Mass Spectral Study of Some Stereoisomeric 2-Thioxo- and 2-Oxo-perhydro-1,3- and 2-Thioxoperhydro-3,1-benzoxazines

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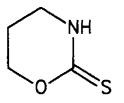
Mass spectral fragmentations of tetrahydro-1,3-oxazine-2-thione, six 2-thioxo- and three 2-oxo-perhydro-1,3- or -3,1-benzoxazines have been examined using metastable ion analysis and exact mass measurement. The fragmentation patterns of the 1,3-benzoxazines clearly differs from those of the 3,1-benzoxazines making it easy to distinguish them from each other. However, the *cis*- and *trans*-fused isomers gave rise to quite similar spectra, although comparison of some fragmentations which favoured one or the other isomer made structural identification possible. The *trans*-fused isomers were always more resistant to fragmentation than the corresponding *cis* forms. In contrast with the thioxo compounds, oxo compounds were very unstable under electron ionization. No gas-phase enolization or thienolization could be found with the compounds studied.

Recently we reported the mass spectral fragmentations of fused ring 2-methyl- and 2-phenylimino-perhydro-1,3-oxazines.[1,2] The results show that their behaviour depends very much on the substitution at position 2 and also to some degree on the stereochemistry of the ring fusion. As a continuation of our systematic study on biologically and pharmacologically important perhydro-1,3-oxazines we now present the fragmentation analysis of some 2-thioxo- and 2-oxo-perhydro-1,3-benzoxazines as well as two 2-thioxoperhydro-3,1-benzoxazines (Scheme 1) under electron ionization.



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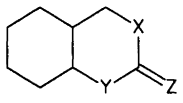

2–10

	X	Y	Z	Ring fusion
2	NH	O	S	*cis*
3	NH	O	S	*trans*
4	NMe	O	S	*cis*
5	NMe	O	S	*trans*
6	O	NH	S	*cis*
7	O	NH	S	*trans*
8	NH	O	O	*cis*
9	NH	O	O	*trans*
10	NMe	O	O	*cis*

Scheme 1. The compounds studied.

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Our main aim was to find fragmentations which would be of considerable value in structure determination. Special attention was paid to the effects of the site and stereochemistry of the ring fusion. Another interesting viewpoint was how the higher polarizability of sulfur (thioxo derivatives) in comparison with oxygen (oxo derivatives) affects the decomposition pathways of the perhydro-1,3-oxazine ring system. All fragmentations discussed were established by metastable ion analysis and the collision induced dissociation (CID) technique.[3] The elemental composition of the principal fragment ions were verified using exact mass measurement.

Results and discussion

2-Thioxo compounds. These compounds were rather stable under electron ionization as can be seen from their 70 eV spectra presented in Table 1 and Fig. 1. The molecular ions always gave rise to the base peak the intensity of which varied from 10–31 % of the total ion current. Compared with the parent compound (**1**) the ring fusion clearly decreased the stability. In all the cases studied the *trans* isomer produced a more intense molecular ion peak than the *cis* isomer which is consistent with the fact that normally – also with other perhydro-1,3-benzoxazines[4] – *cis*-fused isomers are more strained than the *trans* forms.

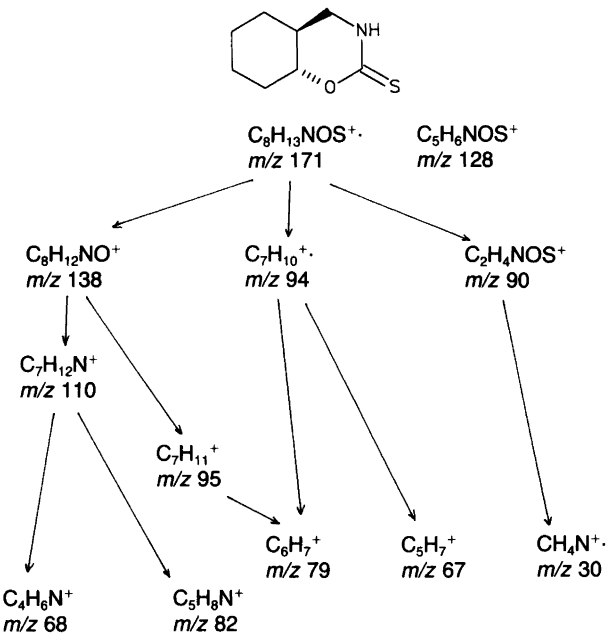
The fragmentations of compound **1** were scant. The most important route started as an α-cleavage reaction with respect to nitrogen or oxygen atoms leading to the elimination of ethene which was followed by equal loss of both CO and $CH_2N\cdot$. The molecular ion also lost $HS\cdot$ and H_2O but neither of these reactions was important.

