 52
J		H - CO$_2$	54 3	54[d] 2	54[d] 3	54[d] 5	82 18	82 10	144[a] 3	68[d] 10

cont'd on the next page

Table 2 - cont'd

K		CO_2	247 / 3	127 / 24	141 / 22	157 / 11	155 / 2	155 / 3	217 / 1	217 / -
L	$HN^{+}=C=CHCO_2CH_3$		99 / <3	99 / 29	99 / 48	99 / 38	99 / 4	99 / 5	99 / 1	99 / 4
N	$H_2N^{+}=C=CHCO_2CH_3$	L + H·	100 / -	100 / 17	100 / 64	100 / 66	100 / 16	100 / 10	100 / -	100 / 2
P		CH_2O	261[e] / 5	141 / 10	155 / 8	171 / 13	169 / 9	169 / 8	231 / -	231 / <1
Q		CH_2O, CO	233 / -	113 / 34	127 / 24	143 / 35	141 / 19	141 / 10	203 / -	203 / 1
R		Q − ·R^1	232 / 4	112 / 10	126 / 18	142 / 43	126 / 18	112 / 8	112 / -	188 / 2
T		R − CO_2	188 / 1	68 / 16	82 / 20	98 / 49	82 / 18	68[d] / 5	68 / -	144 / 1
U		C − (·R^1 + CO_2)	215 / 3	95 / 22	109 / 11	125 / 19	109 / 17	95 / 2	95 / -	171 / -
V		U − H·	214 / 6	94 / 7	108 / 18	124 / 21	108 / 2	94 / 9	94 / 3	170 / 2
W		C − (·R^2 + CO_2)	U	U	U	U	U	123 / 3	185 / 1	185 / -
X		W − H·	V	V	V	V	V	122 / 11	184 / 2	184 / 1

[a] See discussion in text; [b] The RI of compound 6 is not consistant with the corresponding RI values of other derivatives from its group; [c] An alternative fragmentation such as the one depicted in (i) may also explain the higher abundance (100%) of this ion:

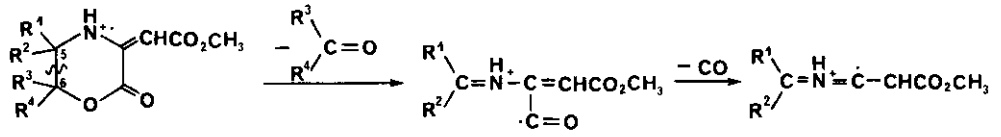
(i)..... 

[d] Ions <m/z 80 over-resolved; [e] This ion is M-CH_4N.

The fragmentation pattern of derivative 2 is presented in Scheme 8.

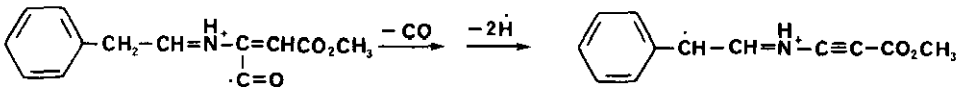
While, in general, the mass spectral fragmentation of the substituted 1,4-oxazines 3-9 followed patterns established by the type of substituents R^1, R^2, R^3 and R^4, it was the nature of R^3 and R^4 that proved to be of significant importance. Thus, based on the stability of the ketone fragment $R^3R^4C{=}O$, the breaking of the C(5)-C(6) bond of the 1,4-oxazine ring (to generate ions A and B) resulted in the formation of three distinctive families of fragment B (Groups 1, 2 and 3 in Scheme 1).

Scheme 1



Ion A			Ion B			
Compd	m/z	RI(%)	Compd	m/z	RI(%)	
1	141	61	3	113	34	
3	141	10	4	113	49	Group 1
4	141	22	5	113	47	
5	141	27				
6	169	9	6	141	19	
7	169	8	7	141	10	Group 2
8	231	-	8	203	-	
9	155	100	9	127	83	Group 3
			1	113	100	

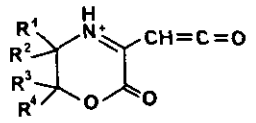
As seen from Scheme 1, the relative intensity (RI) of ions A and B of compounds 6 and 7 was more or less equivalent to that of compound 3, whereas the corresponding values for derivative 8 were dominated by the presence of benzyl group at C(5). In the latter case, the influence provided by the benzyl moiety became apparent since the fragmentation of the molecule led to ion with an m/z 201 (as its version of ion B):



Ion A

m/z 201 (6%)

