Electron Impact Mass Spectrometry of Some 2-(*p*-Bromophenyl)-4,4-disubstituted-5(4*H*)-oxazolones

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The mass spectrometric behaviour of four 2-(*p*-bromophenyl)-4,4-disubstituted-5(4*H*)-oxazolones has been investigated using linked scans, mass analyzed ion kinetic energy spectrometry, accurate mass measurements and collisional spectroscopy. The study shows the formation of similar ions in all cases, with the presence of skeletal rearrangements, leading to highly stable product ions.

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Introduction.

5(4*H*)-Oxazolones, first termed "azlactones" by Erlenmeyer [1], have been known since the last century [2-4]. They have been employed as intermediates in various organic syntheses and polymerizations [5-9].

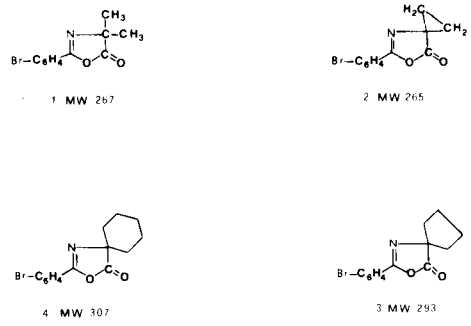
Formation of 5(4*H*)-oxazolones as dehydration products from *N*-acyl-α-amino acids or peptides is a well understood process [10,11]. In the case of chiral, α-monoalkylated α-amino acids this leads to facile racemization in the presence of nucleophiles, with loss of optical purity [12-14], but if two alkyl groups are present on the α-carbon of the α-amino acid this process does not occur. Therefore 5(4*H*)-oxazolones derived from α,α-dialkylated α-amino acids can be successfully used in peptide synthesis [15].

In this connection the use of 2-(*p*-bromophenyl)-4,4-disubstituted-5(4*H*)-oxazolones has led to peptide derivatives which carry a heavy atom, useful for the crystallographic determination of their solid state structure [16-19].

5(4*H*)-Oxazolones derived from *N*-(*p*-bromobenzoyl)-aminoisobutyric acid, *N*-(*p*-bromobenzoyl)-1-aminocyclopropanecarboxylic acid, *N*-(*p*-bromobenzoyl)-1-aminocyclopentanecarboxylic acid and *N*-(*p*-bromobenzoyl)-1-aminocyclohexanecarboxylic acid turned out to be stable, crystalline compounds, allowing the determination of their solid state structures [20-22].

Although oxazole and its derivatives have been extensively studied by mass spectrometry [23,24], very little has been done with 5(4*H*)-oxazolones [25-29].

In the present paper we wish to report the mass spectrometric behaviour of the following 5(4*H*)-oxazolones: 2-(*p*-bromophenyl)-4,4-dimethyl-5(4*H*)-oxazolone (**1**), 2-(*p*-bromophenyl)-4-cyclopropanespiro-5(4*H*)-oxazolone (**2**), 2-(*p*-bromophenyl)-4-cyclopentanespiro-5(4*H*)-oxazolone (**3**) and 2-(*p*-bromophenyl)-4-cyclohexanespiro-5(4*H*)-oxazolone (**4**), using accurate mass measurements, B/E linked scans [30], mass analyzed ion kinetic energy spectrometry [31] and collisional spectroscopy [32].



Formulae

EXPERIMENTAL

Synthesis.

The synthesis of compound **1** has already been published [18].

Compounds **3** and **4**.

Compounds **3** and **4** were prepared from *N*-(*p*-bromobenzoyl)-1-aminocyclopentane-1-carboxylic acid and *N*-(*p*-bromobenzoyl)-1-aminocyclohexane-1-carboxylic acid, respectively, in acetic anhydride at 120° for 20 minutes, as described for **1**, and their characterization is given below:

Compound **3**.

This compound was obtained in a yield of 88%, mp 120-121° (from hot toluene-petroleum ether); pmr (deuteriochloroform): δ 7.72 (m, 4H, phenyl), 2.00 (m, 8H, cyclopentyl CH_2).

Anal. Calcd. for $C_{13}H_{12}NO_2Br$: C, 53.1; H, 4.1; N, 4.8; Br, 27.2. Found: C, 52.9; H, 4.0; N, 4.7; Br, 27.0.