Table 1. The 70 eV mass spectra of the compounds studied. Those peaks included are of relative intensity >5 % of that of the base peak. The spectra are uncorrected for isotopic contributions.

Compound	*m/z* (relative intensity)
1	117 (100) $M^{+\cdot}$, 89 (15), 72 (7), 61 (6), 60 (9), 59 (16), 57 (5), 56 (14), 42 (6), 41 (11), 39 (5), 31 (5), 30 (6), 29 (45), 27 (11)
2	171 (100) $M^{+\cdot}$, 138 (11), 102 (16), 95 (41), 94 (96), 93 (14), 91 (18), 90 (27), 83 (8), 82 (27), 81 (41), 80 (12), 79 (70), 78 (9), 77 (10), 72 (14), 69 (8), 68 (20), 67 (68), 58 (14), 57 (8), 56 (18), 55 (27), 54 (25), 53 (13), 44 (8), 43 (19, 41 (39), 39 (20), 30 (48), 29 (29), 27 (15)
4	185 (100) $M^{+\cdot}$, 152 (24), 142 (8), 109 (11), 104 (38), 96 (9), 95 (21), 94 (38), 93 (5), 92 (11), 82 (12), 81 (22), 79 (20), 72 (5), 68 (9), 67 (42), 57 (7), 55 (15), 54 (13), 53 (6), 44 (58), 43 (39), 42 (38), 41 (20), 39 (11), 29 (5), 27 (7)
5	185 (100) $M^{+\cdot}$, 152 (16), 142 (9), 116 (8), 109 (11), 104 (10), 96 (11), 95 (24), 94 (19), 93 (6), 92 (7), 82 (7), 81 (21), 79 (17), 68 (11), 67 (54), 57 (16), 55 (18), 54 (11), 53 (6), 44 (28), 43 (23), 42 (25), 41 (22), 39 (11), 30 (7), 29 (5), 27 (7)
6	171 (100) $M^{+\cdot}$, 141 (9), 138 (6), 116 (7), 110 (7), 96 (16), 95 (31), 94 (15), 93 (6), 83 (9), 82 (19), 81 (8), 79 (18), 70 (8), 69 (10), 68 (14), 67 (20), 57 (7), 56 (24), 55 (21), 54 (15), 53 (7), 43 (42), 42 (7), 41 (26), 39 (11), 29 (6), 27 (8)
8	155 (13) $M^{+\cdot}$, 111 (5), 110 (12), 96 (6), 94 (25), 83 (16), 82 (37), 81 (12), 80 (7), 79 (29), 77 (5), 70 (11), 69 (12), 68 (39), 67 (45), 57 (13), 56 (24), 55 (23), 54 (25), 53 (9), 44 (7), 43 (21), 42 (10), 39 (22), 30 (100), 29 (19), 27 (18)
10	169 (6) $M^{+\cdot}$, 124 (7), 97 (5), 96 (10), 82 (11), 79 (6), 70 (8), 68 (6), 67 (20), 57 (8), 55 (7), 54 (9), 44 (100), 43 (7), 42 (20), 41 (13), 39 (7), 27 (6)

The ring fusion, especially its site, had a remarkable effect on the primary fragmentations of the ring of the 2-thioxo derivatives. For the 1,3-derivatives (compounds **2–5**) the principal reactions were the same as those for compound **1**, as exemplified for **3** in Scheme 2. α-Cleavage reactions, both with respect to the ring nitrogen and oxygen atoms, were clearly detectable and led to the formation of the ions $[C_2H_4NOS]^+$ and $[C_5H_6NOS]^+$, respectively. The former reaction especially, does not seem to be quite usual with fused ring perhydro-1,3-oxazines.[1,2] It also was more favoured in the *cis*- than in the *trans*-fused isomers; this being one of the reactions which made the differentiation of the isomers possible. The increased basicity of the nitrogen atom in compounds **4** and **5** caused by its methyl substituent[2,5] enhanced the tendency towards α-cleavage reactions.

