Electron Impact Mass Spectrometry of 3-Hydroxy-3,4,5,6-tetrahydro-2*H*-[1]benzoxocines. A Comparison with the Behaviour of Isomeric 2-Hydroxymethyl-2,3,4,5-tetrahydro-[1]-benzoxepines and 1,2-Epoxy-5-(2-hydroxyphenyl)pentane

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The mass spectrometric behavior of 3-methyl-3-hydroxybenzoxocines has been studied in detail by means of linked scans and mass analyzed ion kinetic energy spectrometry. The structure of the molecular ion and the fragmentation processes are strictly related to the structure of the neutral moieties.

The possible isomerization of 3-hydroxy-10-methoxy-3-methyl-3,4,5,6-tetrahydro-2*H*-[1]benzoxocine to 2-methyl-2-[3-(3'-methoxy-2'-hydroxy)phenyl]pentyloxirane and to 2-hydroxymethyl-9-methoxy-2-methyl-2,3,4,5-tetrahydro[1]benzoxepine is investigated.

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Introduction.

The formation of oxygen heterocycles by sulphur ylide annulation from substrates like **1** (see Scheme 1) bearing two reactive sites, a carbonyl and a nucleophilic oxygen, has been extensively studied [1]. Moreover it has been demonstrated that the reaction proceeds *via* the epoxide intermediate **2**, which in some cases can be isolated in the pure form, while in other may undergo intramolecular ring opening directly in the reaction medium. The rate of this transformation depends on the nucleophilicity of the oxygen (which can belong to a phenol [2], to a cyclic β-diketone [3], β-ketoester [4], β-ketoamide [5] or β-diester [5] moiety), the length of the carbon chain (n = 1,2,3) and the steric interaction between substituents on the new forming rings. Larger heterocycles **3** may arise by "endo" cyclization or the smaller ones **4** by competing "exo" process [6].

We have recently found that for n = 3, differently substituted 3-hydroxy-3,4,5,6-tetrahydro-2*H*-[1]benzoxocines **3** (n = 3) could be obtained in high yields from the corresponding ketones **1** or from the epoxides **2** [7].

Following the previous paper [8] dealing with the mass spectrometric behavior of the oxygen heterocycles belonging to these new classes of compounds, we wish to report here a comparative study of electron impact and collisionally induced fragmentation processes of the three isomeric

