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# Retro Diels–Alder and other electron ionization-induced fragmentation reactions of 1,2,3,4-tetrahydrobenzopyran-2,3-dicarboxylic acid derivatives☆

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**Abstract**

The electron ionization-induced fragmentation paths of various substituted 9,9a-dihydro-3a*H*-[1]benzopyrano[2,3-*c*]pyrrole-1,3-diones by use of metastable ions mass spectrometry have been studied. It was found that two main fragmentation pathways are representative for compounds under study. The first starts at the succinimide ring and its pattern mainly depends on the substituents in the benzene ring. The second one corresponds to the retro Diels–Alder reaction (RDA) that takes place at tetrahydropyran-type ring with charge migration.


*Keywords:* EI fragmentation mechanism; Metastable ion; Retro Diels–Alder reaction; Kinetic energy release; Benzopyran derivative

## 1. Introduction

During our studies on the [4 + 2] cycloaddition of aza-*ortho*-xylylenes **2** (6-methylene-cyclohexa-2,4-diene imines, quinone methylene imines), generated via thermal extrusion of $SO_2$ from 2,1-benzisothiazoline-2,2-dioxides **1**, we investigated in detail fragmentations of the obtained 1,2,3,4-tetrahydroquinoline derivatives **3** [1] (Scheme 1).

The molecular ions of the cycloadducts **3** underwent complex fragmentation processes, among which the important ones were: (i) multistep formation of *N*-methylenequinolinium radical cation **4**, and (ii) retro Diels–Alder reaction resulting in a formation of *N*-phenylmaleimide **5** and aza-*ortho*-xylylene radical cation **6** (Scheme 2).

Here, we present results of our studies towards the electron ionization-induced fragmentation of condensed benzopyranopyrrolidinodiones **10a–f** which can be considered as the oxa-analogues of the studied earlier 1,2,3,4-tetrahydroquinoline derivatives **3**. These compounds were obtained in a [4 + 2] cycloaddition of *N*-substituted maleimides **9** to *ortho*-methylenequinones **8** generated via thermal extrusion of $SO_2$ from 3*H*-1,2-benzoxathiole 2,2-dioxides **7** (benzosultones; Scheme 3) [2]. The latter species seem to be important intermediates in chemical and biochemical reaction pathways as it has been reviewed recently [3].

Examination of the 70 eV EI mass spectrum of compound **10a** showed the presence of a peak corresponding to the ion formed in the course of retro Diels–Alder (RDA) fragmentation reaction. Interestingly, the charge was retained on the maleimide fragment rather than on the heterodiene one, i.e., contradictory to the results obtained previously for tetrahydroquinoline derivatives **3** (Scheme 2) [1]. This result seemed to be important, especially due to the fact that hitherto there has been little instances towards RDA processes of tetrahydropyran-type derivatives in the literature. It is well known that RDA fragmentation is common for tetrahydronaphtalenes and their 1-*S* and 1-*N* heteroanalogs [1,4,5]. Recently a paper by Martin and co-workers provided some examples of retro Diels–Alder reaction in reference to chromene-type derivatives under EI, CA and ESI conditions [6].

Our preliminary results prompted us to study EI-induced fragmentation of compound **10a** and also its derivatives bearing substituents in the benzene and succinimide rings (**10b–f**) to get better insight into the RDA process. On the other hand, compounds **10a–f** can be viewed as the derivatives of succin-

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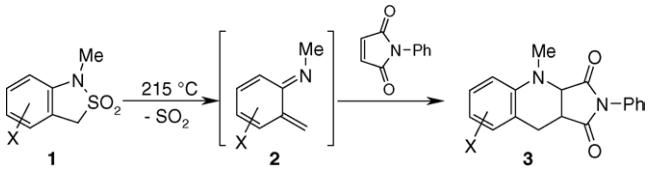
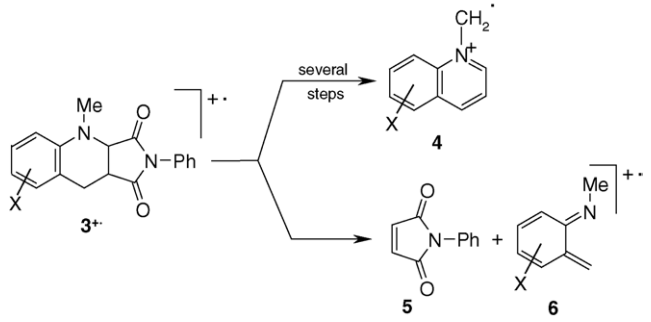
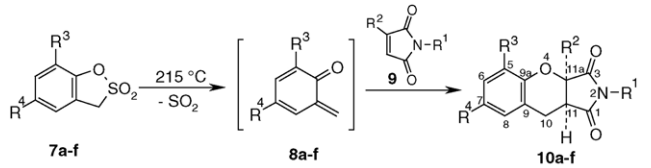



