Electron Ionization Mass Spectra of Some 4β-Phenyl-substituted Cycloalkane-*cis*-fused 1,3-Oxazin-2(3*H*)-ones, -2(3*H*)-thiones and 1,4-Oxazepin-3(4*H*)-ones

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The 70 eV mass spectra of 4β-phenyl-substituted cyclopentane- and cyclohexane *cis*-fused 1,3-oxazin-2(3*H*)-ones, the two related 2-thiones, 6,7-*cis*-trimethylene-5β-phenyl-1,4-oxazepin-3(4*H*)-one and its 2β-methyl derivative were recorded and their fragmentations examined by means of metastable ion analysis, collision induced dissociation technique and exact mass measurement. The fragmentation patterns of the 1,3-oxazin-2(3*H*)-ones were relatively simple: the favored formation of cycloalkene ions implied that a considerable proportion of the molecular ions might possess an enol structure. Changes in the size of the fused cycloalkane ring had little or no effect on the fragmentations. Instead, small changes in the heterocyclic part of the molecule caused remarkable effects on the fragmentation behavior. Compared to 1,3-oxazin-2(3*H*)-ones studied, both 1,3-oxazine-2(3*H*)-thiones and 1,4-oxazepin-3(4*H*)-ones showed much more complicated fragmentation patterns.

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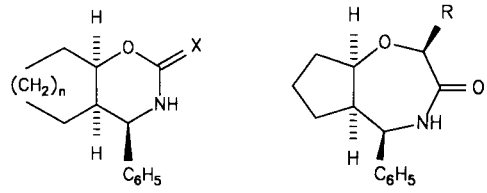
Introduction.

In the course of a systematic study on the mass spectrometric behavior of biologically and pharmaceutically interesting heterocyclic compounds, fragmentations of some unsubstituted cyclohexane-fused 2-thioxo- and 2-oxoperhydro-1,3-oxazines have previously been reported [1]. The 2-thioxo compounds proved to be fairly stable under electron ionization, whereas the related oxo compounds decompose effectively. It is interesting that they give rise to several intense hydrocarbon ion fragments, which is not characteristic to 1,3-oxazine derivatives in general [2,3].

Two 4β-phenyl-substituted cycloalkane-*cis*-fused 1,3-oxazin-2(3*H*)-ones **1** and **2**, the two related 2(3*H*)-thiones, **3** and **4** and two 1,4-oxazepin-3(4*H*)-ones **5** and **6**, as depicted in Scheme 1, were earlier prepared for pharmacological purposes and systematic comparative stereochemical studies [4]. In the synthesis, the cycloalkenebenzonitrile oxide adducts were reduced to phenyl-substituted *cis*-2-aminomethylcyclopentanol and cyclohexanol [5] which were then cyclized *via* carbamates and thiocarbamates to **1** and **2** or **3** and **4**, respectively. Compound **5** and its 2β-methyl derivative **6** were prepared from the aminoalcohols by using 2-chloroacetate or 2-chloropropionate. The nmr data indicated that the phenyl group is equatorial (β) in all of the compounds [4].

Scheme 1



1	X = O	n = 1	5	R = H
2	X = O	n = 2	6	R = CH_3
3	X = S	n = 1		
4	X = S	n = 2		

The aim of this study was to map the effects of various small structural changes in the molecules on their decomposition in comparison with that of 5,6-*cis*-trimethylene-4β-phenyl-1,3-oxazin-2(3*H*)-one (**1**). The effect of the phenyl group on the fragmentation patterns was elucidated by comparison with the related unsubstituted compounds [1]. All fragmentations discussed were established by metastable ion analysis and collision induced dissociation (CID) technique [6]. The elemental composition of the principal fragment ions were verified *via* exact mass measurement.

Results and Discussion.