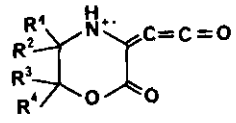
Compounds 3-5 (referred in Scheme 1 as Group 1) have hydrogens as R^1 and R^2 and are distinguished from each other at R^4. The observed difference between their mass spectral behavior and that of the other two groups is most evident from the nature of ion C and its relative intensity (RI):



Ion C $(M\text{-}OCH_3)^+$

Compd	m/z	RI(%)	
3	140	75	
4	154	71	Group 1
5	170	64	
6	168	23	
7	168	17	Group 2
8	230	6	
9	230	3	Group 3
1	260	8	

For an unapparent reason all the derivatives from Group 1 also formed a strong $(\underline{M}\text{-}OCH_3\text{-}H)^{+\cdot}$ ion, while none of the compounds from Groups 2 and 3 did:



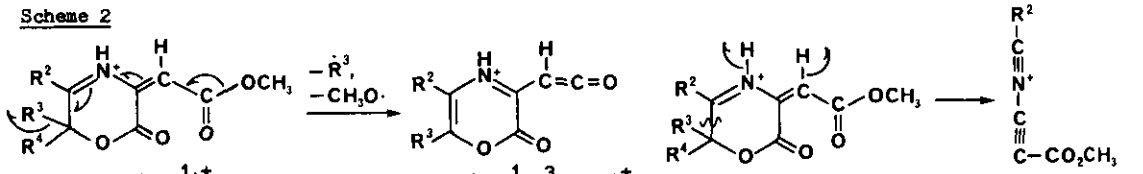
Ion $\underline{D}$ $(\underline{M}\text{-}OCH_3\text{-}H)^{+\cdot}$

Compd	m/z	RI(%)	
3	139	100	Group 1
4	153	60	
5	169	33	
6	167	4	

It should be noted that of all of the remaining derivatives, only compound 6 showed some presence of ion D, suggesting that the observed loss of H· must have originated from either R^3, the secondary nitrogen, or hydrogen from the C(3) chain.

Overall, the fragmentation pattern of compounds from Group 2 indicated the preferential loss of substituent R^3, followed by a loss of CH_3O· and H· as seen in Scheme 2. None of the other compounds formed any significant amount of either ion E or ion F. Ion G, a major fragment in the mass spectra of Group 2 derivatives is probably derived from ion E as a consequence of a ring cleavage.

Scheme 2



Ion $\underline{E}$ $(\underline{M}\text{-}R^1)^+$

Compd	m/z	RI(%)
6	184	81
7	170	78
8	170	100

Ion $\underline{F}$ $(\underline{M}\text{-}R^1\text{-}R^3\text{-}OCH_3)^+$

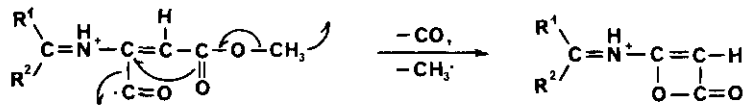
Compd	m/z	RI(%)
6	152	100
7	138	100
8	138	91

Ion E

Ion G

Compd	m/z	RI(%)
6	124	41
7	110	41
8	110	31

The major fragmentation ions of Group 3 compounds have already been defined as ions A and B (Scheme 1). Furthermore, in the mass spectrum of compound 9, a major ion is present at m/z 112. Most likely it is formed by a simple ring closure following the loss of CO and CH_3·:

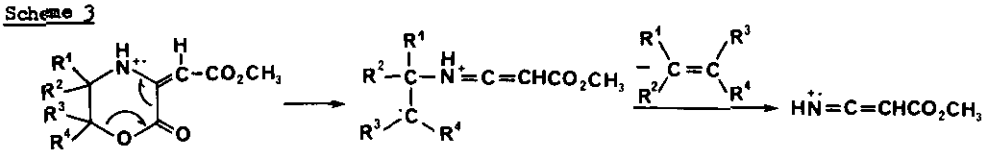


Ion A

Ion H (9, m/z 112, 52%)

It is also possible that ion H may loose CO_2 to generate ion J (Table 2). A loss of CO_2 from $M^{+\cdot}$ to furnish ion K is seen to some extent in all but compound 9, and is most prevalent within the derivatives of Group 1. Ion L may be derived from ion K by way of cleaving the olefin $R^1R^2C{=}CR^3R^4$ (Scheme 3).