Scheme 1. Synthesis of 1,2,3,4-tetrahydroquinoline dicarboxylic acid derivatives.




Scheme 2. Main EI-induced fragmentation products of cycloadducts **3**.




Scheme 3. Synthesis of condensed benzopyranopyrrolidinodiones in a cycloaddition reaction of *ortho*-methylenequinones with *N*-substituted maleimides.

imide bearing alkyl or aryl substituent at the nitrogen atom. EI mass spectra of various *N*-substituted succinimide derivatives have already been studied [8,9], however we did not find any reports concerning compounds with succinimide ring coupled with the oxygen-containing six-membered ring.

## 2. Experimental

Compounds **10a–f** were prepared by refluxing of the mixture of corresponding benzosultones **7a–f** and appropriately substituted maleimides **9** in chlorobenzene [2].

All mass spectra were recorded on AMD-604 (AMD Intectra GmbH, Germany) double focusing mass spectrometer with BE geometry. Standard EI spectra were obtained under the following conditions: electron energy, 70 eV; cathode emission current, 0.5 mA; acceleration voltage, 8 kV; ion source temperature, 200 °C. Samples were introduced using direct insertion probe heated from 30 to 100 °C.

Accurate mass measurements for all significant peaks were performed by the narrow range high voltage scanning technique at a 10,000 resolving power (10% valley definition) using perfluorokerosene (PFK) as the reference compound. The accuracy of mass measurements was better than 10 ppm with exception of a few poorly resolved peaks resulting from ions with the same nominal mass.

Fragmentation pathways were confirmed by MIKE and linked scan B/E = const. daughter ion spectra recorded for metastable decomposition and, in some instances, also for the collisionaly induced dissociation (CID) products. Both MIKE and B/E linked scan spectra were recorded using 30 s scan time. Eight consecutive spectra were averaged to improve signal to noise ratio. In the CID experiments helium was used as the collision gas. The pressure in the collision chamber was set to reduce the parent ion abundance by 50%.

Kinetic energy release ($T_{0.5}$) values were calculated for the peak's widths at 50% of its height and were corrected for the width of the parent ion peak in accordance with the procedure described elsewhere [9]. Series of three consecutive measurements for two selected ions show that the reproducibility of $T_{0.5}$ values is better than 4%.

## 3. Results and discussion

EI (70 eV) mass spectra of compounds **10a–f** are listed in Table 1. Compounds **10a** and **10b** without substituents in positions 5–8 are representative for all compounds under study, so their fragmentation has been studied in detail. Daughter ion spectra recorded for decomposition of molecular ion of **10b** in the first field free region (B/E linked scan) and second field free region (MIKE) show rather complex, however clear pattern, indicating that fragmentation of this ion occurs along several pathways (Fig. 1). The same measurements performed for the molecular ion of **10a** and all important fragment ions, together with the results of the accurate mass measurements, enabled to establish the main fragmentation paths for **10a** and **10b**.

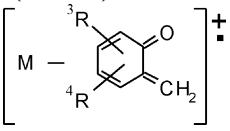
In general, fragmentation reactions of these compounds can be classified in two groups. The first group covers several processes starting within the five-membered succinimide ring. The second group contains fragmentations initiated within the six-membered pyran ring.

