Mass Spectrometry and Chemical Synthesis. The Case of Some Substituted Spiro[1,3-benzodioxole-2,1'-cyclohexanes] [1]

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The electron impact mass spectrometric behaviour of some substituted spiro[1,3-benzodioxole-2,1'-cyclohexanes] has been studied in detail with the aid of linked scans and exact mass measurements. Mass spectrometry has proved to be a valid tool in the structural characterization of the different couples of isomers.

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Introduction.

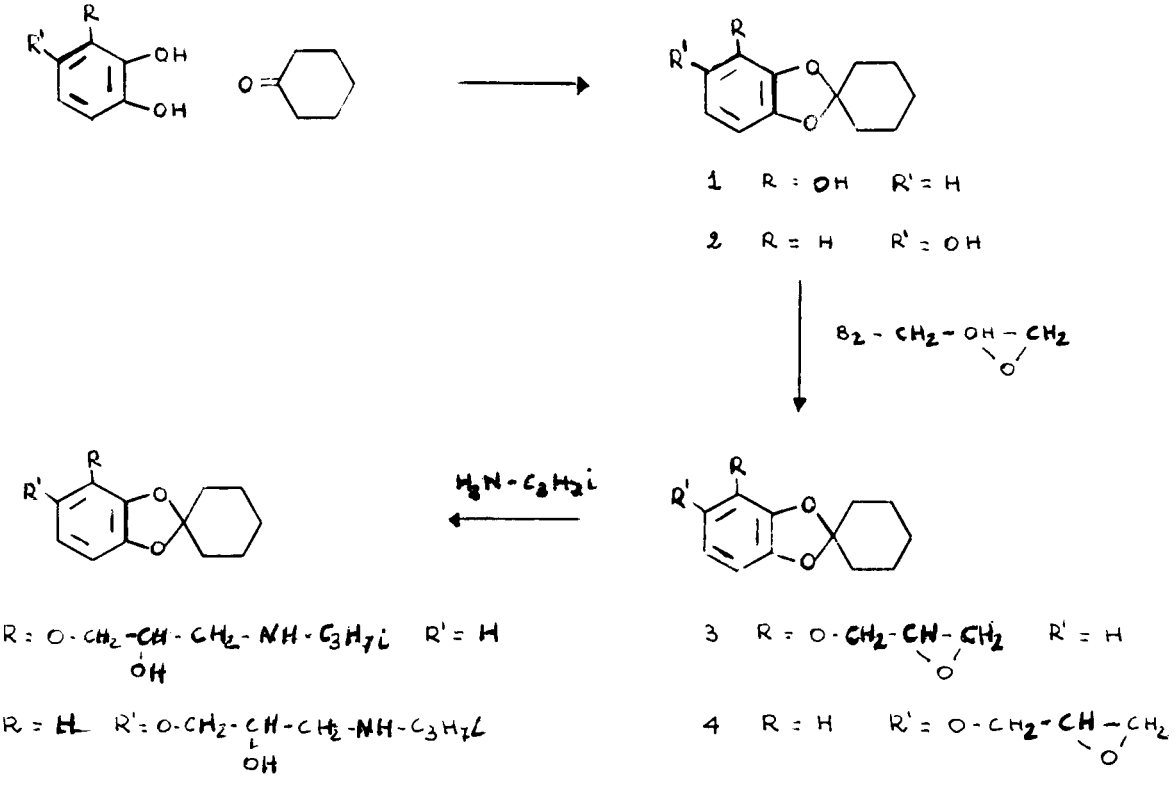
In recent years we proved that mass spectrometry can be employed successfully for testing the reactivity and chemical behaviour of benzodioxole and benzoxathiole derivatives.

It was emphasized that: i) the most abundant EI induced decomposition products are generally the same as those observed by chemical degradation with Grignard reagents [2]; ii) as for as regards the EI induced decomposition products, we found a new synthetic route by synthesizing benzodioxole and benzoxathiole derivatives directly in the CI ion source by reaction of the allenes with catechol and thiophenol respectively [3]; iii) the usual synthetic pathway could be reproduced by introducing catechol, ketones and CH_5^+ ions in the ion source, thus proving that the reaction mechanism must necessarily pass through a protonated ketone intermediate [4].

For these reasons mass spectrometry can be considered, an important tool for chemical synthesis in condensed phase chemistry.

Following our research in the field of 1,3-benzodioxoles with pharmaceutical activity, we have undertaken the syn-