The 70 eV electron ionization mass spectra of the compounds are presented in Figure 1 and Table 1. The fragmentation pattern of 5,6-*cis*-trimethylene-4β-phenyl-1,3-oxazin-2(3*H*)-one (**1**) differed considerably from that of the related unsubstituted oxazinone [1]. Compound **2** behaved rather similarly showing that the size of the hydrocarbon ring had little effect on the fragmentations. In the case of the unsubstituted compound the most important fragmentation pathway started with elimination of CO, which was totally absent with the compounds studied here. Instead, there were two important reaction pathways which were quite insignificant for the unsubstituted compound. First of them started as the elimination of the carbocyclic ring with a simultaneous migration of one hydrogen atom to the heterocyclic part of the molecule (Scheme 2). The ion so formed further lost carbon dioxide giving rise to the

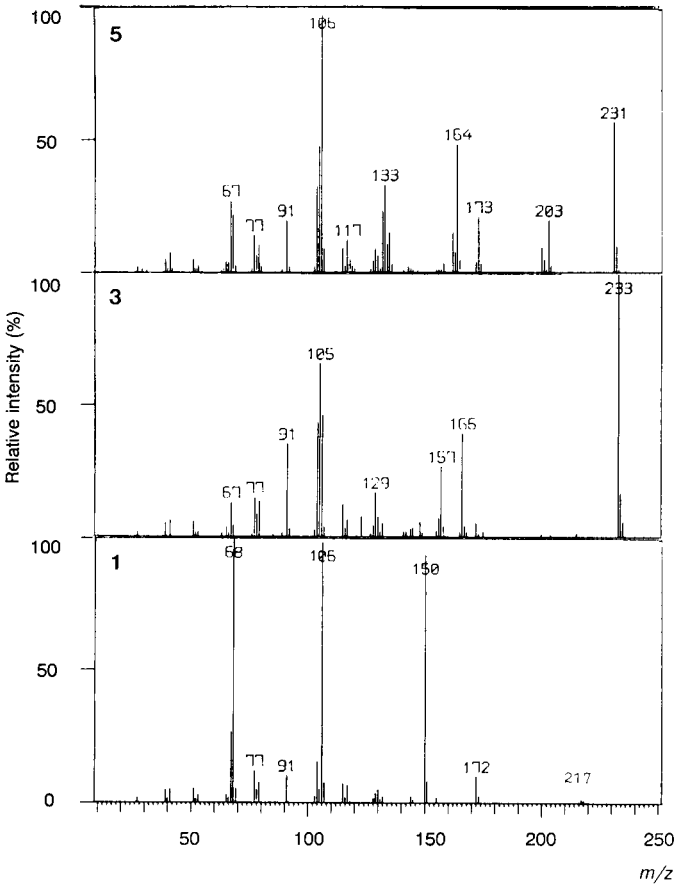


Figure 1. The 70 eV mass spectra of compounds **1**, **3** and **5**.

Scheme 2

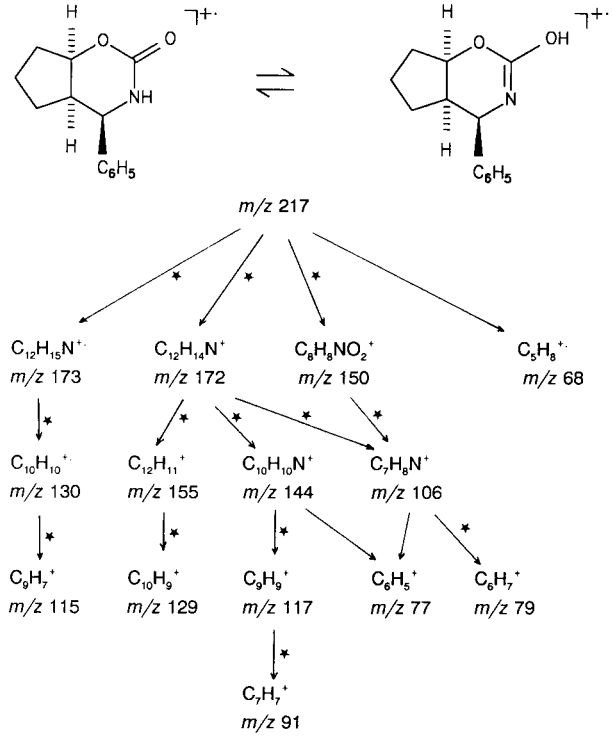


Table 1

The 70 eV Mass Spectra of Compounds **2**, **4** and **6**. Peaks with the Relative Intensities more than 5% from the Base Peak are Shown