Compound **4**.

This compound was obtained in a yield of 82%, mp 88-89° (from hot toluene-petroleum ether); pmr (deuteriochloroform): δ 7.76 (m, 4H, phenyl), 1.90-1.48 (broad m, 10H, cyclohexyl CH_2).

Anal. Calcd for $C_{14}H_{14}NO_2Br$: C, 54.6; H, 4.6; N, 4.5; Br, 25.9. Found: C, 54.5; H, 4.5; N, 4.6; Br, 25.8.

Compound **2**.

To a suspension of *N*-(*p*-bromobenzoyl)-1-aminocyclopropane-1-carboxylic acid (1.0 mmole) in 5 ml of anhydrous ethyl acetate 1.1 mmoles of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride was added to 0° under stirring. After 1 hour at 0° and 3 hours at room temperature the reaction mixture was diluted to 50 ml with ethyl acetate,

cooled and washed with ice-cold water. The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo*, and the product recrystallized from ethyl acetate-petroleum ether, yield 82%, mp 133-134°; pmr (deuteriochloroform): δ 7.73 (m, 4H, phenyl), 1.88 and 1.80 (m, 2+2H, cyclopropyl CH_2).

Anal. Calcd. for $C_{11}H_8NO_2Br$: C, 49.6; H, 3.0; N, 5.3; Br, 30.0. Found: C, 49.7; H, 3.0; N, 5.2; Br, 29.8.

Mass Spectrometry.

All mass spectrometric measurements were performed on a VG ZAB2F instrument operating in ei conditions (70 eV, 200 μA). Samples were introduced *via* direct inlet system without any heating from the probe and with an ion source temperature of 200°. Accurate mass measurements were performed with the peak matching technique at 10,000 resolution (10% valley definition). Metastable transitions were detected either by B/E linked scand [30] or mass analyzed ion kinetic energy spectrometry [31]. Kinetic energy releases $T_{1/2}$ were calculated according to the usual formula [31]. Collisionally activated decompositions [32] were obtained by 8 keV ions colliding with air in the second field-free region. The pressure in the collision cell was such to reduce the main beam intensity to 70% of its usual value.

Results and Discussion.

The electron impact mass spectra of compounds **1-4** are, at first sight, very similar (see Figure 1). For all the compounds the base peak is due to a bromine-containing ionic species, leading to a doublet at m/z 183 and 185. Furthermore the molecular ions are always scarcely abundant, as well as the higher mass fragment ions.

