Electron Impact Mass Spectrometry of Polyannulated Oxygen Heterocycles with Cyclic Orthoester or Acetal Moieties

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The mass spectrometric behaviour of the pairs of diastereoisomeric 3-methyl- and 3-phenyl-substituted 3,11b-epoxy-2,3,4,5,5a,11b-hexahydro-5a-hydroxyoxepino[3,2-*c*][1]benzopyran-6-ones **5**, **6** and **7**, **8** and the pairs of diastereoisomeric 3-methyl and 3-phenyl substituted 3,11a-epoxy-2,3,4,5,5a,11a-hexahydro-5a-hydroxyoxepino[2,3-*b*][1]benzopyran-6-ones **9**, **10** and **11**, **12** has been studied in detail with the aid of exact mass measurements, B/E linked scans, collisional experiments and deuterium labelling. Characteristic ionic species for angularly annulated compounds **5-8** and for linearly annulated ones **9-12** have been found, thus allowing the structural assignment. No differences could be determined in the fragmentation patterns of the diastereoisomeric compounds.

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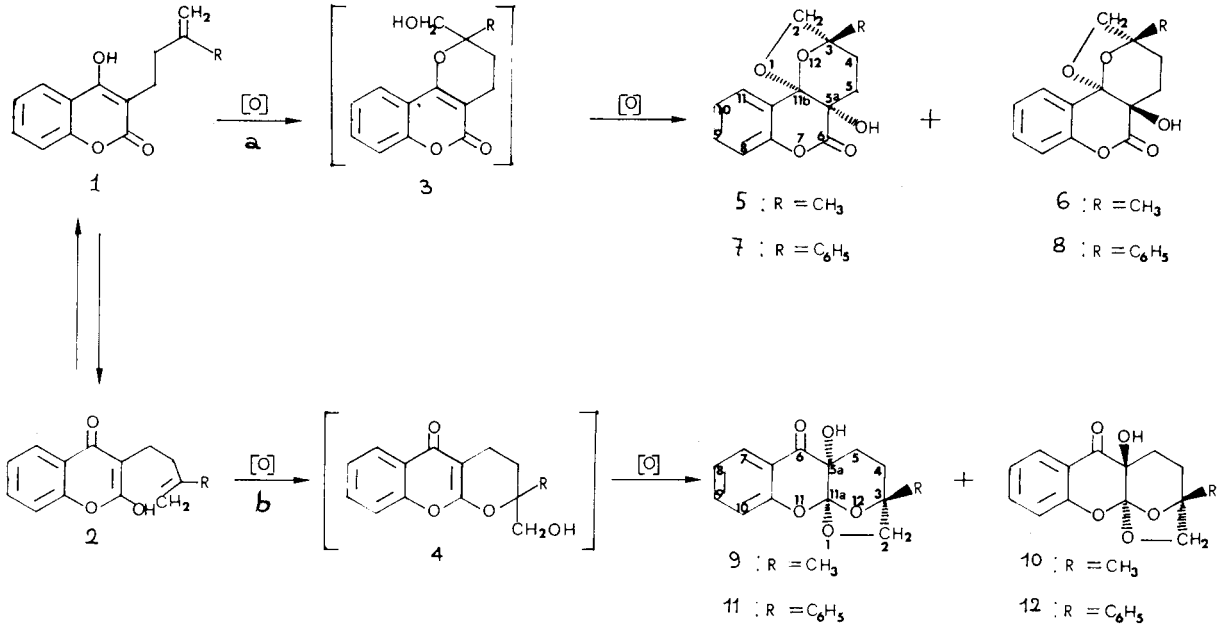
Introduction.