Compound	m/z (Relative Intensity)
2	231 (7) $M^{+\bullet}$, 187 (7), 186 (12), 178 (9), 151 (5), 150 (59), 115 (5), 107 (8), 106 (100), 104 (12), 91 (11), 83 (5), 82 (68), 79 (8), 77 (10), 67 (58), 54 (20), 41 (7), 39 (5)
4	248 (19), 247 (100) $M^{+\bullet}$, 172 (6), 171 (33), 170 (9), 167 (6), 166 (55), 129 (16), 123 (7), 117 (8), 115 (7), 106 (45), 105 (57), 104 (36), 92 (5), 91 (29), 81 (8), 79 (14), 78 (7), 77 (12), 67 (10), 54 (5), 41 (7), 39 (5)
6	246 (11), 245 (57) $M^{+\bullet}$, 217 (7), 202 (12), 201 (19), 200 (24), 178 (20), 176 (14), 174 (7), 173 (32), 172 (11), 162 (13), 158 (17), 143 (6), 134 (9), 133 (23), 132 (10), 130 (17), 129 (16), 128 (6), 117 (26), 115 (12), 107 (9), 106 (100), 105 (30), 104 (24), 91 (24), 80 (6), 79 (11), 78 (6), 77 (13), 68 (19), 67 (40), 66 (9), 45 (8), 41 (7)

$C_7H_8N^+$ ion at m/z 106. This pathway was somewhat favored for the cyclopentane-fused compound **1**, probably because of the higher strain in **1** than that in **2**, which was also reflected in the less intense molecular ion peak of the former.

Another important fragmentation led to the formation of the $C_5H_8^{+\bullet}$ and $C_6H_{10}^{+\bullet}$ ions, at m/z 68 and 82 for **1** and **2**, respectively. For compound **1** this ion gave rise to the base peak in the spectrum. For **2** the m/z 82 ion decomposed quite effectively to the $C_5H_7^+$ and $C_4H_6^{+\bullet}$ ions; implying cyclohexene structure [7].

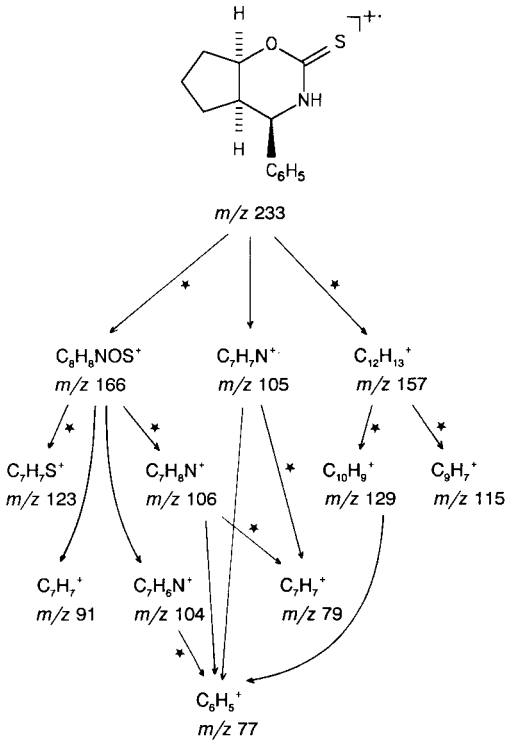
Both primary reactions described above can be rationalized to start as an α-cleavage reaction with respect to the nitrogen atom, in which case the product containing het-

eroatoms, being either ionic or neutral, would be stabilized by conjugation. It is, however, possible that electronic effects of the phenyl group caused some of the molecular ions of compounds **1** and **2** to exist as an enol form (Scheme 2). This assumption is reasonable, although the enol form was not observed in the liquid phase [4], because the enol forms have often been found to be more stable than the keto forms in the gas phase [8]. In this case, the formation of the $C_5H_8^{+\cdot}$ and $C_8H_8NO_2^+$ ions would represent at least formally retro-Diels-Alder (RDA) and (RDA + H) reactions, respectively. This is supported by the fact that related reactions seem to be important for compounds with double bond at the same position of the ring system as the enol form [9].