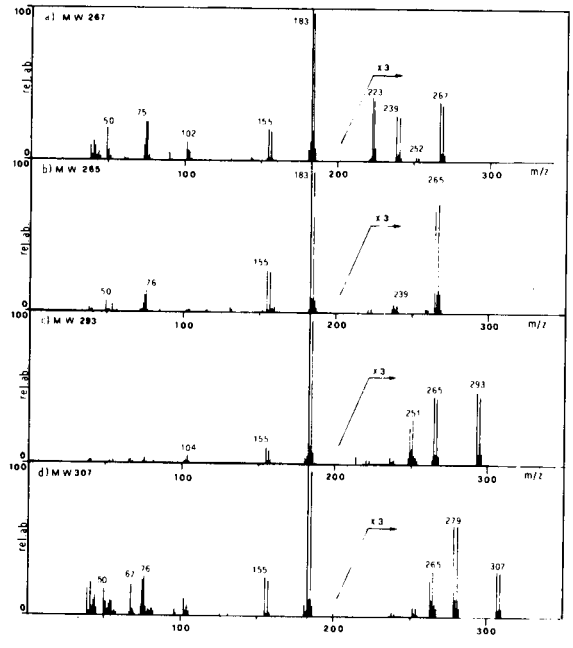
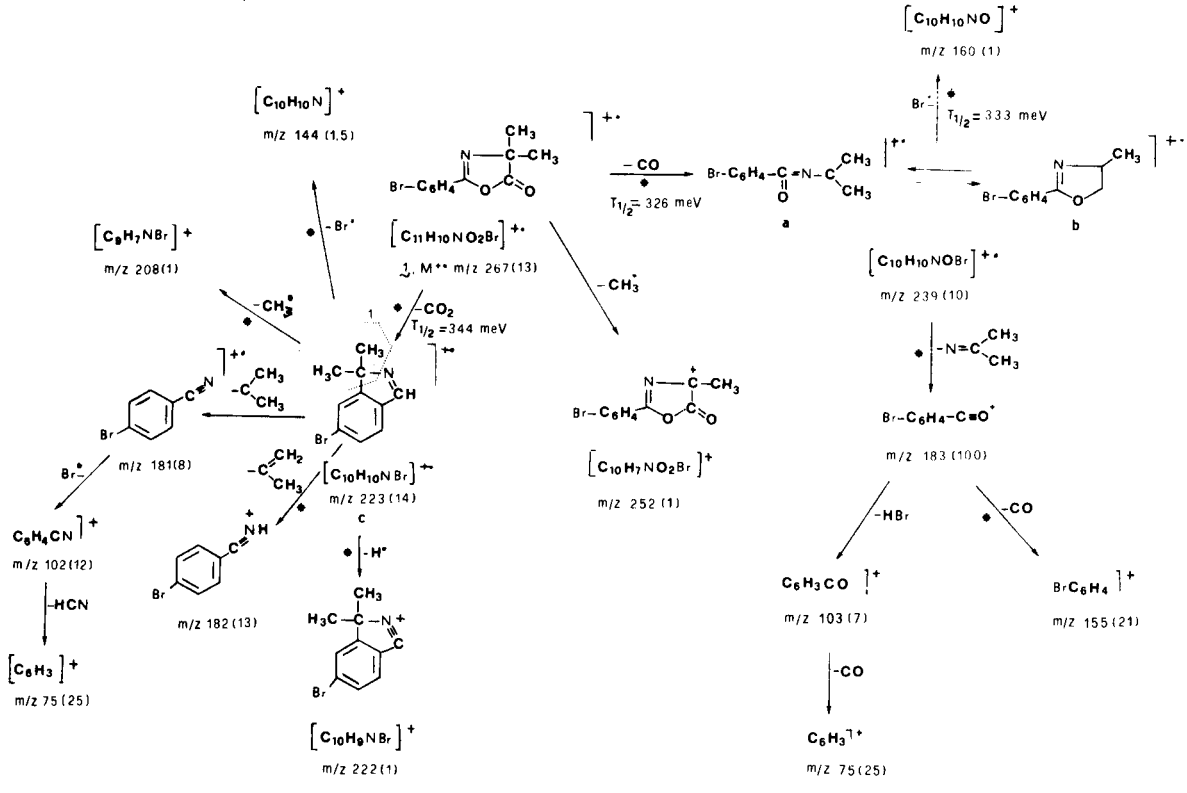


Figure 1. 70 eV EI mass spectra of: a) 2-(*p*-bromophenyl-4,4-dimethyl-5(4*H*)-oxazolone (**1**); b) 2-(*p*-bromophenyl-4-cyclopropanespiro-5(4*H*)-oxazolone (**2**); c) 2-(*p*-bromophenyl-4-cyclopentanespiro-5(4*H*)-oxazolone (**3**); d) 2-(*p*-bromophenyl-4-cyclohexanespiro-5(4*H*)-oxazolone (**4**).

Scheme 1



We will discuss below the mass spectrometric behavior of compound **1-4** separately, in order to put in evidence the existing differences.

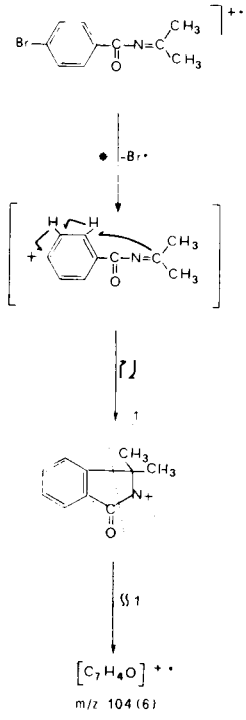
2-(*p*-Bromophenyl)-4,4-dimethyl-5(4*H*)-oxazolone (**1**).

The 70 eV ei mass spectrum of compound **1** is shown in Figure 1a, while the related fragmentation pattern, as obtained by B/E linked scans and accurate mass measurements, is reported in Scheme 1.