Scheme 1



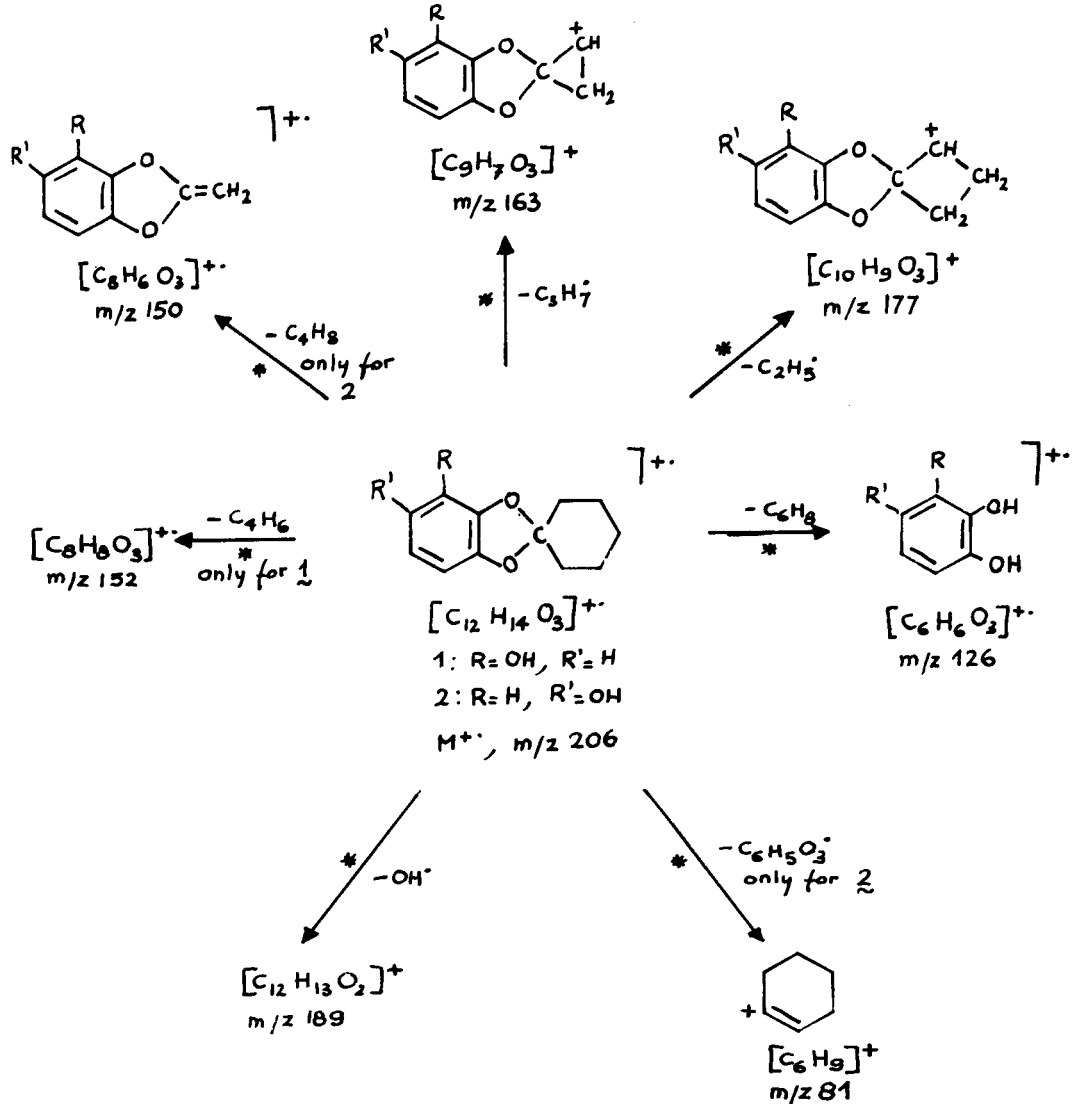
thesis of benzodioxole derivatives exhibiting β-blocking action. The synthetic pathway employed is reported in Scheme 1. 4- or 5-Hydroxy-spiro[1,3-benzodioxole-2,1'-cyclohexanes] (compounds **1** and **2** respectively) were reacted with epibromohydrin in benzene solution. The intermediate compounds **3** and **4** are obtained with different yields (30 and 75% respectively). The yields of final compounds **5** and **6** drop to 1 and 42% respectively.

Persisting in our interest in the mass spectrometric behaviour of benzodioxole and benzoxathiole derivatives and because of its correlations with condensed phase chemistry, we have undertaken the present study with the particular aim of a mass spectrometric characterization of the different isomeric compounds.

Results and Discussion

The mass spectra of compounds **1-6** are shown in Figures 1, 2 and 4 (in each Figure, a couple of isomeric compounds is reported). The differences in relative abundances of molecular as well as fragment ions between the isomeric compounds clearly indicate that the position of the substituent group on the benzene ring strongly affects the EI induced decomposition patterns of this class of compounds. In order to obtain a better description of their mass spectrometric behaviour, and in order to compare it with its condensed phase chemical behaviour, we shall discuss the mass spectrometric data of the different couples of isomers together.

Scheme 2



4-Hydroxy-spiro[1,3-benzodioxole-2,1'-cyclohexane] **1** and 5-hydroxy-spiro[1,3-benzodioxole-2,1'-cyclohexane] **2**.

The common fragmentation pattern of compounds **1** and **2**, as obtained by linked scans and exact mass measurements, is reported in Scheme 2. Abundant molecular ions are present for both isomers and most of the total ion current is due to primary decomposition products (see Figure 1). Peculiar fragmentation pathways are present due to losses of C_4H_8 and $C_6H_5O_3^{\bullet}$ for compound **2** and of C_4H_6 for compound **1**. Also the common fragments at m/z 177 and 163, due to the usual losses of $C_2H_5^{\bullet}$ and $C_3H_7^{\bullet}$ radicals from the spiro moiety [2], exhibit strong differences in relative abundances. For both compounds we found abundant ions at m/z 126 of elemental composition $C_6H_6O_3$, originating from primary losses of C_6H_8 as can be seen from the mechanism reported in Scheme 3.