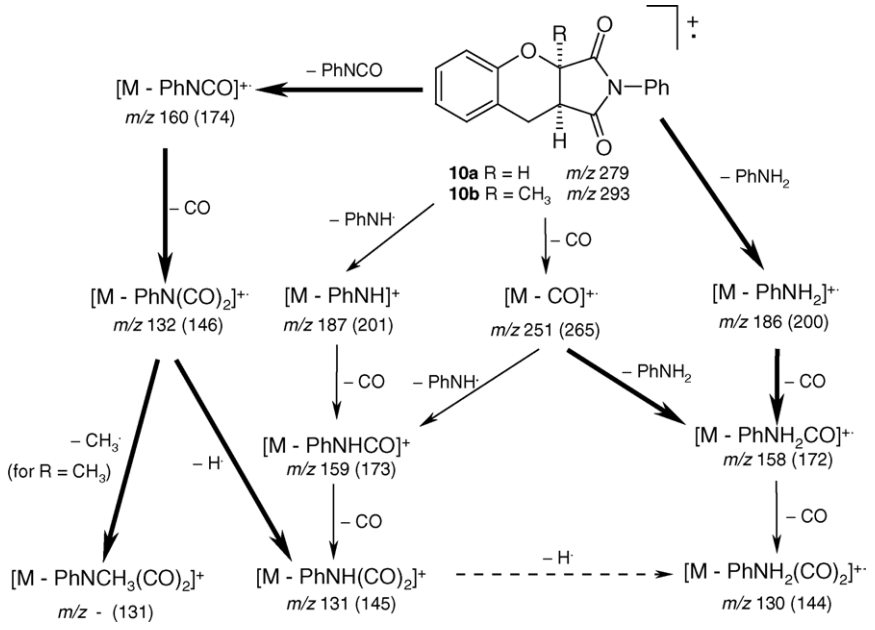
### 3.1. Fragmentation reactions starting within a succinimide ring

Analysis of the 70 eV EI mass spectra of studied compounds, as well as daughter ion mass spectra for their molecular ions, demonstrates clearly that the fragmentation of these ions takes place mainly within the five-membered succinimide ring and proceeds along several pathways (Scheme 4).

These reactions result in a stepwise loss of the $PhN(CO)_2$ fragment accompanied by the loss of one or two hydrogen atoms. Under metastable conditions two decomposition channels distinctly predominate: (i) elimination of $C_7H_5NO$ fragment, most likely phenylisocyanate molecule (PhN = C = O) giving peaks at *m*/*z* 160 for **10a** and *m*/*z* 174 for **10b** as well as, (ii) net loss of aniline yielding peaks at *m*/*z* 186 for **10a** and *m*/*z* 200 for **10b**, as it was shown in Fig. 1. In our regard the driving force for both of these reactions lies in the formation of the cyclic benzoxonium cations. Propositions of mechanisms for both reactions along

Table 1
70 eV mass spectra of 9,9a-dihydro-3a*H*-[1]benzopyrano[2,3-*c*]pyrrole-1,3-diones **10a–f** [*m/z* (relative intensity, %)]