The primary CH_3 loss gives rise to the ions at m/z 252 (1%) and 254. This process occurs quite rapidly, as indicated by its absence in the primary decomposition pathways occurring in the first and second field-free regions (detected by B/E linked scans and MIKE spectrum, respectively).

The loss of CO gives rise to an abundant ionic species at m/z 239 and 241 (10%). The high $T_{1/2}$ value associated with this decomposition pathway (326 meV) suggests a high stability of the product ion formed. Both structures **a** and **b** reported in Scheme 1 can be proposed. The former does not require any skeletal rearrangement and its high stability can be related to the conjugation of the system. The latter, energetically more stable, originates from H rearrangements and ring closure processes. The observed fragmentation pattern of these $[C_{10}H_{10}NOBr]^{+\cdot}$ ions consists of two concurrent decomposition processes: i) $Br^{\cdot}$ loss, with which a high $T_{1/2}$ value is associated (333 meV), and which is clearly apparent in the first and second field-free regions. This seems to indicate that the $Br^{\cdot}$ loss is not due to a simple bond cleavage, but to a concerted process, requiring the formation of an intermediate cation (see Scheme 2).

Scheme 2



ii) The loss of $C_3H_6N^{\cdot}$, leading to the ions at m/z 183, gives rise to the base peak of the spectrum. This cleavage has an associated kinetic energy release of 25 meV, indicative of a fast simple cleavage process. Therefore we are inclined to propose structure **a** for the ions at m/z 239.

The ions at m/z 183 and 185 require further comments. Their structure can be reasonably considered the same as $[M\text{-}OH]^+$ ions originating from ei of *p*-bromobenzoic acid. The related CAD MIKE spectra, however, are not wholly superimposable (see Figure 2). In particular collisionally

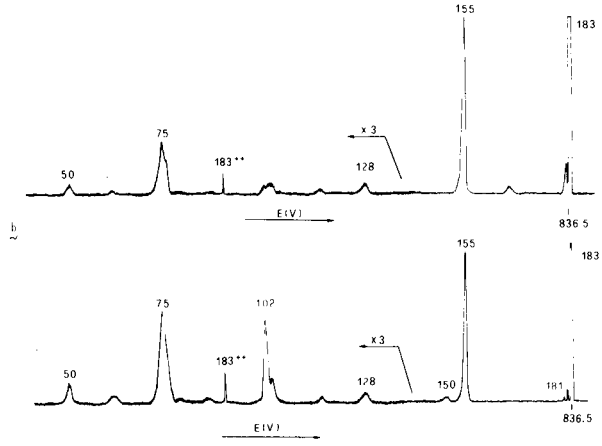


Figure 2. CAD MIKE spectra of ions at m/z 183 originating from: a) *p*-bromobenzoic acid; b) compound **1**.

induced fragment ions at m/z 181 and 102 are present only in the daughter spectrum of ions at m/z 183 originating from **1**. This is due to the overlapping of isobaric ions $[C_7H_4N^{81}Br]^+$, which originate through a different pathway (see below), to the $[C_7H_4O^{79}Br]^{+\cdot}$ ionic species.

The primary CO_2 loss gives rise to the quite abundant ionic species at m/z 223 and 225 (14%). In order to establish the thermal component of this process, spectra were run at different ion source temperatures, leading to the data reported in Figure 3. These results show that the relative abundances of $[C_{10}H_{10}NBr]^{+\cdot}$ (m/z 223 and 225) ions reported in Figure 1a are wholly due to the ei induced decomposition process. The kinetic energy release related to the CO_2 loss is of 344 meV, indicating also in this case the formation of a thermodynamically stable product ion. For this reason we propose the structure **c** in Scheme 1, which accounts for its fragmentation pattern. Cleavage 1 with and without H rearrangement gives rise to the bromine-containing benzonitrilic ions at m/z 181, 183 and 182, 184. The former, with the ^{81}Br isotope, gives rise to the ionic