The synthesis of oxygen heterocycles *via* the electrophilically induced cyclization of unsaturated acids, alcohols and enolates is a well established process [2a-e]. Oxygen released by the peroxyacid or by different peroxides can act as an electrophilic agent in these reactions [3]. When transferred to the double bond of the substrates it generates an unstable, generally not isolable, epoxide which undergoes intramolecular cyclization to final products. While studying such processes starting from 3-(3'-butenyl)-4-hydroxycoumarins in order to synthesize some pyranocoumarins and pyranochromones, we have noticed an interesting bis-hetero-annulation reaction to occur on these substrates [4]. When an excess of *meta*-chloroperbenzoic acid is used to oxidize 3-alkenyl-4-hydroxycoumarins, two atoms of oxygen are released in sequence to the substrates. They can act on the enol-ester form (Scheme 1, path a) to give first 3,4-dihydro-2-hydroxymethyl-2*H*,5*H*-

Scheme 1



pyrano[3,2-*c*][1]benzopyran-5-ones **3**, and 3,11b-epoxy-2,3,4,5,5a,11b-hexahydro-5a-hydroxyoxepino[3,2-*c*][1]benzopyran-6-ones **5-8** as final products [5]. On the contrary, when they act on the keto-enolate form (Scheme 1, path b), they give first 3,4-dihydro-2-hydroxymethyl-2*H*,5*H*-pyrano-[2,3-*b*][1]benzopyran-5-ones **4** [6], and 3,11a-epoxy-2,3,4,5,-5a,11a-hexahydro-5a-hydroxyoxepino[2,3-*b*][1]benzopyran-6-ones **9-12** as final products [7]. In the first step of the reaction sequence oxygen attacks the olefinic double bond giving a single epoxide which promptly cyclizes to give heterocycles **3** and/or **4** depending on the reaction conditions which govern the equilibrium between the two tautomeric forms of the 4-hydroxycoumarin nucleus. In the second step oxygen reacts at the double bond of the ring B of compound **3** or **4** to give in each case two diastereoisomeric epoxides depending on whether the α or β faces of polynuclear molecules **3** and **4** are engaged in the reaction. Therefore the intramolecular ring opening of the epoxides by the neighboring oxymethylene group gives rise in both cases to a pair of compounds having the oxymethylene bridge and the new hydroxyl either on the same side, compounds **5,7,9,11**, or on opposite sides, compounds **6,8,10,12**.

In a previous paper we have already reported the mass spectrometric behaviour of some of the intermediate compounds **3** and **4** [8]. Here we describe the 70 eV electron impact spectrometry of compounds **5-12** as obtained with the aid of exact mass measurements, B/E linked scans, collisional experiments and deuterium labelling of the hydroxyl hydrogen.

EXPERIMENTAL

All mass spectrometric measurements were performed on a VG ZAB 2F instrument operating in electron impact (EI) conditions (70 eV, 200 μA). The samples were introduced *via* direct inlet system with a source temperature of 200°.

Metastable transitions were checked by B/E and B^2/E linked scans [9]. Exact mass measurements were performed with the peak matching technique at 10,000 resolving power (10% valley definition). Collisionally activated decomposition mass analyzed ion kinetic energy (CAD MIKE) spectra [10] were obtained by 8 keV ions colliding with nitrogen in the second field-free region. Pure samples of benzofuran, salicylic acid and benzoic acid were used as a model compounds for collisional experiments. Protonated salicylic acid was obtained in CI (CH_5^+) conditions. Compounds **5-12** were analytically pure samples synthesized and purified according to literature [5,7].

Deuterium labelling of the hydroxyl hydrogen was obtained by simply dissolving the compounds in monodeuteriomethanol and leaving the solution at room temperature for 24 hours.

Results and discussion.