| | **10a** | **10b** | **10c** | **10d** | **10e** | **10f** |
|---|---|---|---|---|---|---|
| $M^{\bullet+}$ | 279 (100) | 293 (66) | 324 (100) | 338 (100) | 361 (100) | 217 (56) |
| $[M - OH]^+$ | – | 276 (2) | 307 (5) | 321 (8) | 344 (4) | 200 (5) |
| $[M - H_2O]^{\bullet+}$ | 261 (2) | 275 (1) | 306 (5) | – | 343 (1) | 199 (2) |
| $[M - CO]^{\bullet+}$ | 251 (5) | 265 (4) | 296 (4) | 310 (2) | – | 189 (2) |
| $[M - R^1NH]^+$ | 187 (7) | 201 (11) | 232 (4) | 246 (2) | – | 187 (3) |
| $[M - R^1NH_2]^{\bullet+}$ | 186 (13) | 200 (28) | 231 (2) | 245 (5) | 268 (14) | 186 (23) |
| $[M - R^1NCO]^{\bullet+}$ | 160 (27) | 174 (50) | 205 (18) | 219 (25) | 242 (23) | 160 (32) |
| $[M - R^1NHCO]^+$ | 159 (12) | 173 (14) | 204 (7) | 218 (3) | 241 (5) | 159 (4) |
| $[M - R^1NH_2CO]^{\bullet+}$ | – | 172 (13) | – | – | 240 (2) | 158 (3) |
| $[M - R^1N(CO)_2]^{\bullet+}$ | 132 (36) | 146 (24) | 177 (54) | 191 (16) | 214 (13) | 132 (30) |
| $[M - R^1NH(CO)_2]^+$ | 131 (82) | 145 (84) | 176 (79) | 190 (28) | 213 (26) | 131 (100) |
| $[M - R^1N(COH)_2]^{\bullet+}$ | 130 (2) | 144 (11) | 175 (2) | 189 (2) | 212 (2) | 130 (6) |
| $[M - R^1N(CO)_2]^{\bullet+}$ | | | | | | |
| –OH | – | 129 (3) | 160 (11) | 174 (9) | – | 115 (3) |
| $-R^2$ | – | 131 (100) | – | 176 (72) | 199 (40) | – |
| $-NO_2$ | – | – | 131 (12) | 145 (6) | – | – |
| –(NO + OH) | – | – | 130 (27) | 144 (17) | – | – |
|  | 173 (7) | 187 (18) | 173 (5) | 187 (14) | 187 (61) | 111 (7) |
| Remaining peaks | 145 (2) | 248 (3) | 294 (3) | 308 (5) | 346 (3) | 149 (3) |
| | 113 (3) | 236 (2) | 279 (5) | 293 (6) | 326 (4) | 148 (4) |
| | 104 (6) | 220 (2) | 278 (3) | 292 (2) | 290 (2) | 141 (3) |
| | 103 (7) | 159 (5) | 249 (2) | 220 (3) | 179 (6) | 106 (4) |
| | 93 (43) | 119 (13) | 219 (2) | 177 (7) | 159 (3) | 104 (7) |
| | 91 (3) | 118 (9) | 188 (2) | 150 (10) | 143 (7) | 103 (12) |
| | 78 (5) | 117 (9) | 147 (5) | 119 (4) | 130 (2) | 102 (6) |
| | 77 (12) | 116 (7) | 119 (20) | 115 (6) | 115 (6) | 91 (4) |
| | | 115 (13) | 103 (9) | 93 (18) | 93 (30) | 78 (27) |
| | | 107 (15) | 102 (6) | 81 (4) | 77 (7) | 77 (29) |
| | | 91 (26) | 93 (89) | 51 (3) | 75 (6) | 52 (10) |
| | | 78 (18) | 77 (20) | | 68 (6) | 51 (23) |




Scheme 4. Important fragmentation pathways of compounds **10a–f**. Main pathways are marked with bold arrows. Some of these channels are observed only for certain derivatives, depending on the substituents at benzene ring. Numbers in parentheses are the *m/z* values of the fragment ions of compound **10b**.

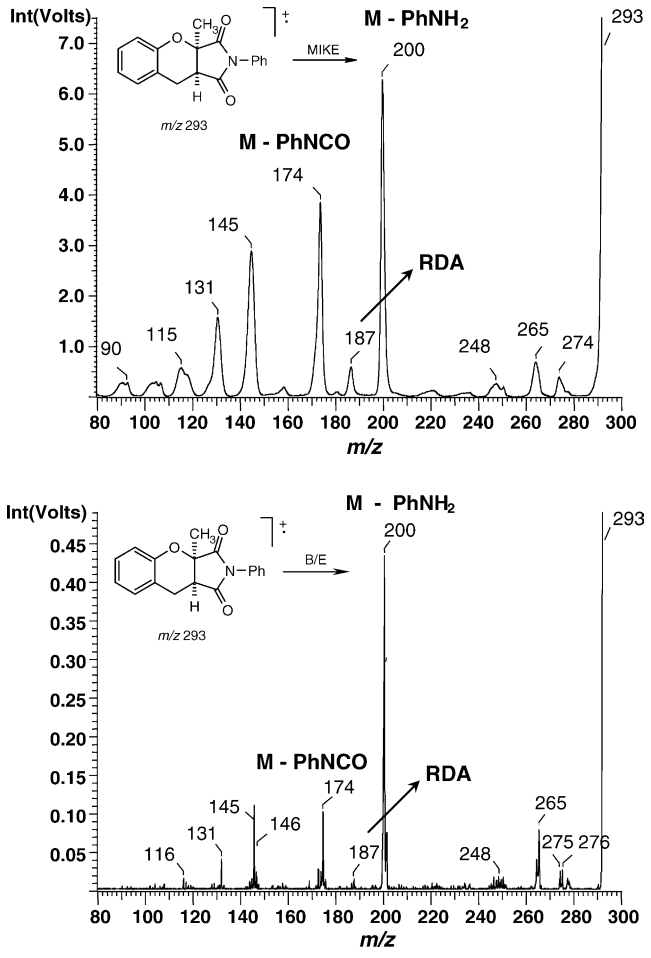
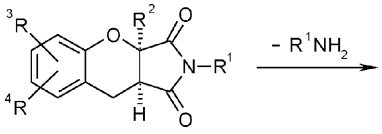



Fig. 1. MIKE and B/E spectra of the molecular ion of compound **10b**.

with the most possible structure of the resulting fragment ions are presented in Schemes 5 and 6, respectively.