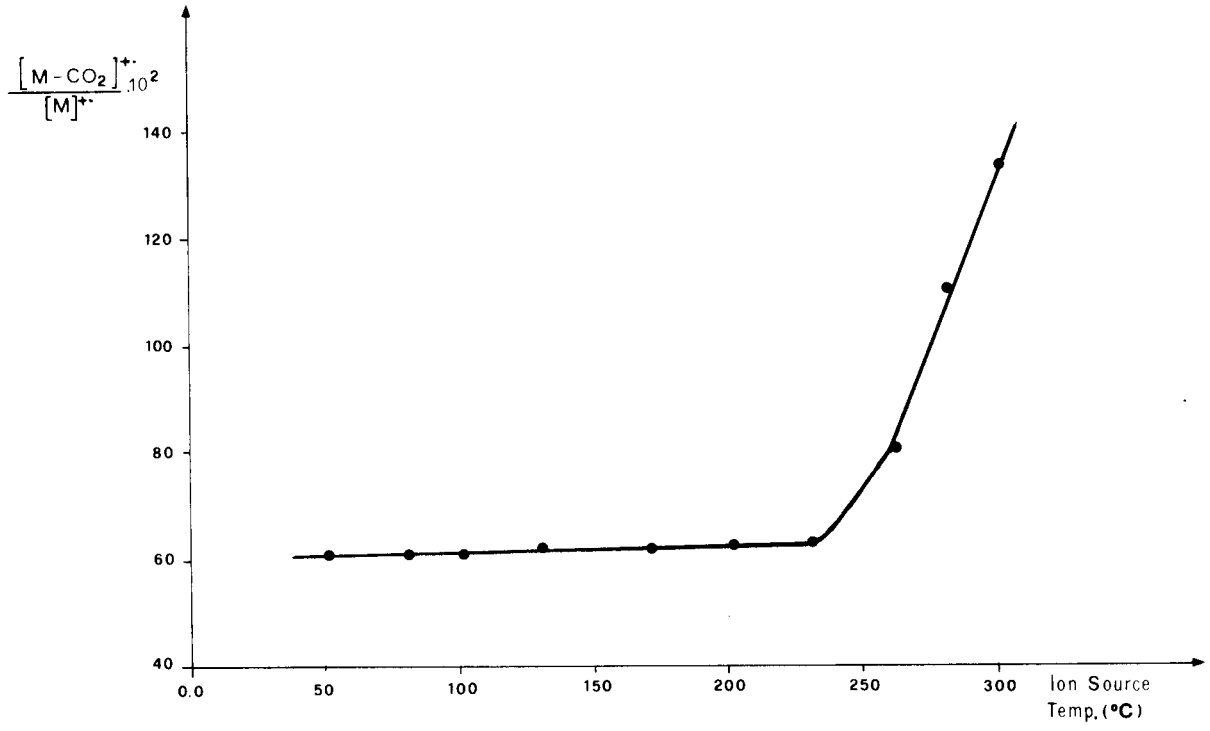


Figure 3. Relative abundance of $[M\text{-}CO_2]^{+\cdot}$ ionic species (m/z 239) originating from compound **1** as a function of ion source temperature.

species at m/z 183, interfering with the $[C_7H_4O^{79}Br]^+$ (m/z 183) ions described above.

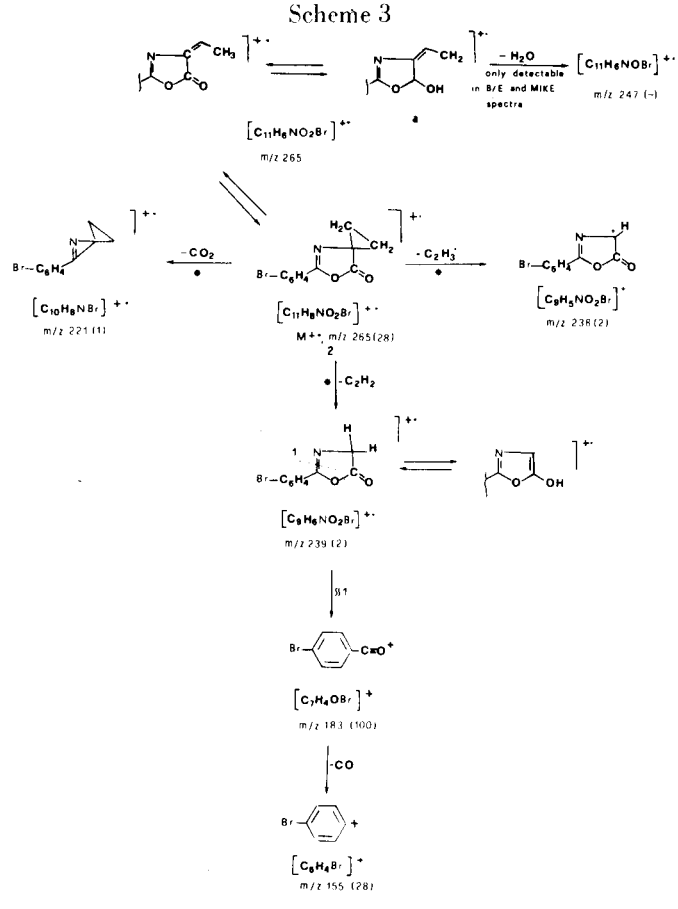
2-(*p*-Bromophenyl)-4-cyclopropanespiro-5(4*H*)-oxazolone (**2**).