In analogy to compound **1**, the molecular ions of compounds **2–5** also eliminated HS· and H_2O. Contrary to the parent compound the loss of sulfhydryl radical was quite an important reaction with these compounds. Fragmentations of the *N*-deuteriated compound **3** showed that the hydrogen atom lost in the latter reaction originated from one of the carbon atoms. This means that these compounds did not form any thienol structures in the gas phase in analogy to their behaviour in the liquid phase[6] even though the enol forms have often been found to be more stable than the keto tautomers in the gas phase.[7] The absence of a retro-Diels–Alder reaction from the molecular or $[M-HS]^+$ ions also verified the above observation because a double bond between C(2) and N(3) would greatly have favoured this reaction.[1,8]



Scheme 2. The main fragmentation routes of compound **3**.

Usually, in the case of nitrogen heterocycles, most of the ion current is carried by nitrogen-containing fragment ions. An interesting feature of the present compounds was that many of the most intense fragment ion peaks represented hydrocarbon ions. These ions are not characteristic of perhydrobenzoxazines in general.[1,2,8] Therefore especially noticeable was the favourable elimination of carbamothioic acid from the molecular ions of compounds **2–5** giving rise to the formation of $[C_7H_{10}]^{+\cdot}$ ions at *m/z* 94. To gain further insight into this reaction the structures of the *m/z* 94 ions were compared with those of the molecular ions of several C_7H_{10} hydrocarbons (M_1–M_4) and to that of the $[M-HBr]^{+\cdot}$ ion from 1-bromo-1-heptyne (M_5) using the collision induced dissociation (CID) technique. To some extent, the molecular ions of norbornene (M_1), nortricyclane (M_2), 1,3-cycloheptadiene (M_3) and 1-methyl-1,4-cyclohexadiene (M_4) retained their structural identity, although some isomerization certainly also took place. In particular, the CID spectra of M_3 and M_4 were very similar (Table 2). This is in

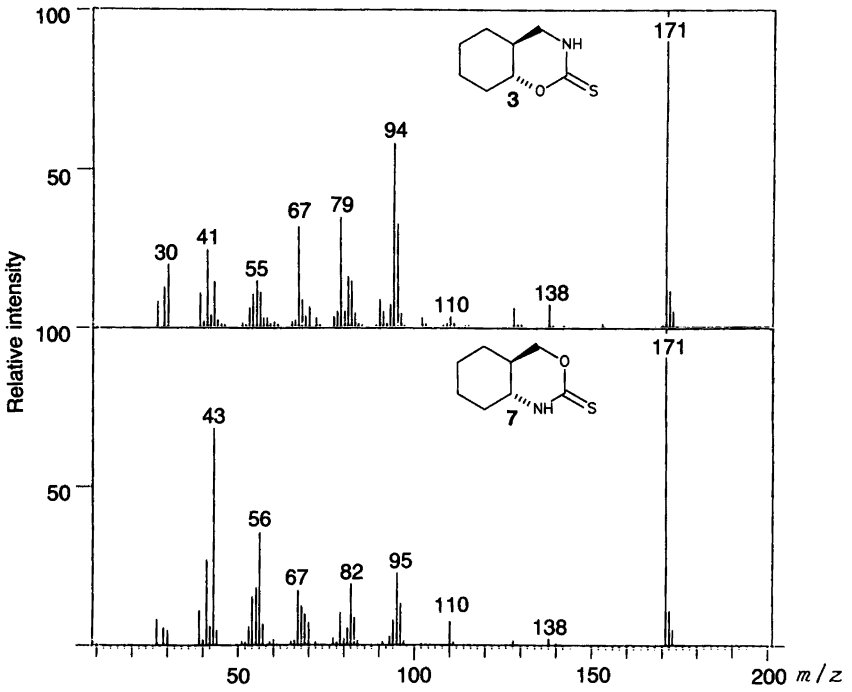
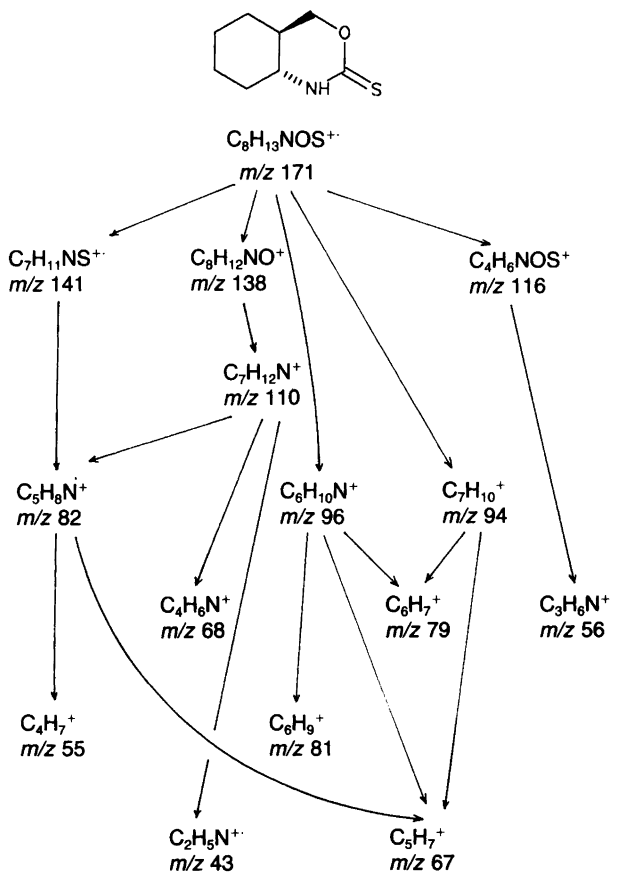