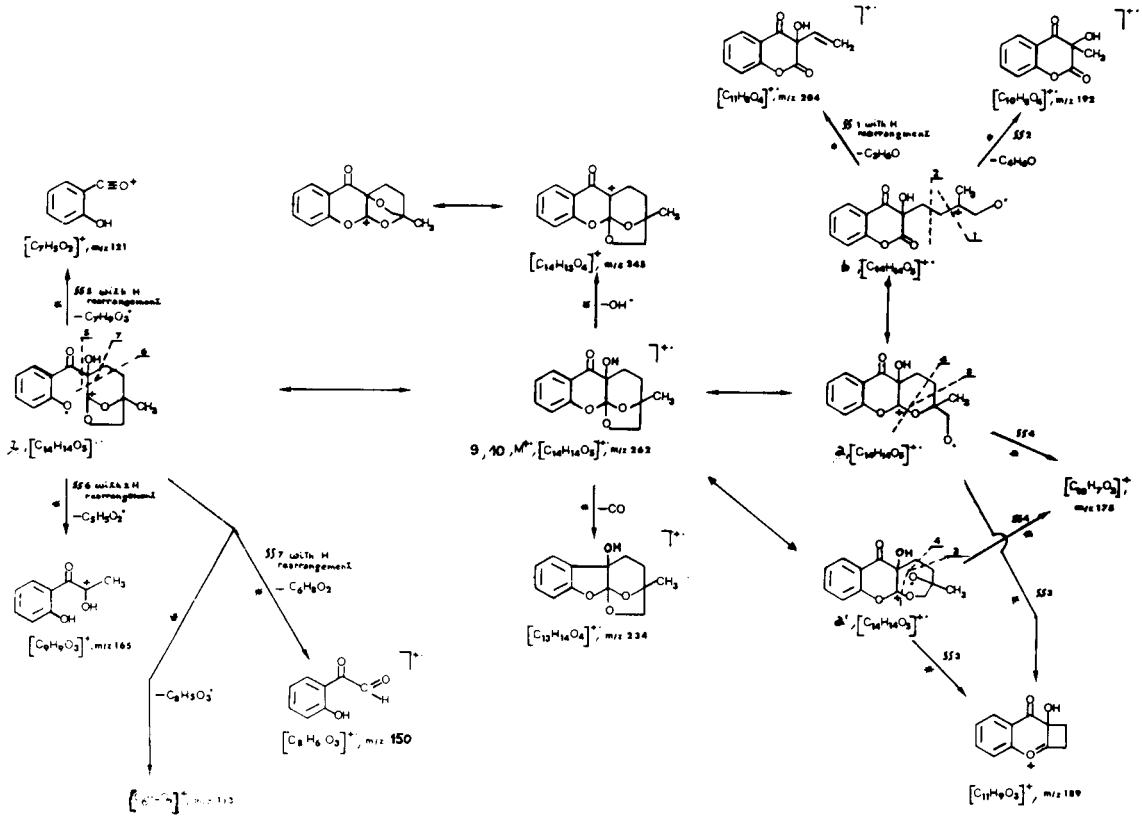
The more significant and abundant ionic species observed for the title compounds, whose composition has been obtained by exact mass measurements, are reported in Table 1.

