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The mass spectrometric behaviour of twenty saturated heterocyclic compounds with a 1,3-oxazin-4-one moiety fused with *cis* or *trans* anellation to a cycloalkane ring (C_5-C_8) was studied. The roles of the C-2 and N-3 substituent(s) were found to be characteristic, while the size of the cycloalkane ring seemed to be unimportant. Some fragmentation processes involving breakdown of the oxazinone ring of the *cis* or *trans* isomers displayed significant stereoselectivity. A striking new decomposition process involving significant chlorine elimination from the molecular ion of some 2-*p*-chlorophenyl derivatives was observed and was studied in some detail.

Introduction.

Fused ring heterocycles with saturated skeletons (among them oxazines) are important from both theoretical (*e.g.* for conformation analysis) and practical (*e.g.* pharmacological) points of view. Various saturated 1,3-oxazin-4-one derivatives have recently been synthesized by condensation of the appropriate *cis* and *trans* 2-hydroxy-1-carboxamides with aldehydes or ketones [2-4]; nmr spectroscopy and X-ray diffraction studies indicate that the ring closure is stereospecific if an asymmetric centre is formed at position C-2. In this case the smaller substituent at C-2 and the hydrogen atom at C-6 have the same steric orientation [5].
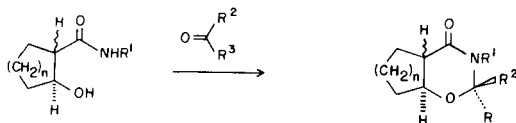
As concerns the mass spectrometric behaviour, no systematic work has appeared on 1,3-oxazines in the literature. A study has been done on the mass spectroscopy of some related unsaturated heterocyclics as 1,2-dihydro-4*H*-2-phenyl-3,1-benzoxazines [6] and a derivative of 4*H*-3,1-benzoxazin-4-one [7]. This fact prompted us to investigate the model compounds **1** to **14** by mass spectrometry to characterize this type of heterocycles, and especially to study the effects of the size of the cycloalkane ring, the nature of the substituents and the stereoisomerism on the electron impact-induced fragmentation. Thus the compounds studied in this paper contain a 5,6 or 7-membered cycloalkane ring with *cis* or *trans* anellation to the oxazinone ring at positions C-5 and C-6; and an aryl substituent, or two methyl groups or a spiro-cycloalkane ring at C-2. Additionally, some *N*-methyl derivatives have been studied for comparison.

4 cis   **4** trans
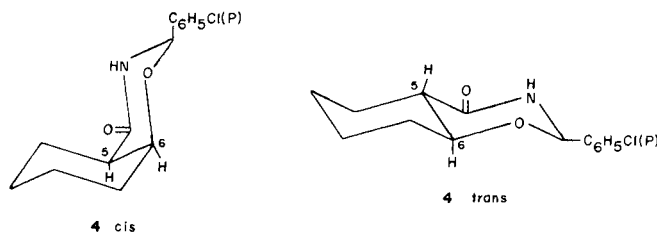
Results and Discussion.

The 70 eV mass spectra of compounds **1** to **14** are depicted in Figures 1 and 4 or given in Table 1. For a more detailed study of the decomposition, low-energy (12 eV) mass spectra, ion kinetic energy (IKE) spectra, and (for some selected ions) daughter ion (B/E) spectra were obtained. When required, elemental compositions of fragment ions were determined by exact mass measurements, and for the diastereomer pair of **4** the NH group was deuterated. To support the proposed decomposition scheme, appearance energy measurements were carried out in some cases.

The main characteristics of the mass spectra are strongly determined by the quality of the substituent(s) at C-2. On this basis the studied compounds can be divided into two main groups: group **A** (where R^2 = aryl and R^3 = H), and group **B** (when R^2 and R^3 are H, CH_3 or a spirocycloalkane ring).

2-Aryl Derivatives (group **A**).