The observed fragmentation pattern (see Figure 1b and Scheme 3) is substantially different from that of compound **1**. First of all, the primary CO loss is in this case completely absent, while cleavages related to the cyclopropanespiro moiety become predominant. Losses of C_2H_3· and acetylene lead to ions at m/z 238, 240 and 239, 241 respectively, well evidenced by B/E linked scans. For the latter, the structure of 2-(*p*-bromophenyl)-5(4*H*)-oxazolone molecular ions can be reasonably proposed.

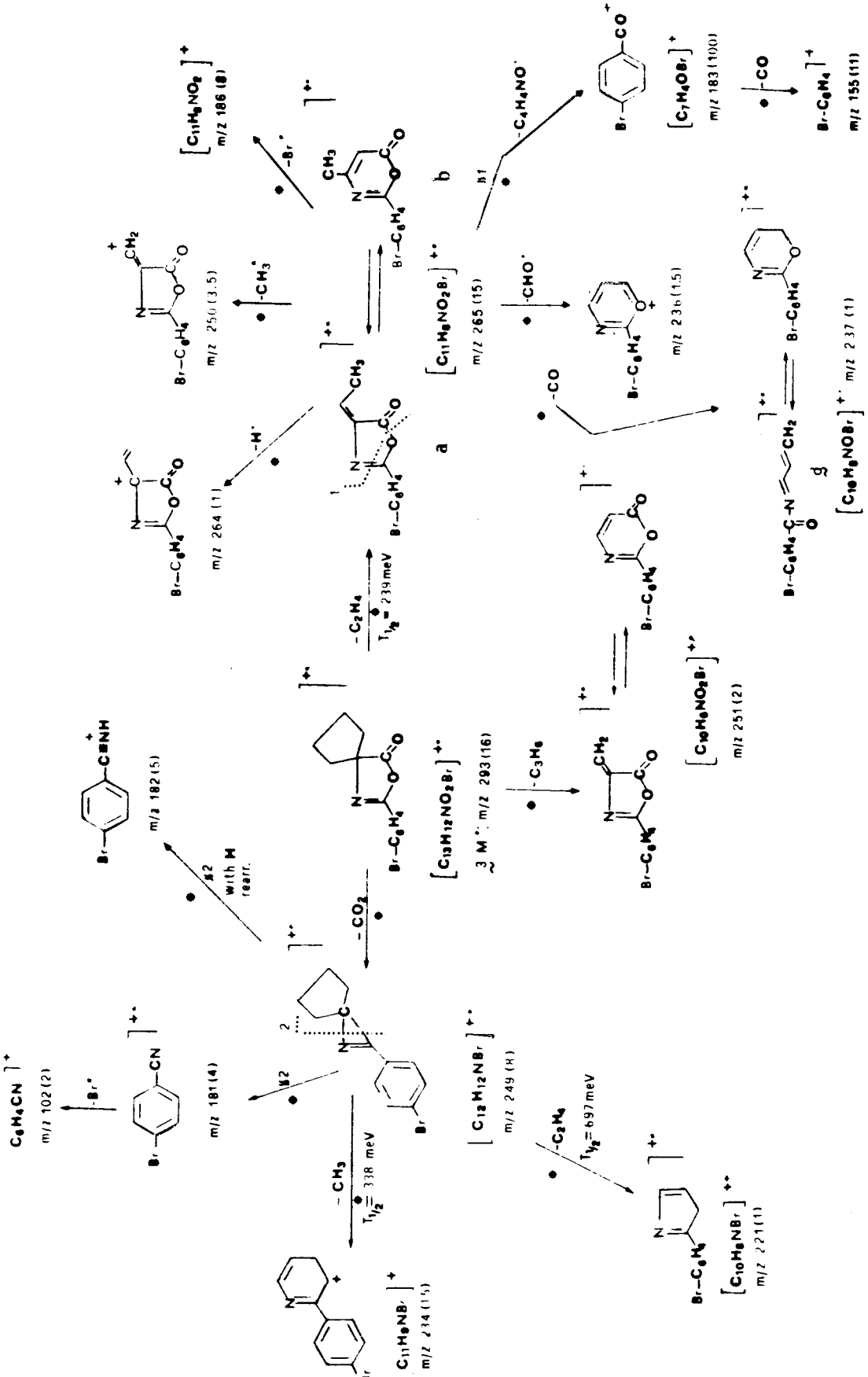
The only other primary fragmentation pathway detectable in the 70 eV EI mass spectrum as well as in B/E linked scans of **2** is due to the CO_2 loss, analogous to that already described for compound **1**, which gives rise to the bromine-containing, azirine-like ions at m/z 221, 223.