CAD MIKE experiments on these ions demonstrate structural identity with $M^{+\cdot}$ of 1,2,3-trihydroxybenzene for ions originating from **1** while for those originating from **2**, they demonstrate structural identity with $M^{+\cdot}$ of 1,2,4-trihydroxybenzene. The strong difference in relative abundance of these ionic species as far as regards, the mass

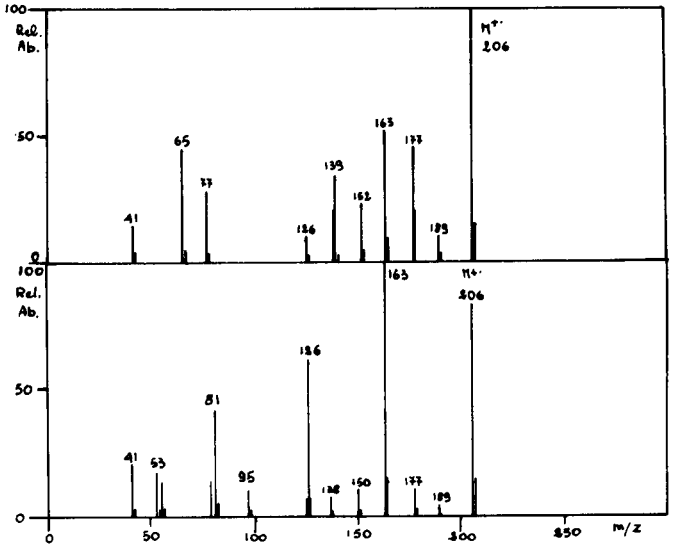
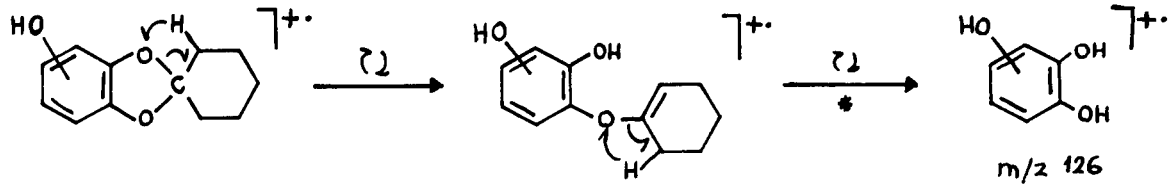
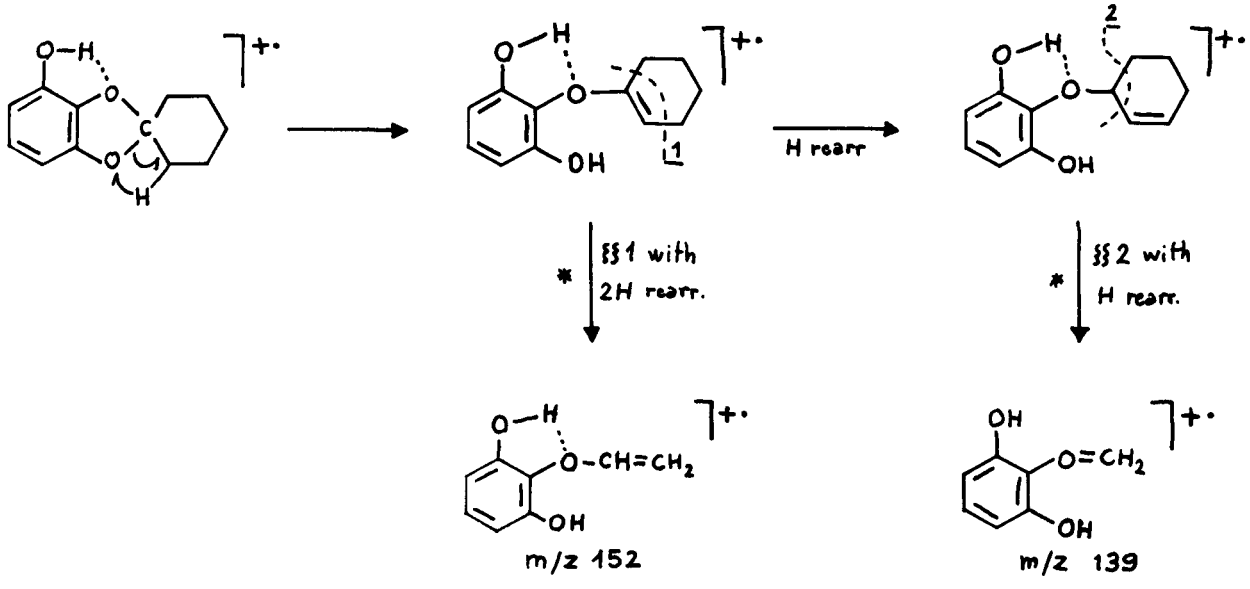


Figure 1. 70 eV EI mass spectra of compound **1** (top) and compound **2** (bottom).