Scheme 1

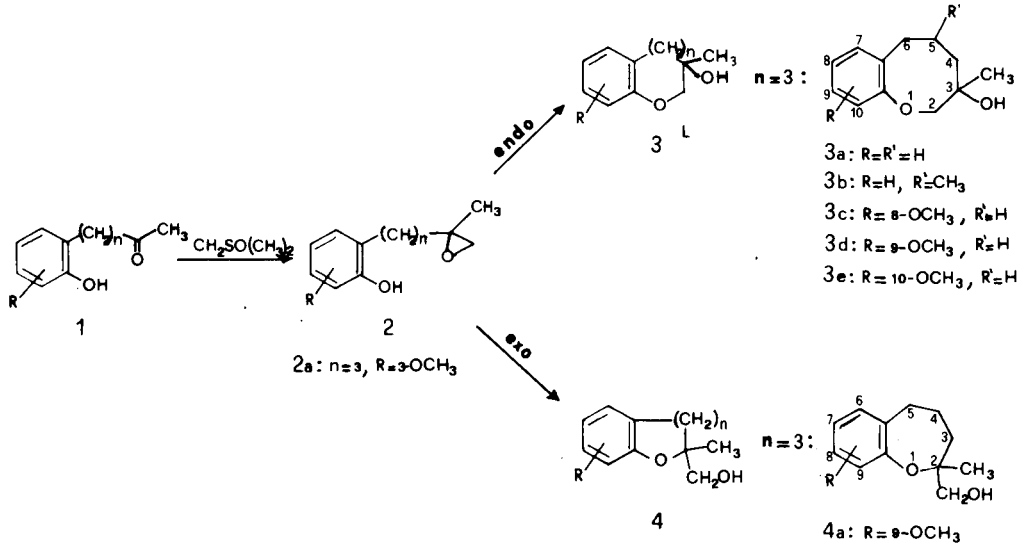
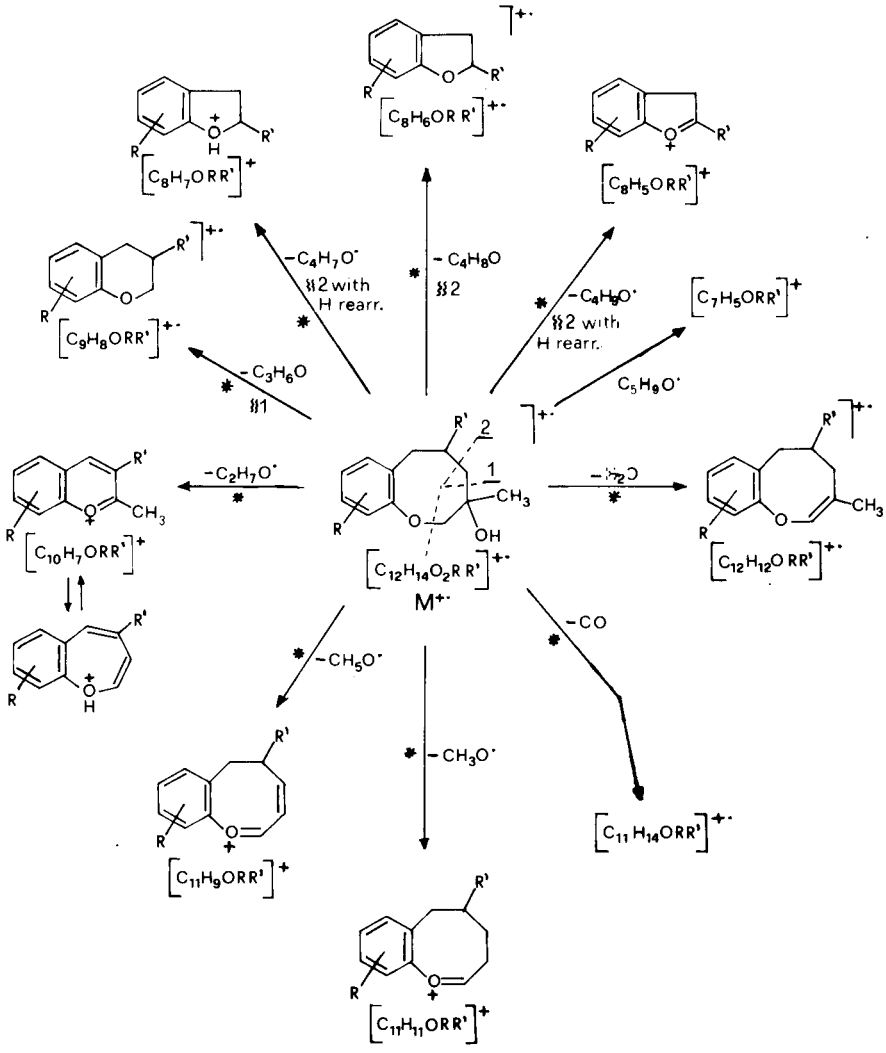


Table 1

E.I. The Most Abundant and Significant Ionic Species Arising from 70 eV EI of Compounds **2a**, **3a-3e** and **4a**

Compounds Ionic Species	**2a**	**3a**	**3b**	**3c**	**3d**	**3e**	**4a**
$M^{+\cdot}$	222 (34)	192 (12)	206 (6)	222 (85)	222 (31)	222 (75)	222 (45)
$[M-H_2O]^{+\cdot}$	204 (16)	174 (3)	188 (4)	204 (35)	204 (11)	204 (7)	204 (11)
$[M-CO]^{+\cdot}$	194 (7)	164 (1)	178 (1)	194 (5)	194 (2)	194 (8)	194 (7)
$[M-CH_3O]^{+}$	191 (21)	161 (2)	175 (2.5)	191 (13)	191 (5)	191 (8)	191 (20)
$[M-CH_5O]^{+}$	189 (41)	159 (12)	173 (10)	189 (44)	189 (24)	189 (42)	189 (50)
$[M-C_2H_7O]^{+}$	175 (5)	145 (3)	159 (3)	175 (15)	175 (8)	175 (5)	175 (6)
$[M-C_3H_6O]^{+\cdot}$	164 (6)	134 (100)	148 (100)	164 (77)	164 (80)	164 (100)	164 (3)
$[M-C_4H_7O]^{+}$	151 (8)	121 (16)	135 (2)	151 (20)	151 (60)	151 (15)	151 (7)
$[M-C_4H_9O]^{+}$	149 (5)	119 (55)	133 (22)	149 (43)	149 (36)	149 (48)	149 (5)
$[M-C_5H_9O]^{+}$	137 (100)	107 (30)	121 (21)	137 (100)	137 (100)	137 (71)	137 (100)

Scheme 2



compounds 2-methyl-2-[3-(3'-methoxy-2'-hydroxy)phenyl]-pentyloxyrane (**2a**), 3-hydroxy-10-methoxy-3-methyl-3,4,5,6-tetrahydro-2*H*-[1]benzoxocine (**3e**) and 2-hydroxymethyl-9-methoxy-2-methyl-2,3,4,5-tetrahydro[1]benzoxepine (**4a**), along with the general behavior of some other differently substituted benzoxocines **3a**, **3b**, **3c** and **3d**.