It seems reasonable to assume that the elimination of phenylisocyanate molecule from the molecular ion of **10b** is preceded by a cleavage of C-3–C-11a bond in the succinimide ring, giving rise to the formation of the stable distonic benzoxonium radical cation **11** (Scheme 5).

Table 2
$T_{0.5}$ values for $R^1NH_2$ elimination under metastable fragmentation conditions from molecular ions of compounds **10a–f**.

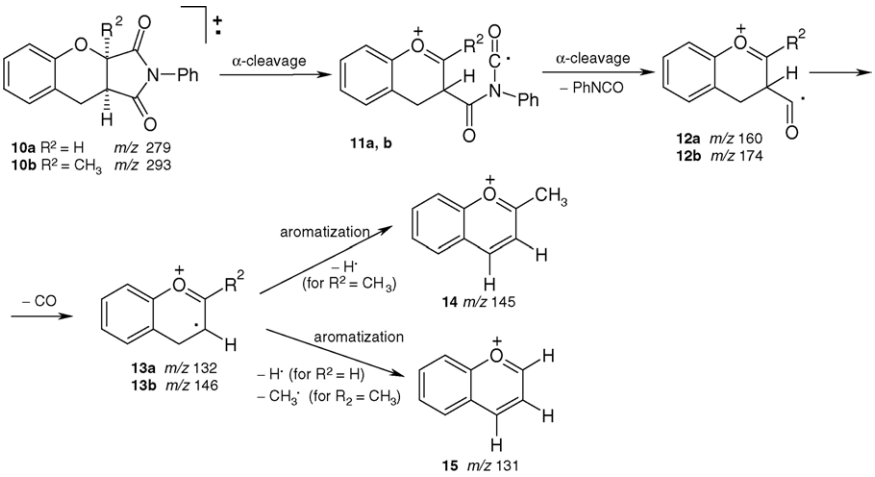



| | $T_{0.5}$ (meV) |
|---|---|
| **10a** $R^1$ = Ph, $R^2$ = H, $R^3$ = $R^4$ = H | 104 |
| **10b** $R^1$ = Ph, $R^2$ = $CH_3$, $R^3$ = $R^4$ = H | 92 |
| **10c** $R^1$ = Ph, $R^2$ = H, $R^3$ = H, $R^4$ = 7-$NO^2$ | 33 |
| **10d** $R^1$ = Ph, $R^2$ = $CH_3$, $R^3$ = H, $R^4$ = 7-$NO^2$ | 56 |
| **10e** $R^1$ = Ph, $R^2$ = $CH_3$, $R^3$ = 5-Cl, $R^4$ = 7-$C^l$ | 63 |
| **10f** $R^1$ = $CH_3$, $R^2$ = H, $R^3$ = $R^4$ = H | 43 |