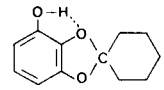
Scheme 3



Scheme 4

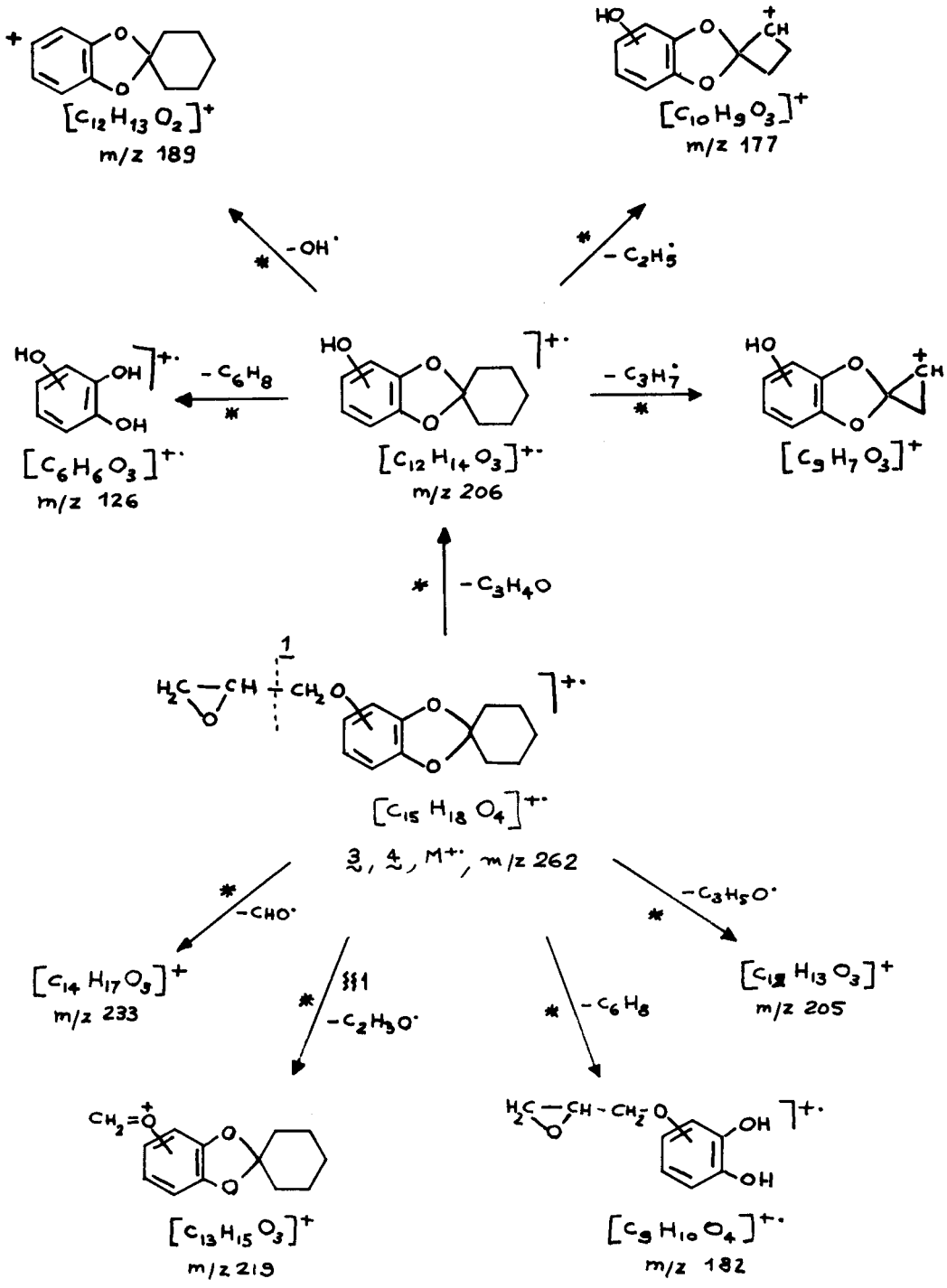


spectra of compounds **1** and **2**, can be reasonably explained by the presence of an intramolecular H bridge between the hydroxyl group and the dioxolic oxygen, in compound **1**, as shown by structure **1a**. The persistence of this H



1a

Scheme 5



bridge in the molecular ion of compound **1** can explain the very low abundance of ionic species at m/z 126, since the H rearrangement present in the four center mechanism (Scheme 3) proves to be strongly inhibited in this case. Furthermore structure **1a** for the molecular ion of **1** can be invoked to rationalize the formation of ionic species at m/z 152 and 139. In fact in these cases (see Scheme 4), the intramolecular H bridge inhibits the second rearrangement of hydrogen on the dioxolic oxygen (Scheme 3), which leads to the cleavage of the cyclohexane ring with H rearrangement. On the contrary compound **2** undergoes the usual fragmentation pathways of the spiro[1,3-benzodioxole] derivatives, with formation of ionic species at m/z 150 and m/z 81. The latter are completely absent in the fragmentation pattern of compound **1**.

4-(2,3-Epoxypropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] **3** and 5-(2,3-Epoxypropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] **4**.