An interesting aspect of the compound **2** behavior is demonstrated by B/E and MIKE spectra of $M^{+\cdot}$. In both cases a well detectable peak at m/z 247, corresponding to primary H_2O loss occurring hence in the first and second field-free regions of the apparatus only, is present. This implies the rearrangement of molecular ions of **2** to an enolic form, through the mechanism reported in the upper part of Scheme 3. The cyclopropanespiro moiety opening

Scheme 3



Scheme 4



and further H rearrangement lead to molecular ions of structure **a** (see Scheme 3) which can be reasonably considered the parent ions for the H_2O loss. It must be stressed that this isomerization process is kinetically slow, as m/z 247 ions can be observed in a time window of $10^{-6} - 10^{-5}$s only.

2-(*p*-Bromophenyl)-4-cyclopentanespiro-5(4*H*)-oxazolone (**3**).

For the 4-cyclopentanespiro derivative, most ei induced decomposition processes are related to the spiro moiety. Ions at m/z 265,267 are exclusively due to primary C_2H_4 loss; high resolution measurements do not show any component arising from primary CO loss, observed for compound **1** (see Figure 1c and Scheme 4). For these $[C_{11}H_8NO_2Br]^{+\cdot}$ ions the same structure of $M^{+\cdot}$ of **2** cannot be proposed, due to the strongly different fragmentation patterns. For the former two different structures can be proposed. The first (**a** of Scheme 4) originates by the spiro ring cleavage and further C_2H_4 loss, while the second implies a ring expansion process, leading to an oxazinone-like six-membered ring. The high kinetic energy release related to the primary ethylene loss ($T_{1/2}$ = 239 meV) can be explained either by the spiro ring cleavage or by the stability of the product ions.

Ions at m/z 265 follow a number of different fragmentation pathways: i) loss of CO; this process can lead, in principle, to "open" ions **d** similar to ions **a** of Scheme 1 or, alternatively, to an oxazine-like six-membered ring; ii) CHO· loss: this fragmentation pathway implies parent ions of enolic structure and gives rise to particularly stable, aromatic ions at m/z 236, 238; iii) C_4H_4NO· loss (cleavage 1 of Scheme 4) leads to the most abundant ionic species at m/z 183, 185, corresponding to $[M\text{-}OH]^+$ ions of *p*-bromobenzoic acid; iv) H·, CH_3· and Br· losses are quite obvious, leading to the ionic species reported in Scheme 4.