Table 1

Mass Spectra of Compounds **1-8**

	Linear				Angular			
Compounds Ionic Species	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
$M^{+\cdot}$	262 (15)	262 (17)	324 (3)	324 (3)	262 (14)	262 (6)	324 (2)	324 (1)
$[M-OH]^+$	245 (2)	245 (3)	—	—	—	—	—	—
$[M-H_2O]^{+\cdot}$	—	—	306 (0.5)	306 (1)	244 (1)	244 (1)	—	—
$[M-CO]^{+\cdot}$	234 (4)	234 (2)	296 (1)	296 (1)	234 (1)	234 (1)	—	—
$[M-C_3H_4O_3]^{+\cdot}$	—	—	—	—	—	—	236 (2)	236 (0.5)
$[M-C_3H_4O]^{+\cdot}$	—	—	—	—	206 (67)	206 (39)	—	—
$[M-C_3H_6O]^{+\cdot}$	204 (0.5)	204 (0.5)	—	—	—	—	—	—
$[M-C_4H_6O]^{+\cdot}$	192 (7)	192 (3)	—	—	192 (10)	192 (6)	—	—
$[C_{11}H_{10}O_3]^{+\cdot}$	—	—	—	—	—	—	190 (6)	190 (2.5)
$[C_{11}H_9O_3]^+$	189 (25)	189 (11)	189 (7)	189 (12)	189 (12)	189 (10)	189 (3)	189 (1.5)
$[C_{10}H_7O_3O]^+$	175 (4)	175 (2)	—	—	175 (14)	175 (8)	—	—
$[C_9H_9O_3]^+$	165 (19)	165 (17)	165 (16)	165 (20)	165 (7)	165 (5)	165 (32)	165 (26)
$[C_{10}H_8O_2]^{+\cdot}$	—	—	160 (25)	160 (36)	—	—	160 (48)	160 (22)
$[C_{10}H_7O_2]^+$	—	—	159 (12)	159 (14)	—	—	159 (21)	159 (12)
$[C_8H_6O_3]^{+\cdot}$	150 (18)	150 (16)	150 (10)	150 (6)	—	—	150 (20)	150 (8)
$[C_7H_7O_3]^+$	—	—	139 (12)	139 (11)	—	—	—	—
$[C_9H_7O]^+$	—	—	131 (15)	131 (16)	—	—	131 (18)	131 (8)
$[C_7H_5O_2]^+$	121 (100)	121 (100)	121 (100)	121 (100)	121 (100)	121 (100)	121 (100)	121 (100)
$[C_8H_6O]^{+\cdot}$	—	—	118 (55)	118 (83)	—	—	118 (48)	118 (64)
$[C_8H_5O]^+$	—	—	117 (48)	117 (62)	—	—	117 (42)	117 (60)
$[C_6H_9O_2]^+$	113 (63)	113 (37)	—	—	—	—	—	—
$[C_7H_5O]^+$	—	—	105 (15)	105 (14)	—	—	105 (7)	105 (2.5)

Scheme 2



At first sight the great difference between the 3-methyl and the corresponding 3-phenyl-substituted derivatives in both series of compounds is worthy of note. Minor, but highly diagnostic, differences are present between similarly substituted [2,3-*b*] annulated, "linear" and [3,2-*c*] annulated, "angular" compounds. On the other hand no clear differences can be noticed between *trans* and *cis* isomers. Their spectra are mainly superimposable, with minor differences only in some relative abundances (also MIKE, see for example Figure 1, and CAD MIKE spectra of $M^{+\cdot}$ species of *trans* and *cis* isomers are practically identical). The fragmentations pattern of cyclic orthoesters, linearly annulated 3-methyl-substituted compounds **9** and **10**, as obtained by linked scans, exact mass measurement, and deuterium labelling experiments, is reported in Scheme 2. The observed fragmentation pathways suggest the presence of molecular species with different structures **a-c**, arising from the cleavages of one of the three different C-O bonds of the orthoester group, taking into account that this part of the molecule represents the weakest one. This aspect is further confirmed by the low abundance on $[M\text{-}OH]^+$ and $[M\text{-}CO]^{+\cdot}$ ionic species, which reasonably arise from molecular species of the same structure of neutrals. Ionic species at m/z 175 and 189 can easily originate from molecular ions of both structrues **a** and **a'**, arising from cleavages of O(1)-C(11a) and C(11a)-O(12) bonds. Further cleavages 3 and 4 on both **a** and **a'** lead to the ions $[C_{11}H_9O_3]^+$ and $[C_{10}H_7O_3]^+$ respectively. A further ring opening reaction leads to molecular ions with structure **b** of Scheme 2, which further decomposes by cleavage of the olefinic chain leading to $[C_{11}H_8O_4]^{+\cdot}$ (m/z 204) and $[C_{10}H_8O_4]^{+\cdot}$ (m/z 192) ionic species. On the other side the cleavages of the O(11)-C(11a) bond gives rise to molecular species **c** from which the formation of $[C_7H_5O_2]^+$ (m/z 121), $[C_9H_9O_3]^+$ (m/z 165), $[C_8H_6O_3]^{+\cdot}$ (m/z 150) and $[C_6H_9O_2]^+$ (m/z 113) ionic species is easily explainable. The first ionic species at m/z 121 leads to a CAD MIKE spectrum identical to that of $[M\text{-}OH]^+$ ions arising from EI of salicylic acid, on the contrary of what we have already observed [8] in the case of pyranocoumarins **3** and pyranochromones **4**. In that case the structure of ions at m/z 121 was identical to $[M\text{-}H]^+$ species of benzoic acid. This fact strongly supports the presence of molecular species **c** highly favoured in the present case for the positive charge stabilization by the two adjacent oxygen. Other primary fragmentation processes are due to HO· loss (leading to ions at m/z 245) and CO loss (giving rise to $[C_{13}H_{14}O_4]^{+\cdot}$ ionic species). For this last fragmentation process, it is reasonable to assume that it arises from the pyrane ring, either because of the related value of kinetic energy release $T_{0.5}$ = 714 meV