If the C-2 substituent is an aryl (chlorophenyl) group (compounds **1** to **8**), the mass spectra exhibit abundant molecular ion peaks (see Figure 1 and Table 1) and the fragmentation is rather complex. The main common decomposition routes (based on metastable peak studies and on low-energy measurements) are shown in Scheme 1. The observed primary decomposition routes can be divided into three main types: 1) bond cleavage β to the nitrogen atom,

leading to ions **e**, **f** and (at least partly) **j**, and - with H re-arrangement to ions **a**; 2) fragmentation of the oxazinone ring, resulting in ions **g**, **i**, **m** and **n** (see Figure 2); (3) loss of a chlorine atom from the molecular ions, giving rise to ion **k**, which was observed in the spectra of **1-5** as a surpri-singly abundant peak.

Cleavage of the heterocyclic ring is usually accompa-nied by rearrangement of one or more hydrogen atoms. These hydrogens migrate towards both the charged and the neutral fragments, making the spectra more complex (*e.g.* besides ion **n**, ions $(n-2)^+$ and $(M\cdot n+1)^+$ are observed).
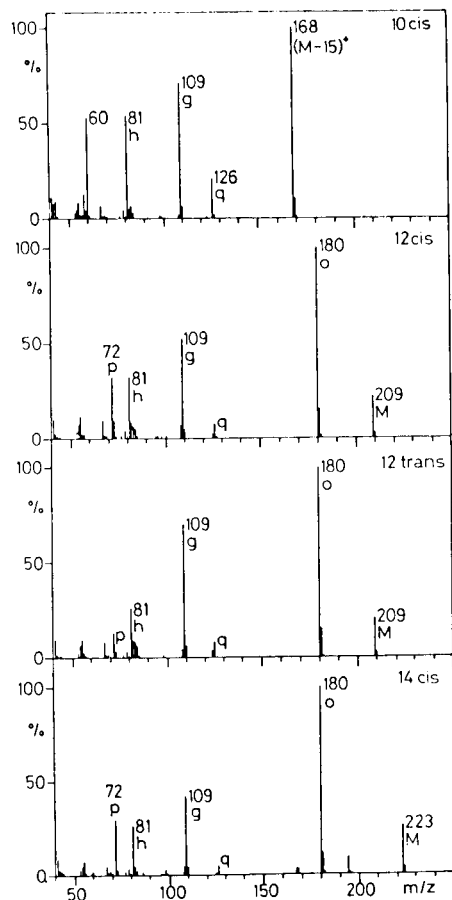

Figure 3. Ion kinetic energy spectra of **4** *cis* and **4** *trans*, obtained at 70 eV.

Figure 1.   70 eV mass spectra of **3** *cis*, **4** *cis*, **4** *trans* and **5** *cis*.
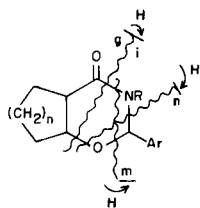
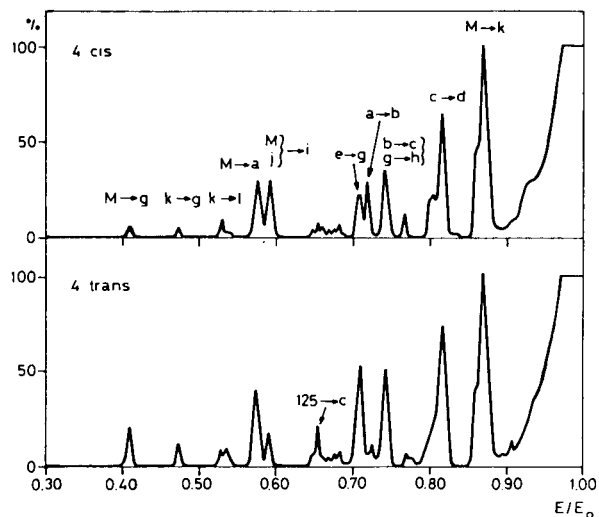Figure 2.   Main decomposition routes of the 1,3-oxazine ring.