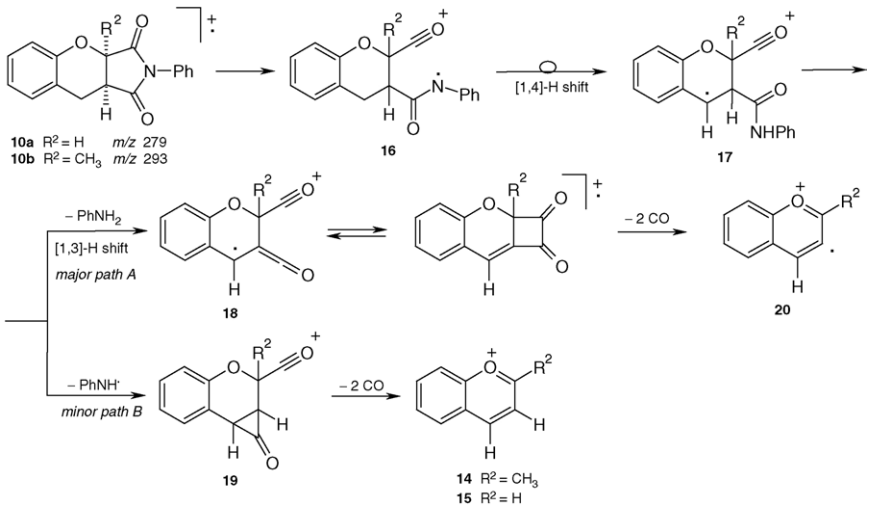
Some suggestions concerning the mechanism proposed can be found in our previous paper concerning the fragmentation of the tetrahydroquinoline derivatives **3** [1]. The fragmentation pattern of succinimidic core discussed in this work turned to be in accordance with our recent observations. Further fragmentation of the $[M - PhNCO]^{\bullet+}$ ion, i.e., loss of CO molecule accompanied by subsequent elimination of $H^-$ leads to the stable chromenylium cations **14** or **15**, for **10b** and **10a**, respectively, which are one of the most abundant ions in EI spectra of **10a** and **10b**. In addition, in the case of compound **10b**, chromenylium cation **15** is formed by a H shift followed by the elimination of the methyl radical (Scheme 5), giving rise to the base peak (*m/z* 131) in the EI spectrum of **10b**. It was proved by the daughter ion spectra that the structures of the *m/z* 131 ions derived from compounds **10a** and **10b** are identical.

Molecular ions of **10a** and **10b** undergo also the loss of the $PhNH_2$ fragment, i.e., formally an aniline molecule, as it was confirmed by daughter ion mass spectra (Fig. 1). The process seems to be much more complicated than it looks at first sight and is accompanied by kinetic energy release (KER) of elevated values (Table 2), as for a direct bond cleavage.

For instance, in the sequence of reaction $M^{\bullet+} \rightarrow [M - PhNH_2]^{\bullet+}$ the highest $T_{0.5}$ value was observed for the least substituted model compound (**10a** $R^2 = R^3 = R^4 = H$) while the smallest one was found for that bearing $NO_2$ group in a ben-




Scheme 5. Mechanistic proposal for an elimination of phenylisocyanate from molecular ion of compounds under study.




Scheme 6. Possible mechanism of $PhNH_2$ (Path A) and $PhNH^{\bullet}$ (Path B) elimination from the molecular ions of compounds under study.

zene ring (**10c**). Assuming that KER values reflect mostly the reverse reaction activation energy and that in all cases the same neutral fragment is eliminated, the conclusion can be drawn that the obtained results could be accounted for the stability of the reaction ionic products. Moreover, the KER data suggest that the skeletal rearrangement must take place before the formation of $[M - PhNH_2]^{\bullet+}$ ion. Most likely the process starts with C-3–N-2 bond cleavage and is followed by a [1,4]-H shift from the methylene group of pyran ring to the N-2 nitrogen atom, that finally leads to the distonic ion **17** (Scheme 6).

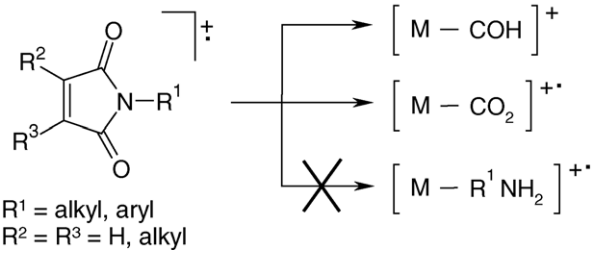
Analysis of the daughter ion mass spectra presented in Fig. 1 indicates that the rearranged ion **17** undergoes predominantly the loss of $PhNH_2$ molecule (Path A) with simultaneous minor elimination of $PhNH^{\bullet}$ radical (Path B). The latter process results in the formation of the cation **19** structure of which is difficult to propose. One of the possibilities is shown in Scheme 6. Inasmuch as the elimination of $PhNH^{\bullet}$ radical does not predominate under metastable conditions it must be accompanied by the high activation barrier. In our opinion the main dissociation channel observed for **10** yields the $[M - PhNH_2]^{\bullet+}$ fragment ion **18**, structure of which can be depicted by the valence isomeric forms (Scheme 6). Most likely, fragment ion **18** is formed in the course of [1,3]-H shift which is followed by a subsequent elimination of two CO molecules leading to distonic benzoxonium odd-electron ion **20**.