Fig. 1. The 70 eV mass spectra for compounds **3** and **7**.

Table 2. The CID spectra of the *m/z* 94 ions generated from different precursors. Intensities are normalized to a total fragment ion abundance = 100. The data are not corrected for metastable peaks. (M_1 = norbornene, M_2 = nortricyclane, M_3 = 1,3-cycloheptadiene, M_4 = 1-methyl-1,4-cyclohexadiene and M_5 = 1-bromo-1-heptyne).

m/z	M_1	M_2	M_3	M_4	M_5	**2**	**3**	**4**	**6**	**7**	**9**
27	0.6	0.2	0.5	0.5	1.5	0.9	0.9	1.1	1.6	1.6	1.0
28	–	–	–	–	–	–	–	–	0.9	1.4	0.7
38	0.8	0.4	0.5	0.5	0.9	0.6	0.6	0.7	0.9	1.0	0.6
39	3.4	2.4	2.8	2.6	6.3	3.6	3.8	4.1	6.0	6.6	3.2
40	0.9	–	0.5	0.5	1-1	0.7	0.7	0.9	1.2	1.4	0.7
41	0.7	0.6	0.5	0.5	4.4	1.8	2.1	2.6	4.7	5.4	2.1
42	–	–	–	–	–	–	–	0.9	1.3	1.6	0.7
43	–	–	–	–	–	–	–	–	–	–	0.9
50	1.0	1.0	1.1	1.3	1.3	1.1	1.1	1.1	1.3	1.3	1.1
51	1.8	1.8	2.2	2.6	3.1	2.5	2.4	2.3	2.6	2.8	2.1
52	0.9	0.7	1.0	1.3	1.6	1.5	1.4	1.4	1.7	1.7	1.3
53	0.8	0.8	1.1	1.4	5.8	2.5	3.0	3.1	4.4	4.7	1.6
54	–	–	–	–	0.8	0.6	0.5	1.1	1.3	1.6	0.7
55	–	–	–	–	13.4	3.1	4.2	3.9	7.6	7.9	0.8
56	–	–	–	–	0.7	–	–	–	0.7	1.0	–
63	1.1	0.8	1.0	1.0	0.9	0.7	0.9	0.8	0.8	0.9	0.9
65	5.5	3.5	3.5	2.5	3.0	2.8	2.8	2.5	3.2	2.7	2.4
66	51.3	16.7	3.2	0.7	1.0	1.7	1.5	1.4	1.5	1.4	1.8
67	7.9	3.3	0.5	–	18.8	4.5	6.8	6.4	12.6	13.3	1.3
68	–	–	–	–	1.0	–	–	1.6	2.1	2.4	–
69	–	–	–	–	–	–	–	–	–	0.9	–
77	8.2	14.7	17.0	17.5	11.4	14.3	13.3	12.0	9.8	9.1	13.9
78	2.4	4.4	4.8	5.4	2.1	3.9	3.8	3.4	2.8	2.3	4.5
79	2.8	28.7	35.2	41.2	13.8	36.1	33.4	26.6	18.5	15.1	37.9
80	–	2.7	3.4	3.3	3.6	4.0	4.5	4.0	4.2	4.5	5.1
81	–	–	–	–	–	–	–	7.1	1.6	2.0	0.8
89	–	–	0.5	0.4	–	–	–	–	–	–	–
91	8.3	13.9	16.7	13.5	3.5	10.9	10.0	9.4	5.3	4.1	11.6
92	1.4	3.4	3.9	3.2	–	1.9	2.0	1.8	1.3	1.1	2.2



Scheme 3. The main fragmentation routes for compound **7**.

accordance with earlier metastable ion results.[9] Compounds **2–4** gave almost identical CID spectra which bore close resemblance to those of M_3 and M_4, although were not completely identical. Our results show that, most probably, a mixture of different structures was formed.