Also for these compounds strong differences in relative abundances of ionic species are present (see Figure 2). The

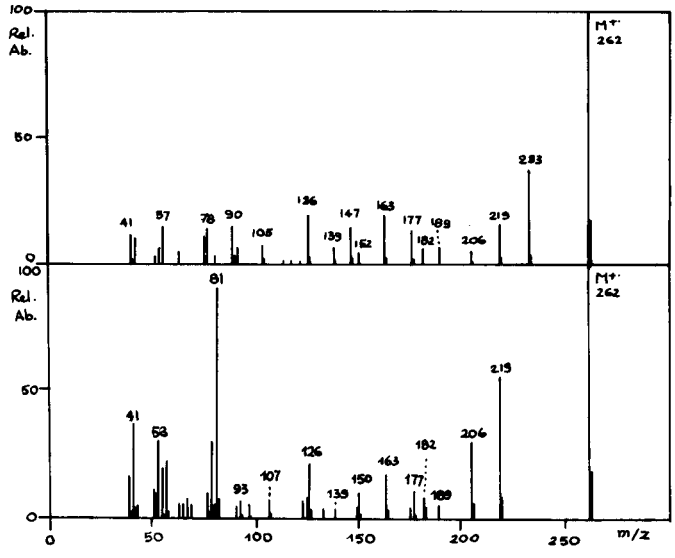
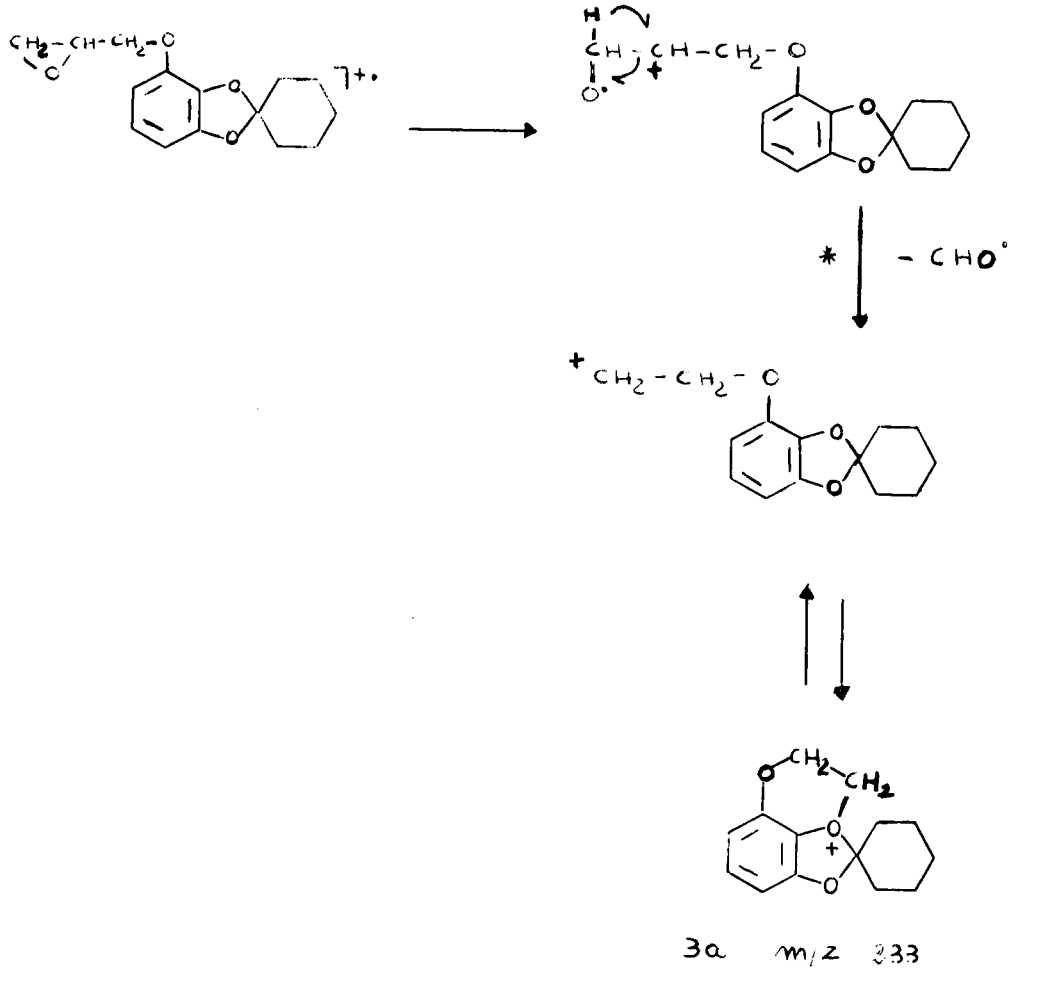


Figure 2. 70 eV EI mass spectra of compound **3** (top) and compound **4** (bottom).