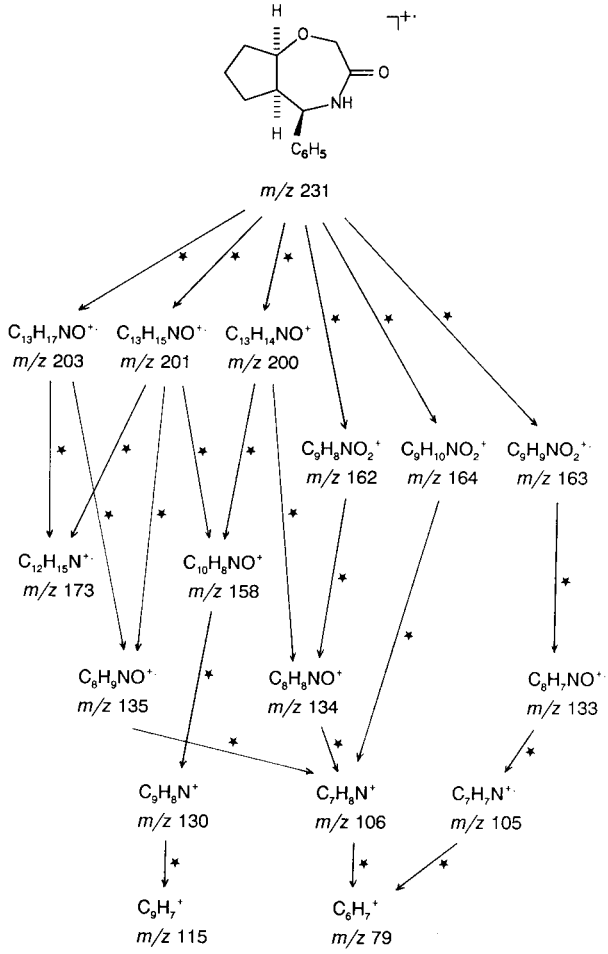
The presence of a thiocarbonyl instead of the carbonyl group had a marked effect on the fragmentation behavior as can be seen from the spectra of compounds **3** and **4** (Figure 1, Table 1). In addition to the increased stability of the molecular ions a larger number of prominent fragment ions were observed than in the case of the related oxo compounds. The most striking difference from compounds **1** and **2** was, however, the practically complete absence of the hydrocarbon ions at m/z 68 and 82 for **3** and **4**, respectively. This either implies that no thienolization took place or that the substitution of the oxygen for the sulfur changed the relative ionization energies for the products so that only (RDA + H) reaction was possible to occur, because $(M-68)^{+\cdot}$ and $(M-82)^{+\cdot}$ ions were missing, which proved that no RDA reaction took place. In any case if the thienol form was present its significance was much smaller than that of the enol form for compounds **1** and **2**. The general fragmentation patterns (Scheme 3) closely resembled those of the related unsubstituted compounds [1]. The role of the hydrocarbon fragments was not, however, so important. Instead, the positive charge tended to remain with the nitrogen containing fragment ions. The most abundant fragment was the $C_7H_7N^{+\cdot}$ at m/z 105, which was formed directly from the molecular ion.

The enlargement of the heterocyclic ring stabilized the molecules of **5** and **6** against electron ionization (Figure 1 and Table 1) relative to **1** and **2**, but not as much as does the thioxo group in **3** and **4**. The introduction of the 2β methyl group in the 1,4-oxazepine ring had practically no effect on the decomposition behavior of **5**. The most important fragmentation pathway was analogous to that observed with the other compounds studied, namely, the

Scheme 3



Scheme 4



successive losses of $C_5H_7^{\cdot}$ and $C_2H_2O_2$ from the molecular ion giving rise to the $C_7H_8N^+$ ion at m/z 106 (Scheme 4). This also was the base peak in the spectra. The eliminations of CO, CH_2O and $CH_3O^{\cdot}$, leading to six- and five-membered ring contraction products, were also important: this seems to be typical of compounds containing seven-membered ring [10,11].

EXPERIMENTAL

Syntheses and structural characterization of the compounds studied have been presented elsewhere [4]. 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 at temperatures 383-443 K. Accurate mass measurements were carried out at a nominal 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 the transmission of the main beam was reduced to 33% of the value in the absence of collision gas.

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