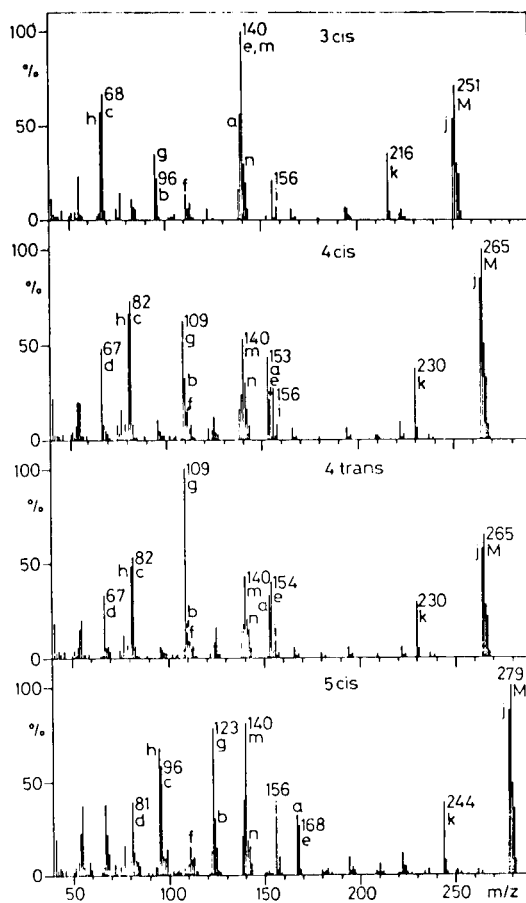

Figure 4.   70 eV mass spectra of **10** *cis*, **12** *cis*, **12** *trans* and **14** *cis*.

Table 1

The 70 eV mass spectra of compounds **1** *cis*, **2** *cis*, **5** *trans*, **6** *cis*, **7** *cis*, **8** *cis*, **9** *cis*, **9** *trans*, **10** *trans*, **11** *cis*, **13** *cis* and **13** *trans*

1 *cis*
m/z (I%):

253 (10), 252 (17), 251 (32), 250 (32), 225 (5), 223 (16), 216 (10), 197 (10), 196 (5), 195 (32), 194 (8), 166 (8), 166 (8), 158 (5), 156 (18), 143 (8), 142 (28), 141 (32), 140 (100), 139 (29), 138 (14), 113 (7), 112 (4), 111 (8), 102 (5), 97 (9), 96 (26), 85 (8), 84 (14), 77 (18), 75 (5), 68 (32), 67 (54), 55 (18), 51 (5), 46 (5), 41 (10)

2 *cis*
m/z (I%):

253 (11), 252 (21), 251 (37), 250 (36), 223 (7), 216 (18), 195 (12), 194 (6), 166 (6), 158 (5), 156 (17), 143 (5), 142 (20). 141 (22), 140 (100), 139 (37), 138 (21), 113 (11), 112 (11), 111 (21), 96 (21), 95 (34), 85 (11), 84 (17), 83 (12), 77 (20), 76 (5), 75 (16), 69 (6), 68 (92), 67 (99), 66 (9), 65 (5), 56 (6), 55 (37), 53 (11), 51 (11), 50 (6), 46 (6), 42 (6), 41 (21), 40 (6)

5 *trans*
m/z (I%):

282 (5), 281 (32), 280 (36), 279 (94), 278 (63), 245 (5), 244 (31), 224 (5), 222 (13), 194 (8), 168 (40), 167 (20), 166 (6), 158 (5), 156 (16), 142 (22), 141 (19), 140 (76), 139 (45), 138 (16), 125 (15), 124 (20), 123 (100), 122 (12), 113 (7), 111 (12), 99 (9), 97 (7), 96 (45), 95 (63), 83 (7), 82 (7), 81 (29), 80 (5), 79 (5), 77 (12), 69 (7), 68 (16), 67 (30), 59 (5), 55 (29), 54 (14), 53 (5), 41 (17)

6 *cis*
m/z (I%):

267 (4), 266 (5), 265 (12), 264 (10), 230 (0.2), 170 (2), 155 (10), 154 (100), 153 (6), 152 (8), 143 (4), 141 (12), 139 (4), 125 (3), 111 (3), 95 (14), 77 (3), 68 (20), 67 (17), 60 (11), 58 (3), 55 (3), 42 (4), 41 (3)