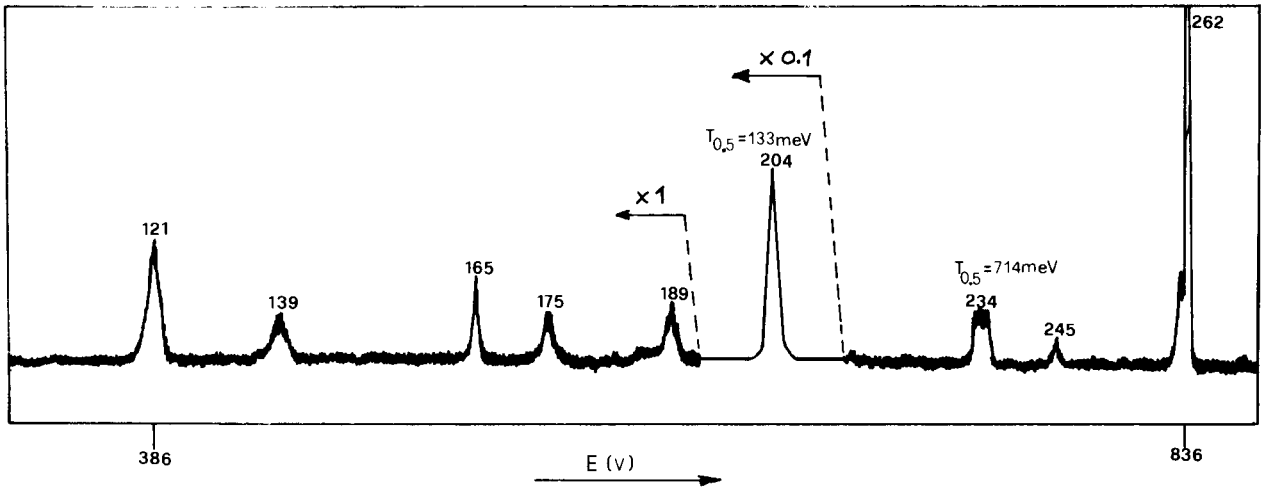


Figure 1. MIKE spectrum of $M^{+\cdot}$ of compound **9**, identical to that of $M^{+\cdot}$ of compound **5**.

(particularly high and well related to a ring cleavage; compare this value with that related to the primary C_3H_6O loss, $T_{0.5}$ = 133 meV, due to simple bond cleavage), which supports the presence of differently structured molecular ions. The low abundance of these two ionic species can be considered as a further evidence of the presence of the more favoured structures **a**, **a'**, **b** and **c** of the molecular species. A quite different behaviour is observed for the phenyl substituted orthoester **11** and **12** as can be seen by Table 1.