The greater stability of the perhydro-3,1-benzoxazine ring system compared with the perhydro-1,3-benzoxazine sysem[4] was reflected by the more intense molecular ion peaks of compounds **6** and **7** (17.2 and 18.4% from the total ion current) than those of compounds **2** and **3** (9.1 and 15.2% from the total ion current). For the same reason, the first-mentioned compounds retained better their structural identity with respect to each other. Some fragmentation pathways of compounds **6** and **7** (Scheme 3) were identical with those of related 1,3-derivatives. Ion intensities, however, varied adequately for easy differentiation of the positional isomers (Table 1 and Fig. 1). The CID spectra of the *m/z* 94 ions generated from compounds **6** and **7** most resembled that of M_5. They differed, however, clearly from related spectra generated from perhydro-1,3-benzoxazines (Table 2); this indicates that the actual fragmentations were different although they apparently led to formally similar results. Another typical feature, namely, the elimination of $C_2H_3OS\cdot$ directly from the molecular ions of compounds **6** and **7**, was completely absent from compounds **2–5**. In addition to the above-mentioned fragmentations, the molecular ion of the *cis*-fused isomer (compound **6**) eliminated CH_2O and $C_4H_7\cdot$ which seem to be typical of this stereochemistry.[1]

It is worth noting that in the spectra of compounds **2, 3, 8** and **9** the *m/z* 82 ions consisted of practically equal amounts of the compositions $C_5H_8N^+$ and $C_6H_{10}^{+\cdot}$ of which the former corresponds to the ion *m/z* 96, $C_6H_{10}N^+$ in the spectra of compounds **4, 5** and **10**. In the case of compounds **6** and **7** the ion at *m/z* 82 had the composition $C_5H_8N^+$ only.

2-Oxo compounds. The fragmentations of the 2-oxo derivatives (**8–10**) differed considerably from those of the 2-thioxo compounds, as exemplified by **8** in Scheme 4 and for **9** in Fig. 2. First, the stability of molecular ions was much lower, which is a typical difference between oxygen and sulfur compounds.[10] Secondly, in contrast with most sulfur derivatives, most of the ion current was carried out by nitrogen-containing fragment ions. Both of these phenomena result from the higher polarizability of the sulfur atom. Compounds **8–10** did eliminate carbamic acid from their molecular ions but this reaction was much less significant than the loss of carbamothioic acid from compounds **2–7**. The CID spectrum of the *m/z* 94 ion from compound **9** (Table 2) shows very clearly that here a mixture of different structures was also formed. All other primary fragmentations were connected with the oxygen atoms. Molecular ions lost both carbon monoxide and carbon dioxide as well as $C_3H_5O_2\cdot$ (Scheme 4). Related fragmentations were absent from the spectra of thioxo compounds. Also in con-

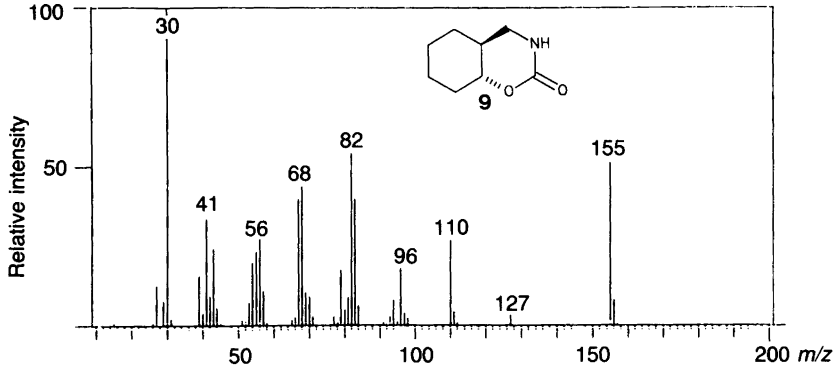
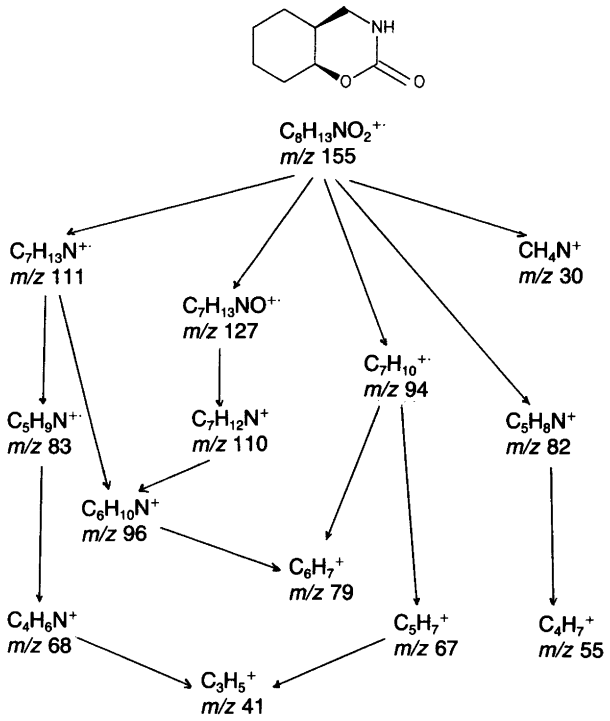


