

Luca Simonotti, Carmine Pasqualucci\* and Giorgio Pifferi

I.S.F., Laboratories for Biomedical Research,  
20090 Trezzano s/N., Milan, Italy

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The mass spectra of a series of *N*- and *O*-substituted 2-morpholinols were considered and the complex fragmentation pattern explained on the basis of evidences reported in the literature and of experimental data (high resolution, metastable ions). The primary fragmentations are given by inductive cleavage due to the heteroatoms, while ring contractions, through retro Diels-Alder reactions, form most of the secondary pattern with different ions related to *N*- and *O*-substituents. Moreover, hemiacetals in the tautomeric hydroxyaldehyde form undergo an  $\alpha$ -cleavage.

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In the biotransformation of morpholine-containing drugs, some ring hydroxylated metabolites were recently isolated [1-4]. In particular, the 2-morpholinol derivative plays an important role in the biological elimination of tri-thiozine, a new antisecretory and antiulcer drug [5].

Because these compounds have an unusual chemical structure which has not been previously described, a number of 2-morpholinols having different substituents on the nitrogen atom and on the hydroxy group were synthesized and their chemical and pharmacological properties investigated [6,7,8].

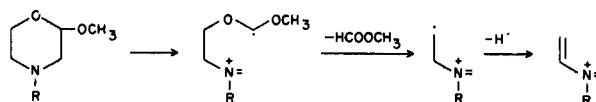
This report describes the mass fragmentation behavior of compounds 1-14 (Table 1), both for a general interest of characterization of this new class and for an evaluation of the diagnostic utility of mass spectrometry in the identification and assignment of new structural features.

The general fragmentation pattern, shown in Scheme 1, has been deduced from details of the mass spectra given in Table 2, on the basis of elemental compositions determined by high resolution measurements (Table 3) and metastable transitions (Table 4).

It is clear that the mass spectrum is strictly related to the substituents on the nitrogen or oxygen atom. When these are benzyl or benzoyl groups there is considerable "i" (inductive) cleavage to the heteroatom leading to the corresponding ions; cleavage adjacent to the nitrogen atom appears to be preferred as indicated by compound 7.

Elimination of R'O from the molecular ion to give the low intensity ion A, follows a typical fragmentation of acetals [9].

When R' is an ethyl or an arylalkyl group, a hydrogen migration from R' and the splitting of a neutral aldehyde lead to ion B (Table 4). This has been indicated as an ionized morpholine structure because of its fragmentation to ion F which resembles morpholine [10]. Ion F is present concurrently as the daughter ion of the molecular one in the fragmentation of the *O*-methyl derivatives 8 and 9. In analogy with piperidine ring-containing compounds [11], the following mechanism could also be drawn:



The loss of hydrogen from F to E is supported by metastable transition relative to compound 9.

Moreover, the molecular ion of compounds 3, 4 and 6, 7 where R' is an arylalkyl group, fragments to ion C. This is indicated in Scheme 1 as the resonance limit structure of oxonium ion. Concomitantly, in the spectra of hemiacetals 11-14, this ion could be formed from the loss of the acetalic hydrogen atom. Biellmann and Hirth [12] demonstrated by isotopic labeling studies that the hydrogen atom expelled from the molecular ion of aromatic amides originates from the aromatic ring. However if such a mechanism occurred in our compounds, ion [M - H]<sup>+</sup> should be formed also in the fragmentation of benzamides 8 and 9.

The presence of the *N*-substituent influences the further fragmentation of ion C: the metastable transitions suggest ion C as precursor both of ion D for *N*-unsubstituted derivatives, and of ion E, which is characteristic of this class of compounds. The two pathways can be rationalized by two resonance limit structures of oxonium and immonium ions as triggers of retro Diels-Alder (RDA) reactions. The indicated isomeric ions for E are referred to the described fragmentation pattern of azetidine derivatives [13].