7 *cis*
m/z (I%):

281 (7), 280 (8), 279 (22), 278 (16), 244 (0.2), 170 (5), 169 (10), 168 (100), 167 (6), 154 (9), 152 (8), 143 (5), 141 (14), 139 (6), 111 (5), 110 (8), 109 (23), 82 (17), 81 (15), 67 (20), 60 (8), 54 (8), 42 (5), 41 (5)

8 *cis*
m/z (I%):

295 (15), 294 (18), 293 (44), 292 (19), 258 (0.6), 224 (5), 183 (11), 182 (100), 170 (9), 156 (5), 154 (28), 153 (23), 152 (17), 143 (5), 141 (19), 140 (5), 139 (10), 125 (8), 124 (10), 123 (39), 113 (6), 112 (11), 111 (6), 110 (15), 99 (5), 97 (5), 96 (19), 95 (24), 86 (8), 81 (25), 77 (7), 73 (11), 68 (15), 67 (26), 60 (10), 58 (6), 55 (15), 54 (14), 42 (11), 41 (11)

9 *cis*
m/z (I%):

170 (15), 169 (100), 168 (50), 141 (7), 140 (6), 127 (5), 126 (8), 115 (7), 114 (73), 113 (5), 112 (5), 110 (16), 109 (49), 108 (5), 100 (5), 99 (6), 98 (10), 84 (5), 83 (8), 82 (14), 81 (45), 80 (5), 79 (8), 70 (8), 69 (6), 68 (5), 67 (50), 60 (29), 59 (5), 58 (9), 55 (20), 54 (20), 53 (6), 45 (5), 44 (76), 43 (20), 42 (25), 41 (15)

9 *trans*
m/z (I%):

170 (11), 169 (70), 168 (100), 126 (9), 125 (5), 114 (5), 110 (9), 109 (59), 108 (6), 99 (5), 98 (14), 97 (5), 84 (7), 83 (8), 82 (26), 81 (39), 80 (6), 79 (6), 71 (5), 70 (10), 69 (7), 68 (5), 67 (34), 60 (14), 58 (12), 57 (9), 55 (25), 54 (17), 53 (5), 45 (10), 44 (78), 43 (18), 42 (22), 41 (18)

10 *trans*
m/z (I%):

183 (0.1), 169 (11), 168 (100), 126 (19), 110 (5), 109 (59), 83 (6), 82 (6), 81 (59), 79 (5), 67 (9), 60 (54), 59 (6), 58 (18), 54 (11), 53 (6), 43 (15), 42 (14), 41 (19)

11 *cis*
m/z (I%):

195 (21), 167 (14), 166 (100), 112 (9), 95 (46), 94 (6), 84 (7), 83 (5), 82 (5), 73 (10), 72 (38), 68 (30), 55 (10), 54 (5), 41 (11)

Table 1, continued

13 *cis*
m/z (I%):

223 (28), 195 (16), 194 (100), 140 (8), 123 (45), 110 (7), 109 (59), 108 (6), 96 (7), 95 (39), 84 (13), 83 (6), 82 (7), 81 (40), 79 (7), 73 (11), 72 (32), 68 (6), 67 (23), 56 (7), 55 (39), 54 (19), 53 (10), 42 (6), 41 (23)

13 *trans*
m/z (I%):

223 (20), 195 (18), 194 (100), 140 (6), 124 (6), 123 (64), 122 (5), 96 (6), 95 (36), 84 (9), 81 (9), 73 (6), 72 (20), 68 (5), 67 (17), 55 (29), 54 (11), 53 (6), 41 (19)