Scheme 3

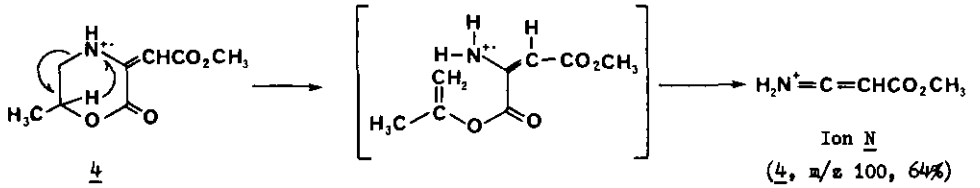


Ion K $(M-CO_2)^{+\cdot}$ (4, m/z 141, 22%)

Ion L (4, m/z 99, 48%)

Although it was more pronounced in compounds 4 and 5 (Group 1), the mass spectra of all derivatives with a hydrogen at C(6) (with the exception of 8) showed an ion at m/z 100. This very likely resulted from a transfer of C(6) hydrogen, or a hydrogen from one of the R substituents (Scheme 4).

Scheme 4

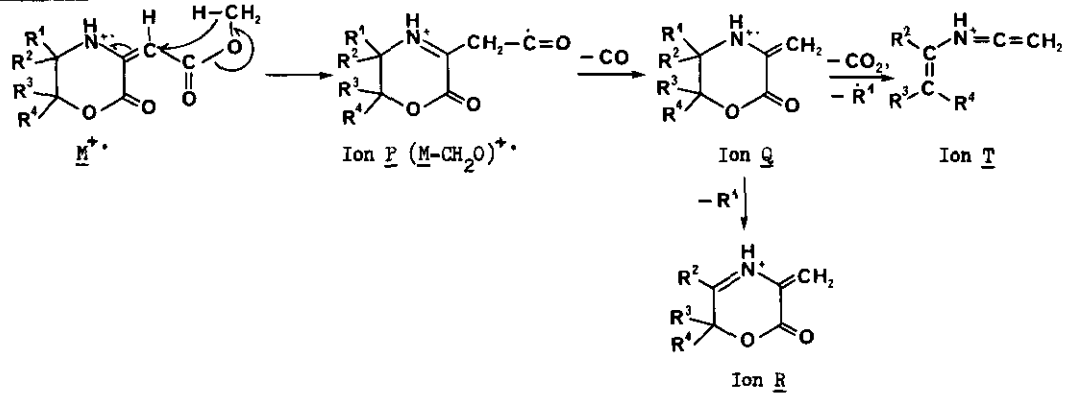


4

Ion N (4, m/z 100, 64%)

Finally, there is also the possibility that some other fragmentation processes (as the ones depicted in Schemes 5 and 6) may account for the presence of some ions seen in the mass spectra of derivatives 1 and 3-9, resulting in mass values that overlap ions generated by different mechanisms.