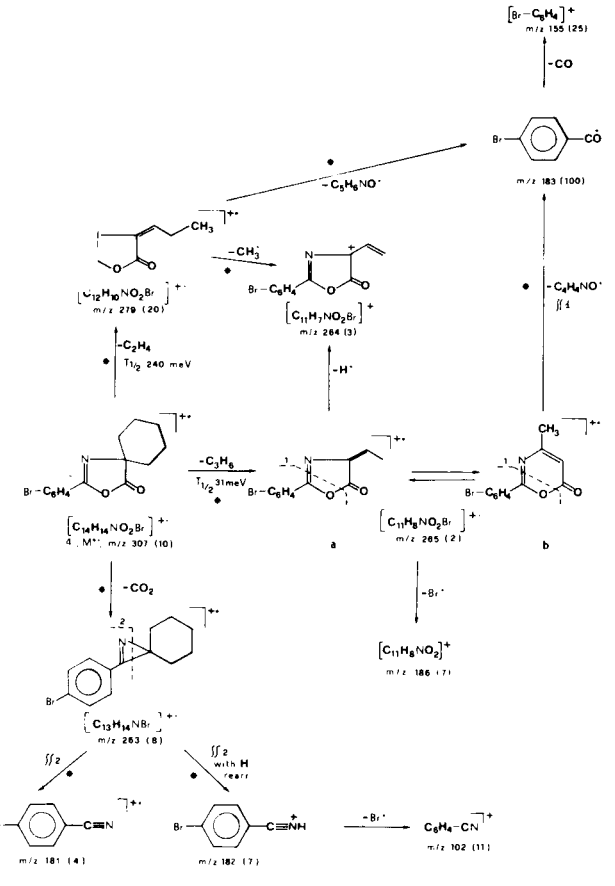
In B/E linked scan spectrum primary loss of propene is observed, giving rise to $[C_{10}H_6NO_2Br]^{+\cdot}$ ions (m/z 251, 253), for which two different structures, both highly stable, can be proposed.

The primary CO_2 loss is still present. In the present case the condensation reaction proposed for **1** cannot be operative, due to the steric hindrance of the spiro group; consequently the formation of an azirine ring is suggested, as often proposed in mass spectrometry of nitrogen-containing heterocyclic system [24]. Cleavage 2 is in agreement with such structure, leading to *p*-bromobenzonitrile ions. The high $T_{1/2}$ value related to the CH_3· and C_2H_4 losses from $[C_{12}H_{12}NBr]^{+\cdot}$ ions strongly suggests the occurrence of ring formation reactions, leading to thermodynamically highly stable product ions.

2-(*p*-Bromophenyl)-4-cyclohexanespiro-5(4*H*)-oxazolone (**4**).

As observed for compound **3**, primary C_2H_4 loss is identified, with a practically identical kinetic energy release value ($T_{1/2}$ = 240 meV). These $[C_{12}H_{10}NO_2Br]^{+\cdot}$ ions further decompose (see Scheme 5 and Figure 1d) through CH_3· loss

Scheme 5



and C_5H_6NO· loss to form $[BrC_6H_4CO]^+$, the most abundant ionic species in the mass spectrum.

The primary C_3H_6 loss is emphasized: it still gives rise to ions **a** and **b** already described for compound **3** but in the present case the $T_{1/2}$ value associated with this fragmentation process is particularly low (31 meV), suggesting that the C_3H_6 loss originates from an open structure of the spiro ring, through a simple bond cleavage. Furthermore, the fragmentation pattern of these ionic species is less complex than that observed for **3** (compare Schemes 4 and 5). Primary EI induced CO_2 loss is also present, leading to azirine ions at m/z 263, 265 which behave as the analogous ones (m/z 249, 251) described for **3**.

Conclusions.

At first sight the mass spectra of compounds **1-4** seem to be quite similar, with the same base peak at m/z 183, 185 and higher mass fragments of scarce abundance. But a deeper analysis, obtained using B/E linked scans and MIKE spectrometry, has allowed us to highlight clear dif-

ferences. While for **1** methyl loss and the cleavage of 5(4*H*)-oxazolone ring with CO loss are the only primary decomposition pathways, in the case of spiroalkane substituted compounds (**2-4**), fragmentation processes related to the spiro moiety become predominant. The occurrence of skeletal rearrangements are evidenced by the kinetic energy release values associated with the decomposition pathways. Collisionally activated decomposition spectra have proved that the base peak is always due to the $[BrC_6H_4CO]^+$ fragment which in all the cases does not originate from primary decomposition pathways.

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