EXPERIMENTAL

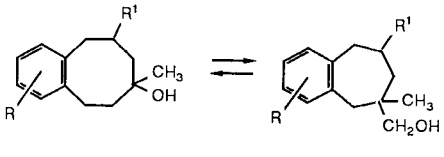
All mass spectrometric measurements were performed on a VG ZAB2F instrument operating in electron impact conditions (70 eV, 200 μA). Samples were introduced *via* direct inlet system with an ion source temperature of 200°. Metastable transitions were detected either by B/E linked scans [9] or by mass analyzed ion kinetic energy spectrometry (MIKES) [10]. While B/E = const linked scans lead to the detection of metastable decompositions of a selected ionic specie occurring in the first field-free region of a double focusing instrument, the MIKE spectra describe the decomposition processes of a selected ionic specie occurring in the second field-free region. Accurate mass measurements were performed with the peak matching technique at 10,000 resolving power (10% valley definitions). Collisionally activated decompositions 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 at 60% of its usual value.

Compounds **2a**, **3a-3e** and **4a** were analytically pure samples synthesized and purified according to the literature [7]. OD derivatives were obtained simply dissolving the compounds in monodeuteriomethanol and deuterium oxide (1:2).

Results and Discussion.

The most abundant ionic species arising from EI of benzoxocines **3a** to **3e** are reported in Table 1. By means of B/E linked scans and exact mass measurements, the common fragmentation pattern reported in Scheme 2 has been obtained. The primary loss of H_2O, observed for all the compounds, is particularly favoured for compound **3c** and **3e** with respect to the other ones. These results are in agreement with the electron donating power of the methoxy group *para* and *ortho* positioned, which favours the formation of the conjugated enol ether (see Scheme 2). The loss of CO gives rise to scarcely abundant fragment ions, but for **3e**.

In the metastable supported losses of $CH_3O^{\cdot}$ and $CH_5O^{\cdot}$ the hydroxyl group is implicated for all the compounds, as proved by the deuterated derivatives. This behavior suggests the occurrence to some extent of an isomerization process of the molecular ions consisting in a contraction from eight- to seven-membered ring.



An analogous behavior (contraction from seven- to six-membered ring) was already found for 3-hydroxy-2,3,4,5-tetrahydro-1-benzoxepines which partially isomerize to the corresponding 2-hydroxymethylcromane isomers [8a].

Cleavages 1 and 2 of the oxocine ring reported in Scheme 2 (losses of C_3H_6O, $C_4H_7O^{\cdot}$, C_4H_8O, $C_4H_9O^{\cdot}$) and the loss of $C_5H_9O^{\cdot}$ are responsible for the most abundant fragments present in the mass spectra of compounds **3a-3e**, for which benzopyran- and benzofuran-like structures can be proposed. In particular, the structures of ionic species $[C_8H_7ORR']^+$ and $[C_8H_6ORR']^{+\cdot}$ were confirmed by collisional experiments using $[M+H]^+$ and $M^{+\cdot}$ ions of the corresponding benzofuranes like models. Consequently the most abundant ionic species seem to arise from a two step mechanism, the first of which could reasonable involve cleavage of the O-C(1) bond, formally the retrosynthetic process. In order to further investigate on the structure of molecular species of compounds **3**, we have thought of interest to compare the mass spectrometric behavior of **3e** with those of isomeric compounds **2a** and **4a** (see Schemes 1 and 2).

The mass spectrometric behavior of **3e** is substantially different from those of **2a** and **4a**, while **2a** and **4a** lead to mass spectra practically superimposable. In table 2 the B/E and MIKE spectra of $M^{+\cdot}$ of **2a**, **3e** and **4a** are reported. Also in this case **2a** and **4a** result very similar, suggesting the isomerization to a common structure. It is well known that if the MIKE spectra of two ions with the same elemental composition are superimposable both in intensity ratios and kinetic energy release values, this implies their structural identity. In fact ions having the same elemental composition but different structures must differ, at least partially, in their vibrational and rotational frequencies and consequently in the activation energies of subsequent decomposition reactions. In turn, different activation energies will lead to different intensity ratios of the decomposition products [11].