Scheme 5



$M^{+\cdot}$

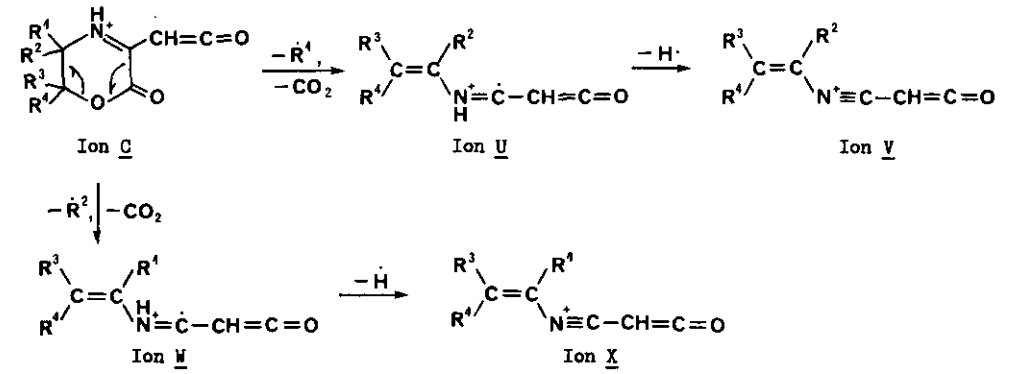
Ion P $(M-CH_2O)^{+\cdot}$

Ion Q

Ion T

Ion R

Scheme 6



Ion C

Ion U

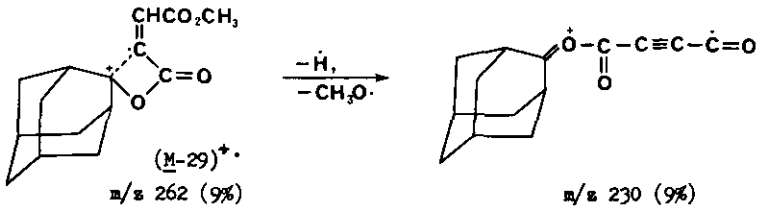
Ion V

Ion W

Ion X

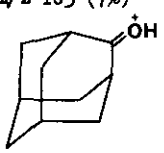
The mass spectral behavior of the adamantane-spiro-1,4-oxazine derivative 1 was strongly influenced by the presence of the adamantane ring system. The latter, being attached in a spiro fashion to the 1,4-oxazine ring imparted greater stability on the entire molecule, which in turn, was reflected in the fragmentation pattern. Thus, of all 1,4-oxazine derivatives studied, compound 1 was the only one showing in its mass spectrum an M-29 fragment, which by high resolution mass spectrometry was attributed to the loss of CH_2=NH. The fragmentation pattern of derivative 1 is presented in Scheme 7.

Scheme 7



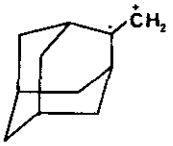
Also present in the mass spectrum of compound 1 were the following fragments:

m/z 107 (3.1%)
m/z 106 (4%)
m/z 105 (7%)



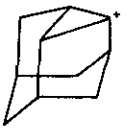
m/z 151 (7.2%)

m/z 92 (3%)
m/z 91 (5%)



m/z 148 (21%)

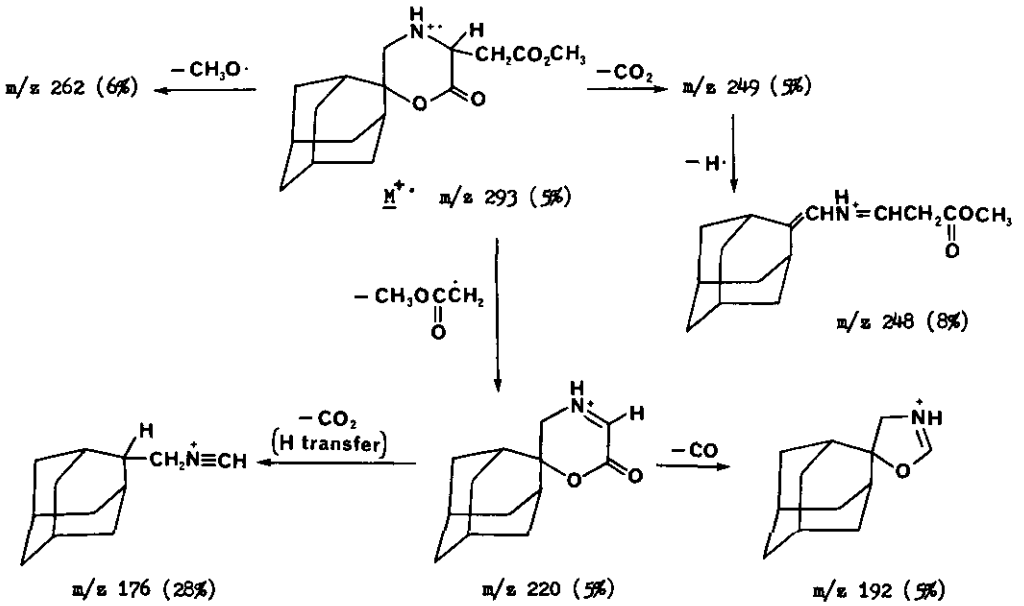
m/z 79 (5%)
m/z 77 (3%)



m/z 133 (3%)