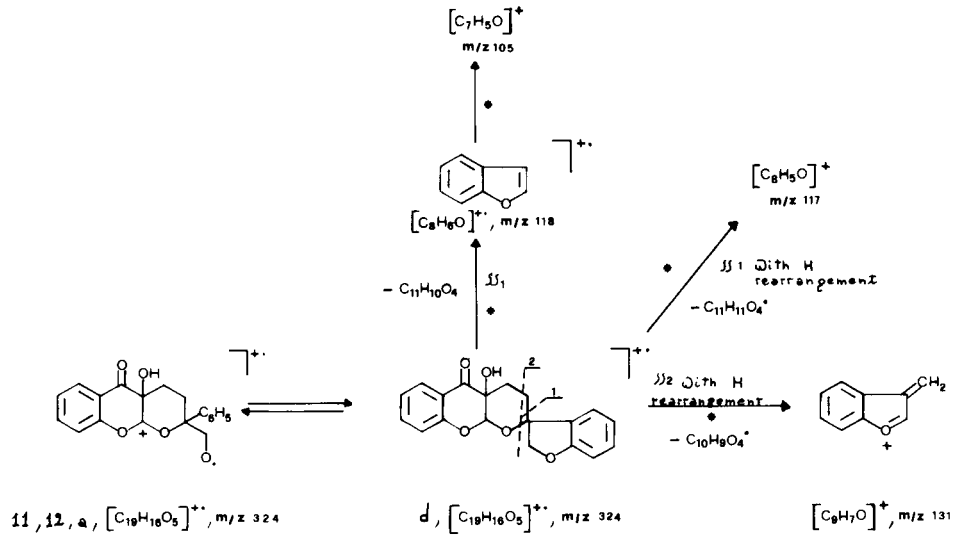
In any event, most of fragmentation products for these compounds can be explained by the presence of differently structured molecular species, similar to those reported in Scheme 2 for **9** and **10**. Molecular ions of structure **c** are still present, leading to ionic species at m/z 121 (base peak), still due to dehydroxylated salicylic acid), 150 and 165, identical to those described above for compounds **9** and **10**. However the ionic species complementary to $[C_9H_9O_3]^+$ (m/z 165) species, completely absent in the methyl derivatives, become for compounds **11** and **12** readily detectable at m/z 159 and 160, due to the presence of the phenyl group which decreases the ionization energies of the fragments in which it is contained.

The cleavage of the carbon oxygen bond of the methyleneoxy bridge leads to molecular ions of structure **a** of scheme 2, responsible for the formation of the $[C_{11}H_9O_3]^+$ species (m/z 189). Other primary fragmentation pathways lead to scarcely abundant ions at m/z 306 (H_2O loss) and m/z 296 (CO loss). For ionic species at m/z 139, of elemental formula $C_7H_7O_3$, deuterium labelling of the hydroxyl H atom, proves that it is retained in the fragment ion. Their CAD MIKE spectrum is identical to that of $[M+H]^+$ ions of salicylic acid, obtained in Cl (CH_5^+) conditions. The interaction of the oxygen radical of **a** with the phenyl ring and further H rearrangement reasonably lead (in this case) to molecular ions of structure **d** (see Scheme 3). Further cleavages 1 and 2 of the tetrahydropyrano ring give rise to the particularly abundant ions at m/z 118, 117 and 131. The CAD MIKE spectrum of the first ionic species (m/z 118) is identical to that of $M^{+\cdot}$ of benzofuran, giving confirmation to the proposed structure **d** of Scheme 3.

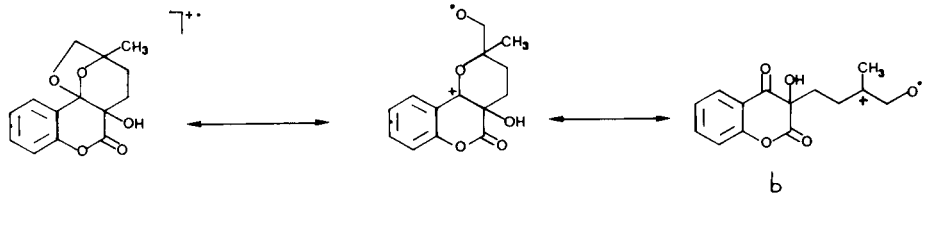
It must be emphasized that most of the total ion current is due to fragments containing the substituent phenyl group, in contrast to that observed for the methyl derivatives. The "angularly annulated" methyl and phenyl substituted compounds **5-8** show mainly the same fragmentation patterns observed for "linearly annulated" isomers **9-12** (see Table 1 and Schemes 2 and 3), proving that the cleavages of carbon oxygen bonds of the acetal group lead to an open structure similar to route **b** of Scheme 2 for compounds **5** and **6** while the interaction of the methylenoxy radical with the phenyl group leads reasonably to a benzotetrahydrofuran derivative of structure **e** (see Scheme 4) in a similar way as for structure **d** of Scheme 3.