Table 2

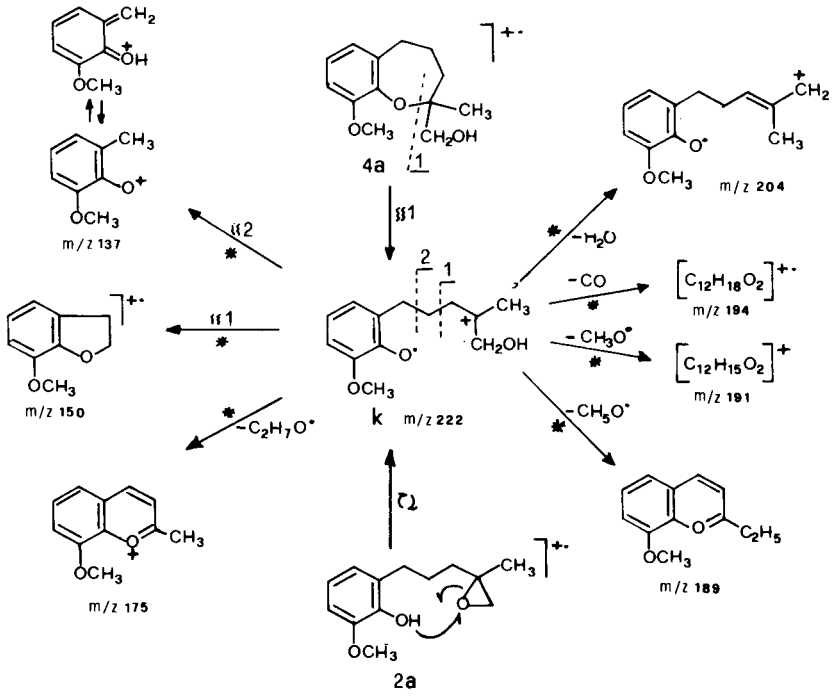
B/E and MIKE Spectra of $M^{+\cdot}$ (m/z 222) of the Isomeric Compounds **2a**, **3e** and **4a**

Compounds	**2a**		**3e**		**4a**	
m/z	B/E	MIKES	B/E	MIKES	B/E	MIKES
204	100	100	100	100	100	100
194	13	4	12	9	14	3
191	8	7	10	5	3	2
189	15	8	24	16	15	6
175	5	7	5	7	7	9
164	-	-	58	78	-	-
150	0.5	1	4	7	0.5	1
137	0.1	0.1	1	2	0.1	0.1

In the present case, the isomerization of **2a** and **4a** to a common structure could originate through different mechanisms due to: i) thermal processes before ionization: ii) EI.

In order to test these two possibilities we have performed two different kinds of experiments. The ion source

Scheme 3



temperature was varied in the range of 100-300°, and no changes were observed in the MIKE spectra. These observations rule out the existence of thermally induced isomerization. Operating in charge exchange conditions using $Xe^{+\cdot}$ as the reactant species, no changes in the MIKE spectra were observed. Under these ionization conditions a smaller amount of energy is deposited in the molecular species, than the average amount under electron impact conditions.

Hence the isomerization process is not thermal and requires a given amount of internal energy, already available in charge exchange conditions. We propose the mechanism reported in Scheme 3. Structure *g* of Scheme 3 accounts for the most of the observed fragmentation pathways common to both **2a** and **4a** compounds (see Scheme 3). Furthermore the formation of ions at m/z 175 and 189 is reasonably due to a first slow CH_3OH loss, implicating the benzylic hydrogen followed by fast $CH_3\cdot$ or $H\cdot$ losses respectively. These fragmentation processes, which require extensive H rearrangements, are strongly favoured by the formation of highly stable, aromatic benzopyrilium ions.

Conclusions.

The mass spectrometric behavior of 3-methyl-3-hydroxybenzoxocines **3** can be rationalized on the basis of the structure of the neutral moieties. Most of fragmentation processes are related either to the substituent groups in position 3 or to cleavages of the oxocine ring, thus leading to a clear structural characterization of this class of compounds.

On the contrary 2-hydroxymethyl-2-methylbenzoxepine (**4a**) and the isomeric epoxide compound **2a** isomerize to molecular ions of common structure. This behavior is in agreement with that observed in solution chemistry, where **2a** in acidic or neutral media rapidly leads to **4a**, *via* a carbocation or a charged species similar to *g* ions of Scheme 3.

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