Fig. 2. The 70 eV mass spectra for compound **9**.



Scheme 4. The main fragmentation routes for compound **8**.

trast with the thioxo derivatives, the oxo compounds did not eliminate hydroxyl radical from their molecular ions. Therefore, in analogy to the thioxo compounds no enolization of the oxo compounds took place in the gas phase. The base peak in the spectra of compounds **8** and **9** represented the ion $[CH_4N]^+$ at *m/z* 30, which most probably was formed directly from the molecular ion although its formation did not give rise to any metastable peaks.

Experimental

Synthesis and structural characterization of the compounds studied have been presented elsewhere.[6] All measurements were made on a Jeol JMS-D300 mass spectrometer equipped with a JMA-2000H data system. Typical source conditions were: temperature 443 K, electron energy 70 eV, ionization current 300 μA and acceleration voltage 3 keV. Samples were introduced with a solid inlet probe below 410 K. Accurate mass measurements were carried out at a resolving power of 5000–10000. Metastable ion analyses were performed with linked scans at constant *B/E*. In CID experiments helium was added to the first field-free region so that transmission of the main beam was reduced to 33 % of its value in the absence of collision gas. CID spectra for structural studies were recorded one after another, keeping the conditions as constant as possible.

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References

1. Pihlaja, K., Vainiotalo, P., Fülöp, F. and Bernáth, G. *Rapid Commun. Mass Spectrom. 2* (1988) 229.
2. Vainiotalo, P., Fülöp, F., Bernáth, G. and Pihlaja, K. *J. Heterocycl. Chem. 26* (1989). *In press.*
3. For leading reviews, see: (a) Levsen, K. and Schwarz, H. *Angew. Chem., Int. Ed. Engl. 15* (1976) 509; (b) Cooks, R. G., *Collision Spectroscopy,* Plenum Press, New York 1978; (c) Levsen, K. and Schwarz, H. *Mass Spectrom. Rev. 2* (1983) 77; (d) McLaffert, F. W., *Tandem Mass Spectrometry,* Wiley, New York 1983.
4. Fülöp, F., Pihlaja, K., Mattinen, J. and Bernáth, G. *J. Org. Chem. 52* (1987) 3821.
5. Vékey, K., Tamás, J., Fülöp, F. and Bernáth, G. *J. Heterocycl. Chem. 22* (1985) 523.
6. (a) Stájer, F., Szabó, A. E., Fülöp, F., Bernáth, G. and Sohár, P. *Heterocycles 19* (1982) 1191; (b) Fülöp, F., Csirinyi, Gy., Bernáth, G. and Szabó, J. A. *Synthesis* (1985) 1149.
7. (a) Maquestiau, A. and Flammang, R. *Mass Spectrom. Rev. 1* (1982) 237; (b) Heinrich, N., Koch, W., Frenking, G. and Schwarz, H. *J. Am. Chem. Soc. 108* (1986) 593 and references therein.
8. Pihlaja, K., Vuorilehto, L., Bernáth, G. and Fülöp, F. *Report Series in Chemistry, Special Report No. 17,* 6. The 2nd National Symposium on Mass Spectrometry, University of Oulu, Finland 1984.
9. Dale, A. J., Weringa, W. D. and Williams, D. H. *Org. Mass Spectrom. 6* (1972) 501.
10. Budzikiewicz, H., Djerassi, C. and Williams, D. H. *Mass Spectrometry of Organic Compounds,* Holden-Day, San Francisco 1967.

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