Scheme 6



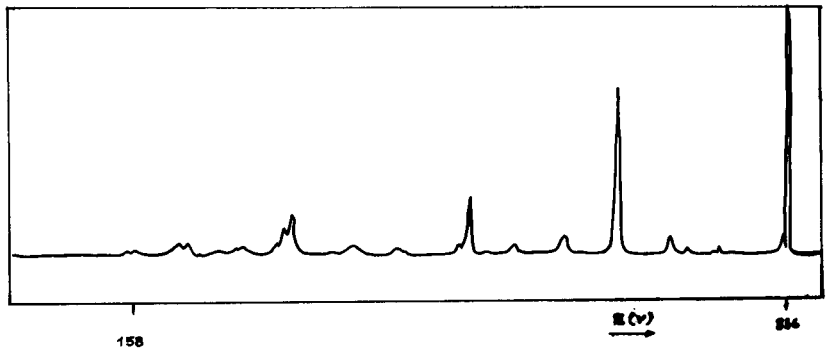
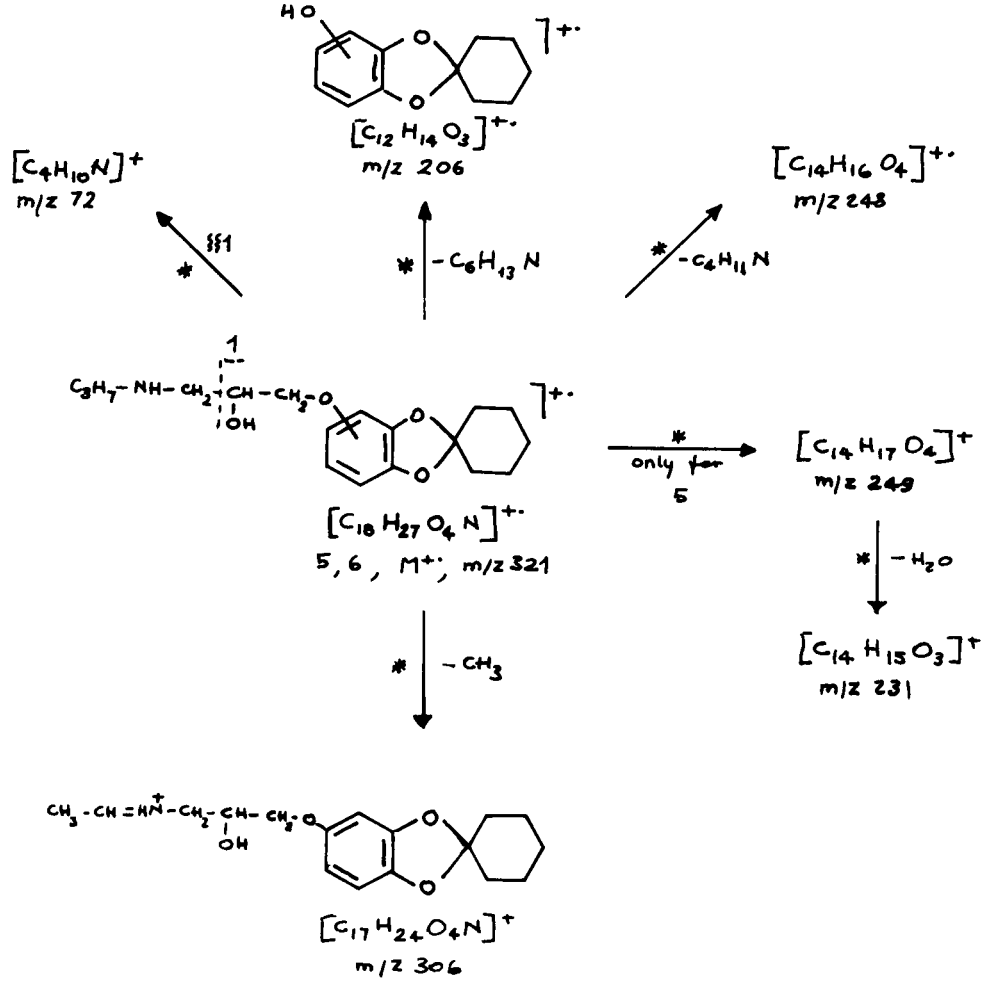


Figure 3. CAD MIKE spectrum of ionic species at m/z 206 originating from EI of compound **3**, identical to that of $M^{+\cdot}$ of compound **1**.

Scheme 7

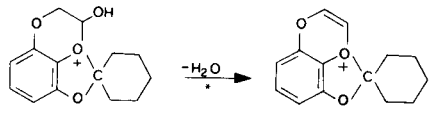


common fragmentation pattern, reported in Scheme 5, shows primary losses of C_3H_4O, $C_3H_5O^{\cdot}$, and $C_2H_3O^{\cdot}$, all easily related to cleavages of the 2,3-epoxypropoxy moiety. As proved by CAD MIKE experiments, the first of these leads to ions at m/z 206 having the same structure of the molecular ions of compounds **1** and **2** respectively (see Figure 3). These ionic species further decompose giving rise to ions at m/z 126, 150, 189, 177, 163 and 205. The cleavage of the dioxolic ring is also present in this case, which leads to ions $[C_9H_{10}O_4]^{+\cdot}$ (m/z 182), whose structure was confirmed by CAD MIKE experiments. A diagnostic ionic species is present at m/z 233 for compound **3** only, for which exact mass measurements give the elemental composition $C_{14}H_{17}O_3$, corresponding to the primary loss of $CHO^{\cdot}$. This behaviour can be explained by invoking the mechanism reported in Scheme 6, *i.e.* by a cleavage of the epoxide ring with loss of $CHO^{\cdot}$. The further cyclization reaction leading to structure **3a**, favoured by entropic factors, is completely forbidden for compound **4**. As already observed, abundant ionic species $[C_6H_9]^+$ (m/z 81) are present for compound **4** only.

4-(2-Hydroxy-3-isopropylaminopropoxy)spiro[1,3-benzodioxole-2,1'-cyclohexane] (**5**) and 5-(2-Hydroxy-3-isopropylaminopropoxy)spiro[1,3-benzodioxole-2,1'-cyclohexane] (**6**).

The mass spectra of compounds **5** and **6** are reported in Figure 4, while the related fragmentation pattern is reported in Scheme 7. The primary fragmentation processes are all related to the propanolol chain and lead to ions at m/z 306, 248 and 206. The ions m/z 206 have the structures of the corresponding hydroxy-derivatives, as proved by CAD MIKE experiments, and further decompose in the same way as the molecular ions of compounds **1** and **2**.