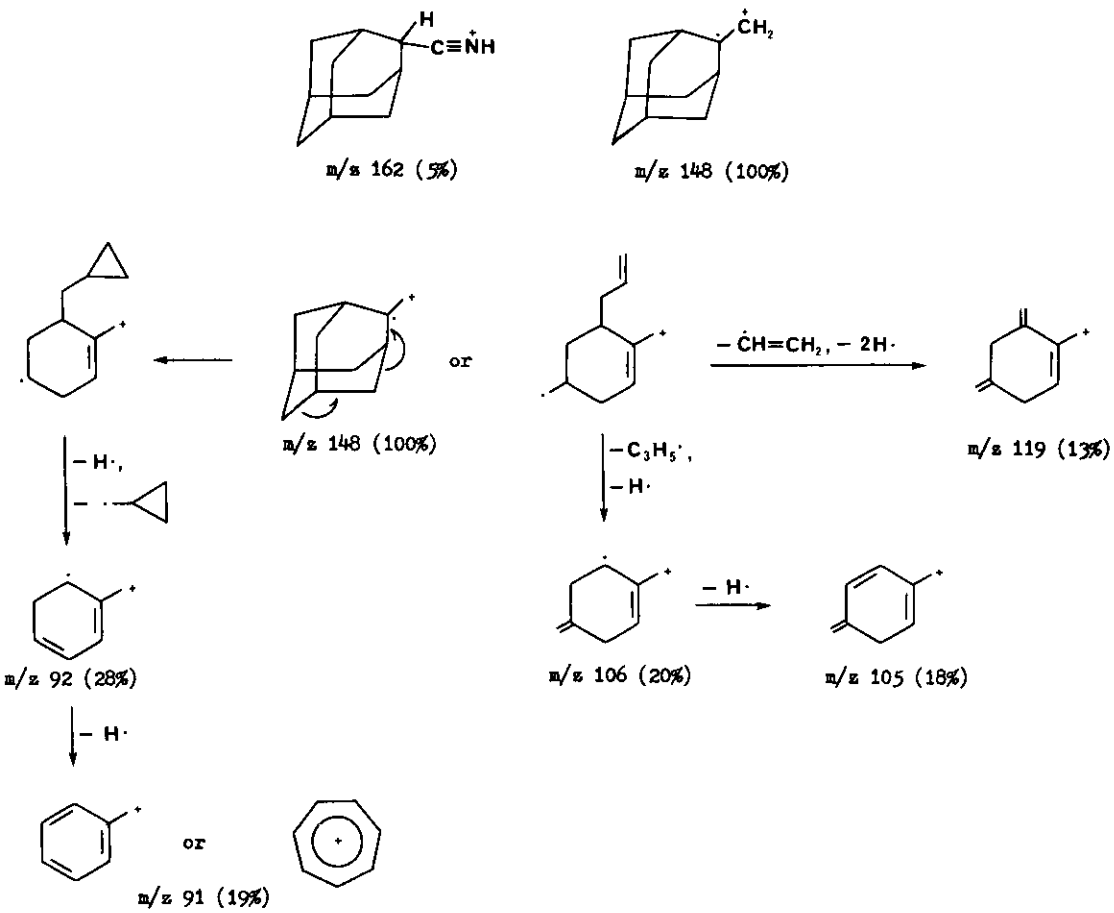
Lacking an exomethylene double bond at C(3), the spiro derivative 2 displayed a distinct fragmentation pattern (Scheme 8). The ester side chain acted as an effective leaving group, while the adamantane portion of the molecule provided stability for the vast majority of fragmentation ions.

Scheme 8

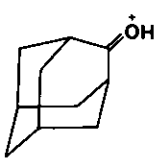


Other fragmentation ions of importance for compound 2 are depicted in Scheme 9; the majority of them are typical for the adamantane ring system [3-6].

Scheme 9

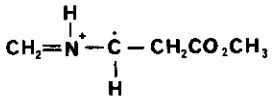


Curiously enough there was no major ion at m/z 151 (ion Y) or m/z 150.

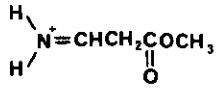


Ion Y (m/z 151, 3%)

One reason that may account for the very low amount of ion Y (at only 3%) is that the initial charge in $M^{+\cdot}$ is centered on the nitrogen atom (Scheme 8). The only fragmentation ions present in the mass spectrum of compound 2 that did not involve the adamantane ring system were at m/z 115 and m/z 102 (analogous to ions B and N, respectively):



m/z 115 (3%)



m/z 102 (31%)

EXPERIMENTAL

An Extranuclear Laboratories Inc. quadrapole with an electron impact source was adjusted to give a good match to the EPA standard spectrum of decafluorotriphenylphosphine. Samples were introduced with a heated solids probe set 25-35°C above the melting point of each compound, and a 1.0 milliamp ionizing current was used.
Compound 1 was also submitted to Shrader Analytical and Consulting Laboratories Inc. (Detroit, Michigan) for a high resolution mass spectrum.

REFERENCES

1. V. St. Georgiev, G. B. Mullen, and C. G. Acker, Heterocycles, 1986, 24, 751.
2. G. B. Mullen, V. St. Georgiev, and C. G. Acker, Heterocycles, 1986, 24, 1285.
3. J. W. Greidanus, Can. J. Chem., 1971, 49, 3210.
4. R. L. Greene, W. A. Kleschick, and G. H. Wahl, Jr., Tetrahedron Let., 1971, 4577.
5. Th. Kuster and J. Seibl, Org. Mass Spectrometry, 1976, 11, 458.
6. R. J. Waltman and A. C. Ling, Can. J. Chem., 1979, 58, 2189.

Received, 16th May, 1986