In the mass spectra of hemiacetals 10-14, another fragmentation is present which gives ion H and ion H'; this could derive from the tautomeric open chain hydroxyaldehyde through cleavage of the bond adjacent to nitrogen atom. The following cyclic structures could be the stabilizing forms:

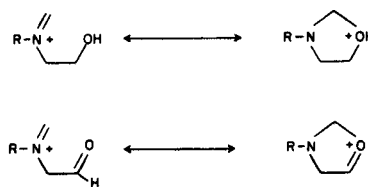
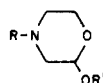


Table 1  
N- and O-Substituted 2-Morpholinols



Compound No.	R	R'
1 [a]	H	H
2	H	Ethyl
3	H	Benzyl
4	H	4-Methoxybenzyl
5	Benzyl	Ethyl
6	Benzyl	Benzyl
7	Benzyl	4-Methoxybenzyl
8	3,5-Dimethoxy-4-hydroxybenzoyl	Methyl
9	3,4,5-Trimethoxybenzoyl	Methyl
10	Benzyl	H
11	Benzoyl	H
12	4-Nitrobenzoyl	H
13	3,5-Dimethoxy-4-hydroxybenzoyl	H
14	3,4,5-Trimethoxybenzoyl	H

[a] Available as the hydrochloride.

In the unsubstituted *N*-derivatives only high resolution measurements allowed the assignment of the peak at *m/z* 57 to the above mentioned ion **F** or to the ion **G**. The latter could be derived from ion **A** through an RDA reaction. Finally, compound **I**, available only as the hydrochloride, shows a peculiar fragmentation characterized by a basic peak at *m/z* 30. This has been attributed to ion  $\text{CH}_2\text{NH}_2^+$  recurring in the mass spectra of secondary cyclic amines [14].

In conclusion, the fragmentation pathways (Scheme 1) of the 2-morpholinols considered can be summarized as follows: a "i" cleavage of the R-N and R'-O bonds with charge retention on the substituents R and R'; "i" cleavage of the exocyclic ether bond leading to an unsaturated morpholine ion **A** or to ion **B** through hydrogen migration when R' is an ethyl or arylalkyl moiety; elimination of R' and rearrangement to oxonium and immonium ions (**C**); ring fragmentation triggered by the nitrogen atom when R' = H.

These primary fragmentations should be followed by a secondary step that, through RDA reactions, leads to ions **D**, **E**, **F** and **G**.

Table 2  
Fragmentation of 2-Morpholinols  
*m/z* (relative intensity)

Compound	M <sup>+</sup>	R <sup>+</sup>	R''	A	B	C	D	E	F	G	H	H'	CH <sub>2</sub> NH <sub>2</sub> <sup>+</sup>
1	103 (12)			86 (4)				56 (43)	57 (71)		74 (14)	72 (4)	30 (100)
2	131 (6)		29 (45)	86 (17)	87 (6)		73 (4)	56 (45)		57 (100)			
3	193 (2)		91 (63)	86 (5)	87 (45)	102 (49)	73 (100)	56 (77)	57 (30)				
4	223 (3)		121 (99)	86 (2)	87 (22)	102 (100)	73 (98)		57 (6)				
5	221 (3)	91 (100)		176 (3)	177 (8)	192 (2)		146 (25)					
6	283 (2)		91 (100)		177 (43)	192 (31)		146 (15)	147 (3)				
7	313 (-)	91 (100)	121 (28)		177 (14)	192 (16)		146 (6)					
8	297 (13)	181 (100)		266 (2)				236 (33)	237 (7)				
9	311 (18)	195 (100)		280 (2)				250 (29)	251 (6)				
10	193 (5)	91 (100)						146 (21)			164 (2)		
11	207 (10)	105 (100)				206 (22)		160 (39)			178 (5)		
12	252 (10)	150 (100)				251 (18)		205 (43)			223 (8)	221 (4)	
13	283 (18)	181 (100)				282 (11)		236 (14)			254 (4)		
14	297 (24)	195 (100)				296 (18)		250 (12)			268 (4)		

Table 3  
High Resolution Measurements

Compound	Ion	Calcd.	Found
1	E	56.05002	56.04974
2	G	57.03404	57.03351
3	F	57.057849	57.05812
4	C	102.05550	102.05546
	B	87.068414	87.068450
	D	73.028950	73.028950
14	E	250.107934	250.10820

Table 4  
Significant metastable transitions recorded by DAD1 mass spectrometry

Compd 4	Compd 6	Compd 9	Compd 14