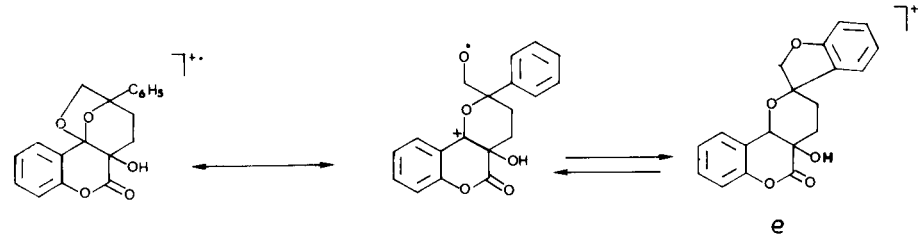
Some peculiar fragmentation pathways are present only for the "angular" isomers **5-8**. More precisely for the methyl derivatives primary water loss is observed, while the OH· loss is completely absent. Abundant ionic species at m/z 206, for which exact mass measurements gave elemental formula $C_{11}H_{10}O_4$, corresponds to a primary loss of C_3H_4O. Its formation can be explained by the rupture of the oxymethylene bond, followed by the cleavage 1 of the pyran ring, as reported in Scheme 5. An analogous behaviour (C_3H_5O· loss) has already been observed for 2-methyl-2-hydroxymethylpyranocoumarins and 2-methyl-2-hydroxymethylpyranochromones (**3** and **4** of Scheme 1) [8]. Furthermore phenyl substituted compounds **7** and **8**, besides the $[C_{11}H_9O_3]^+$ ion present for all the compounds, show the

Scheme 3

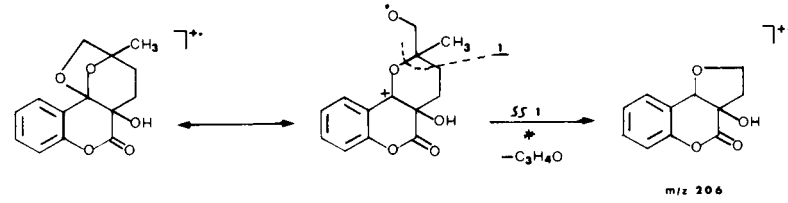


Scheme 4





Scheme 5



formation of $[C_{11}H_{10}O_3]^{+\cdot}$ ions (m/z 190), originating from an analogous process above described (SS 3 of Scheme 2) with H rearrangement and a peculiar fragmentation pathway leading to $[C_6H_{12}O_2]^{+\cdot}$ (m/z 236) ionic species, originating through a primary and unusual $C_3H_4O_3$ loss.

Finally it must be noted that CAD MIKE spectra of ionic species at m/z 121 are identical to that of $[M-H]^+$ species of benzoic acid, proving that the same rearrangement already observed [8] for pyranocoumarins **3** and pyranochromones **4** occurs also in the present cases, in contrast to that observed for the cyclic orthoesters **11** and **12**.

Conclusions.

In the mass spectra of all the compounds belonging to both series, of the differently annulated isomeric heterocycles we studied *i.e.* the cyclic orthoesters "linearly annu-

lated'' and the cyclic acetals ''angularly annulated'' ones, the most abundant ionic species arise from primary fragmentation processes involving cleavage of carbon-oxygen bonds of the orthoester or acetal group. Some fragment ions are common to both series, since they originate from common open chain precursors, while others are characteristic, allowing the structural identification of angular *vs* linear compounds. However either electron impact or collisional spectrometry fail in the characterization of stereoisomeric compounds and this can be explained reasonably by the fact that most fragmentation processes involve molecular structures which have lost the diastereoisomeric differentiation.

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