First hint supporting the proposed scheme of fragmentation was given in our earlier paper [1], where there was also observed the loss of $PhNH_2$ fragment, however from molecular ions of compounds **3** (Scheme 2). On the basis of the daughter ion spectra, as well as deuterium labeling experiments, we proposed the mechanism according to which the molecular ion rearranges by the C-1–N-2 bond breakage followed by fast hydrogen (deuterium) atom transfer from $CH_3$ ($CD_3$) group at N-4 atom to N-2 one. On the other hand well-documented fragmentation pattern of succinimide ring alone [7,8] demonstrates that elimination of $PhNH_2$ fragment does not occur from its molecular ions (Scheme 7).

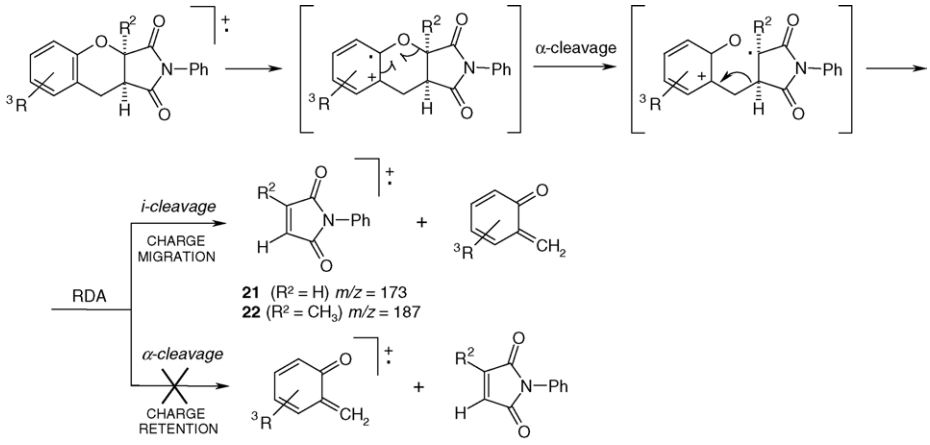
Comparison of all data mentioned above suggests that in the case of compounds **10a–f** methylene group of pyran ring is the most likely source of a proton during an initial [1,4]-H shift step of the molecular ion. Examination of molecular models shows that such proton shift is geometrically possible.

### 3.2. Unimolecular fragmentation starting within a pyran ring

Screening of mass spectra acquired for all compounds under study revealed the presence of the important peak corresponding to the ion with *m/z* 173 and a formula $C_{10}H_7NO_2$ for **10a** ($R^2 = H$) or *m/z* 187 ($C_{11}H_9NO_2$) for **10b** ($R^2 = CH_3$). The MIKE spectrum recorded for the molecular ions of compounds **10a–f** (see representative MIKE spectrum for **10b** in Fig. 1) demonstrated that they are formed directly from the molecular ions. The same outcome concerning the origin of these ions was also confirmed by parent ion mass spectra ($B^2/E$ linked scan) acquired for the ions of interest. These data suggest that both fragment ions may have the structure of the corresponding *N*-phenylmaleimides: **21** (for $R^2 = H$) and **22** (for $R^2 = CH_3$), respectively (Scheme 8). To prove this assumption CID-MIKE and CID-B/E linked scan spectra were recorded for *m/z* 173 ion derived from the molecular ion of compound **10a** and that of the model compound **21** (Fig. 2).




Scheme 7. Main fragmentation pathways for radical cations of the succinimide derivatives bearing alkyl or aryl substituents at nitrogen atom.




Scheme 8. Retro Diels–Alder type fragmentation reaction (RDA) of compounds **10a–f** with charge migration.

Very high similarity of these spectra strongly supports the hypothesis stated above. Slight differences in the intensities of some peaks corresponding to the appropriate product ions can be rationalized in terms of different energy of *m/z* 173 ions to have not been compensated fully by collision-induced dissociation. This result can be rationalized by the retro Diels–Alder (RDA) type fragmentation with a charge migration (Scheme 8). It is quite important to note that this outcome is opposite to that obtained previously for the structural analogues **3** (Scheme 2), in which the oxygen atom in a six-membered heterocyclic ring was replaced by N-$CH_3$ fragment. In that case the charge was retained on the azadiene RDA fragment **6** [1].