The base peak is due to cleavage 1 (see Scheme 7) which leads to $[C_4H_{10}N]^+$ (m/z 72) ions. The formation of abundant ionic species at m/z 249 is observed for compound **5** only, and can be explained by a mechanism identical to that reported in Scheme 6, which leads to ionic species **5a**. These ions further decompose through H_2O elimination, giving rise to the particularly stabilized species $[C_{14}H_{15}O_3]^+$ (**5b**).



5a, m/z 249 5b, m/z 231

In conclusion mass spectrometry has proved to be a valid tool in the structural characterization of the different couples of isomers. Furthermore the peculiar decomposition pathways of 4-substituted compounds, which show an interaction between the substituent groups and the benzodioxolic oxygen, could suggest the presence of analogous interactions in condensed phase which could explain the different yields obtained.

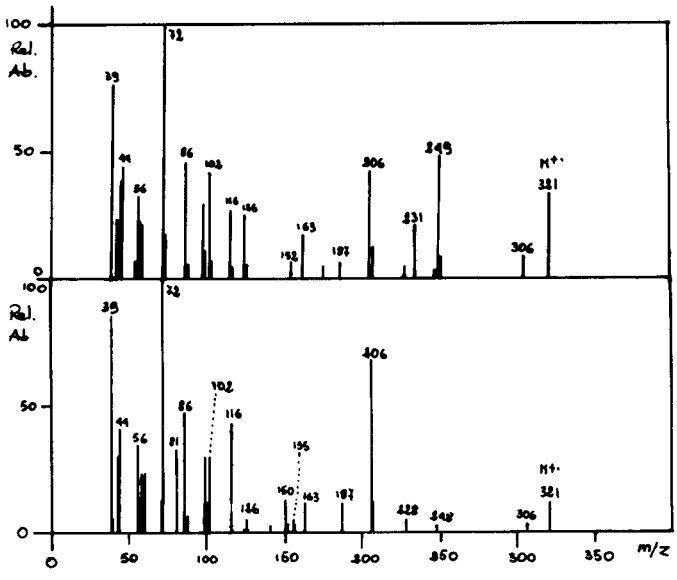


Figure 4. 70 eV EI mass spectra of compound **5** (top) and compound **6** (bottom).

EXPERIMENTAL

All mass spectrometric measurements were performed on a VG ZAB2F instrument operating in electron impact (EI) mode (70 eV, 200 μA). The samples were introduced in direct electron impact (DEI) [5] conditions, with a source temperature of 200°C. Metastable transitions were detected by B/E and B^2/E linked scans [6]. Exact mass measurements were performed with the peak matching technique at a 30000 resolving power (10% valley definition). Collisionally activated decomposition mass analyzed ion kinetic energy (CAD MIKE) spectra were obtained by 8 keV ions colliding with air in the second field-free region. The pressure in the cell was such to reduce the main beam intensity by 20% of its usual value. Melting points were determined using an electrothermal capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 157G spectrophotometer. The nmr spectra were determined on a Varian EM 360L spectrometer; chemical shifts were measured in ppm (δ) using tetramethylsilane as an internal reference. Microanalyses for CHN were carried out on Carlo Erba model 1106 Elemental Analyzer. Compounds **1-6** were analytically pure samples synthesized and purified as described below.

Starting Materials.

1,2,3-Trihydroxybenzene, 1,2,4-trihydroxybenzene, cyclohexanone, epibromohydrin, cetyltrimethylammonium bromide, isopropylamine, as well as all the solvents, were commercial products and have been used without further purification.

4-Hydroxyspiro[1,3-benzodioxole-1,2'-cyclohexane] (**1**).

To powdered sodium hydroxide (100 mmoles) a solution of 1,2,3-trihydroxybenzene (6.3 g, 50 mmoles) in 40 ml of dimethyl sulphoxide was added dropwise with stirring under nitrogen. The mixture was stirred at

60° for 2 hours and cyclohexanone (4.9 g, 50 mmoles) was added dropwise. The reaction mixture was stirred at 120° for 2 hours following addition. The mixture was acidified using 5% hydrochloric acid and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulphate and, after removal of the chloroform, the resulting residue was recrystallized from ethanol giving 6.7 g (65%) of a white-pink powder, mp 115-116°; ir (potassium bromide): 3180, 1625, 1605, 1255, 1170, 1140, 1075, 1055, 1020, 1000, 950, 920, 905, 890, 850, 835, 800, 725 cm^{-1}; nmr (deuteriochloroform): δ 1.2-1.4 (m, CH_2, 10H), 5.88 (s, OH, 1H, deuteriumoxide exchanged) and 6.1-6.45 (m, aromatic, 3H).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.87; H, 6.83.

5-Hydroxyspiro[1,3-benzodioxole-2,1′-cyclohexane] (**2**).

The desired compound **2** was obtained by a procedure similar to that described for 1, starting from 1,2,4-trihydroxybenzene (6.3 g, 50 mmoles), as a white powder (5.7 g, 55% yield), mp 90-91°; ir (potassium bromide): 3300, 2940, 2860, 1620, 1500, 1485, 1400, 1370, 1285, 1210, 1160, 1135, 1110, 1070, 975, 950, 900, 835, 790 cm^{-1}; nmr (deuteriochloroform): δ 1.95-1.43 (m, CH_2, 10H), 3.83 (s, OH, 1H, deuterium oxide exchanged) and 6.00-6.56 ppm (m, 3H, aromatic).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.87; H, 6.85.

4-(2,3-Epoxypropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] (**3**).

To an excess of epibromohydrin (4.11 g, 30 mmoles), a solution of 1 (2.06 g, 10 mmoles) and of cetyltrimethylammonium bromide (36 mg, 0.1 mmole) in 5 ml of 50% sodium hydroxide solution was added. The reaction mixture was stirred at 60° for 6 hours. After cooling, the organic layer was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent, the resulting residue was purified by column chromatography on silica gel using a mixture of chloroform-*n*-hexane (7:1) as eluent to give **3** as dark yellow oil, 0.8 g (30%), bp 162-164° (3 mm); ir (film): 2940, 1625, 1600, 1495, 1290, 1250, 1220, 1200, 1170, 1140, 1075, 1050, 1030, 1000, 970, 950, 920, 880, 850, 835, cm^{-1}; nmr (deuteriochloroform): δ 1.5-2.2 (m, -CH_2, 10H), 2.50-2.86 (m, CH_2-CH, 2H), 3.12-3.36 (m, C*H*-CH_2, 1H), 3.68-4.20 (m, CH_2-O, 2H), and 6.33-6.70 (m, aromatic, 3H).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.70; H, 6.91.

5-(2,3-Epoxypropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] (**4**).

The desired compound **4** was obtained by a procedure similar to that described for **3** giving a yield of 75% as yellow oil, bp 180° (8 mm); ir (film): 2940, 2860, 1630, 1500, 1420, 1370, 1285, 1270, 1250, 1225, 1205, 1190, 1170, 1130, 1080, 1040, 1030, 980, 960, 930, 880, 830 cm^{-1}; nmr (deuteriochloroform): δ 1.90-1.43 (m, CH_2, 10H), 2.86-2.55 (m, CH_2-CH, 2H), 3.08-3.36 (m, CH_2-C*H*, 1H), 3.70-4.11 (m, CH_2-O, 2H) and 6.06-6.66 (m, aromatic, 3H).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.69; H, 6.91.

4-(2-Hydroxy-3-isopropylaminopropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] (**5**).

A mixture of **3** (1.3 g, 5 mmoles) and isopropylamine (30 ml) was stirred and refluxed for a night. After cooling, the excess of isopropylamine was evaporated *in vacuo* and the resulting residue was recrystallized from diisopropylether to give 16 mg (1%) of white powder, mp 95-96°; ir (potassium bromide): 3300, 2930, 2850, 1620, 1500, 1450, 1370, 1280, 1245, 1200, 1170, 1140, 1100, 1070, 1030, 970, 900, 880, 830, 780 cm^{-1}; nmr (deuteriochloroform): δ 0.85-1.10 (d, CH_3, 6H), 1.56-2.13 (m, CH_2, 10H), 2.86-3.10 (m, CH_2-NH-C*H*, 3H), 3.6-4.3 (m, C*H*-CH_2-O, 3H), 4.76 (s, OH and NH, 2H, deuterium oxide exchanged), 5.8-6.5 (m, aromatic, 3H).

Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.25; H, 8.48; N, 4.37.

5-(2-Hydroxy-3-isopropylaminopropoxy)spiro[1,3-benzodioxole-2,1′-cyclohexane] (**6**).

The desired compound **6** was obtained by a procedure similar to that described for 5 giving a white powder (0.7 g, 42% yield) mp 79-80°; ir (potassium bromide): 3300, 2930, 2840, 1630, 1495, 1450, 1370, 1340, 1270, 1240, 1200, 1170, 1140, 1110, 1060, 1020, 970, 905, 890, 840, 820, 785 cm^{-1}; nmr (deuteriochloroform): δ 0.97-1.04 (d, CH_3, 6H), 1.88-1.33 (m, CH_2, 10H), 2.88 (s, OH and NH, 2H, deuterium oxide exchanged), 2.44-3.00 (m, CH_2-NH-C*H*, 3H), 3.52-4.08 (m, C*H*-CH_2-O, 3H) and 6.16-6.64 (m, aromatic, 3H).

Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: 67.27; H, 8.44; N, 4.38.

Acknowledgement.

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REFERENCES AND NOTES

[1] Partially and preliminarily communicated at the XIV Congresso della Società Chimica Italiana, Grado (TS), September 1984.

[2] P. Traldi, U. Vettori, A. Maccioni and G. Podda, *Org. Mass Spectrom.*, **17**, 201 (1982); P. Traldi, U. Vettori, A. Maccioni and G. Podda, *Heterocycles*, **19**, 1575 (1982).

[3] G. Podda, A. Maccioni, U. Vettori, S. Daolio and P. Traldi, *Org. Mass Spectrom.*, **18**, 275 (1983).

[4] G. Podda, A. Maccioni, S. Daolio and P. Traldi, *J. Heterocyclic Chem.*, **22**, 557 (1984).

[5] P. Traldi, U. Vettori and F. Dragoni, *Org. Mass Spectrom.*, **17**, 587, 1982.

[6] A. P. Bruins, K. R. Jennings and S. Evans, *Int. J. Mass Spectrom. Ion Phys.*, **26**, 395 (1978).