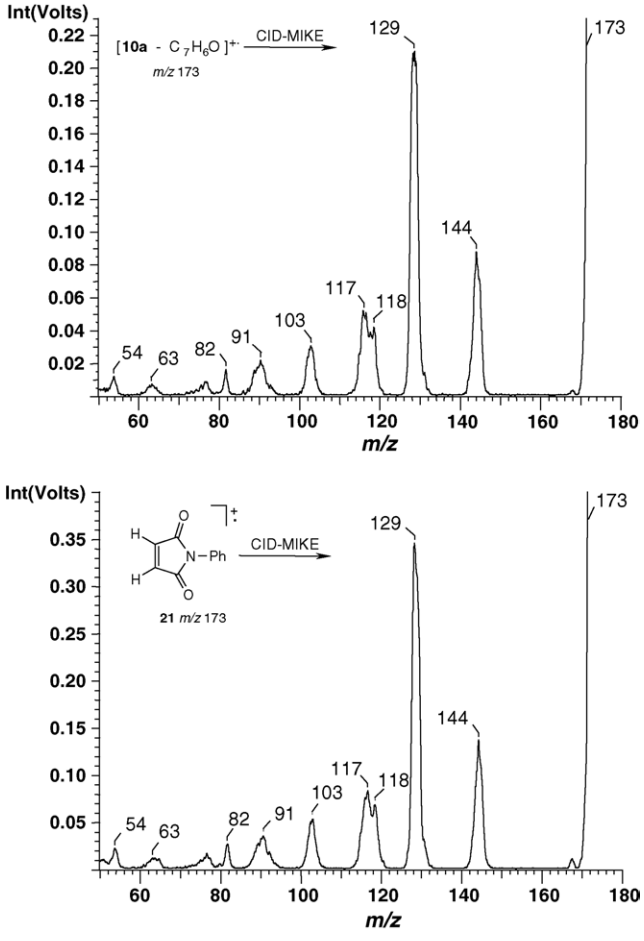



Fig. 2. CID-MIKE spectra of the RDA fragment obtained from the molecular ion of compound **10a** and molecular ion of *N*-phenylmaleimide (**21**).

### 3.3. Fragmentation channels of 7-nitro derivatives *10c* and *10d*

In general, the fragmentation patterns of compounds with a nitro group in position 7 (**10c** and **10d**) are similar to the fragmentation of unsubstituted compounds (**10a** and **10b**) and thus follow the same routes as presented in Scheme 4. However, the presence of a nitro group causes some important changes. In the mass spectra of compounds **10c** and **10d** the presence of peaks due to $[M-30]$ ions were observed. Accurate mass measurements revealed that their composition does not correspond to the elimination of NO but rather to the $[M-2O+2H]^{\bullet+}$ ion ($C_{17}H_{14}N_2O_3$ for **10c** or $C_{18}H_{16}N_2O_3$ for **10d**). This result can be rationalized by reduction of the nitro group to the amino one in the ion source of mass spectrometer. Such process is quite common for electron ionization of the aromatic nitro compounds, however often is misinterpreted in terms of a nitrogen oxide elimination [10–12].

It is interesting to note that unlike the primary fragmentation of unsubstituted compounds **10a** and **10b**, significant loss of OH radical from molecular ions is observed in the case of nitro analogues, both **10c** and **10d**. This reaction proceeds roughly in the same rate for both nitro analogues, differing by the substituent at 11a position. This result indicates that the presence of 11a substituent does not affect the OH elimination reaction. In our regard the driving force for reaction discussed is an increased acidity of protons at 10 position for **10c–d** when compared to **10a–b** due to the presence of strong electron withdrawing nitro group in the benzene ring. This in turn makes it possible to open the more favorable reaction channel of [1,5]-H shift from methylene moiety to the oxygen atom of the carbonyl group followed by the loss of OH radical.

## 4. Conclusions

EI-MS experiments, including fragmentation studies and accurate mass measurements, carried out for the condensed benzopyranopyrrolidinodiones **10a–f** demonstrated that these compounds undergo fragmentations along several pathways. Among them two groups of unimolecular decompositions seem to be the most representative and worth highlighting:

(i) Fragmentations within a succinimide-type ring, namely an elimination of phenylisocyanate as well as a net loss of aniline. The pattern of these processes depends strongly on the kind of substituents in the studied compounds.
(ii) Electrocyclic retro Diels–Alder reaction (RDA) that takes place at tetrahydropyran-type ring. It was observed that this reaction proceeds yielding corresponding maleimide as the ionic product.

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