[a] All peaks of abundance not less than 5% are given.
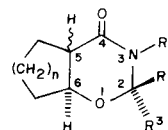
| Compound	n	R¹	R²	R³
1 *cis*	1	H	H	2-Cl-Ph
2 *cis*	1	H	H	3-Cl-Ph
3 *cis*	1	H	H	4-Cl-Ph
4 *cis*	2	H	H	4-Cl-Ph
4 *trans*	2	H	H	4-Cl-Ph
5 *cis*	3	H	H	4-Cl-Ph
5 *trans*	3	H	H	4-Cl-Ph
6 *cis*	1	CH₃	H	4-Cl-Ph
7 *cis*	2	CH₃	H	4-Cl-Ph
8 *cis*	3	CH₃	H	4-Cl-Ph
9 *cis*	2	CH₃	H	H
9 *trans*	2	CH₃	H	H
10 *cis*	2	H	CH₃	CH₃
10 *trans*	2	H	CH₃	CH₃
11 *cis*	1	H	-(CH₂)₅-	
12 *cis*	2	H	-(CH₂)₅-	
12 *trans*	2	H	-(CH₂)₅-	
13 *cis*	3	H	-(CH₂)₅-	
13 *trans*	3	H	-(CH₂)₅-	
14 *cis*	2	H	-(CH₂)₆-	

Comparison of the mass spectra of compounds **3** *cis*, **4** *cis* and **5** *cis* (see Figure 1) reveals that the size of the fused cycloalkane ring has practically no effect on the main primary decomposition routes. Even the abundance ratios of the main common primary fragment types are similar. This is in accordance with the observation that the cycloalkane ring remains intact in these fragments. At the same time the extent of fragmentation of ions **c, d** and **h** varied significantly with the ring size; the breakdown is more extensive when the cycloalkane ring is larger.

Some insignificant alkyl losses occur from the molecular ions (propyl and butyl groups from the cyclohexyl and the cycloheptyl rings, respectively; the common 28 m/z elimination is CO), but their abundance is less than 1 Σ%.

The presence of a methyl substituent on the nitrogen atom (compounds **6** *cis*, **7** *cis* and **8** *cis*) has a very strong effect on the mass spectra. Such large effects have been observed for other compounds which contain several

Scheme 1
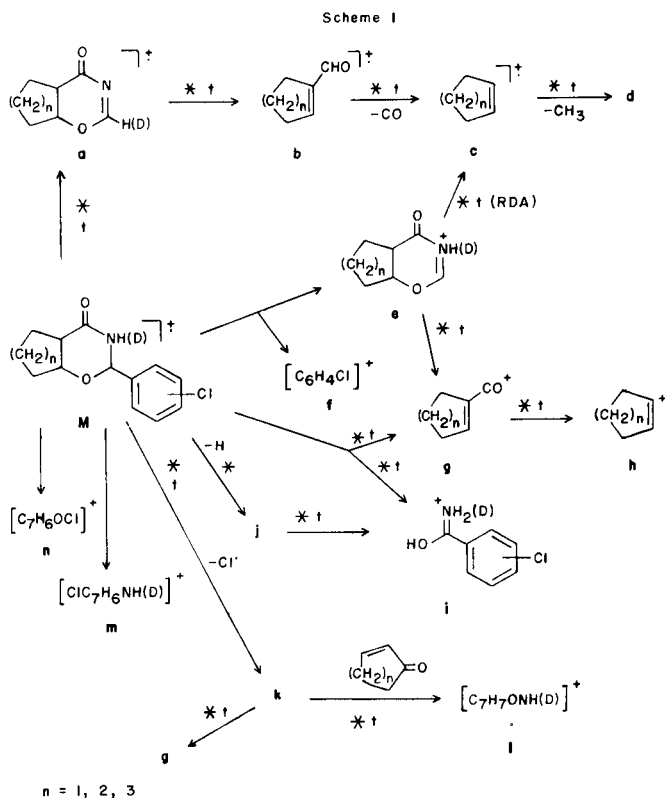
n = 1, 2, 3

Fragmentation routes for **1-5**; n = 1, 2, 3. * denotes 2nd, and † denotes 1st FFR metastable transitions. The latter was observed for the diastereomer pair of **4**. D-Labelling was accomplished for **4**; where indicated, the label is higher than 90%.

Scheme 2
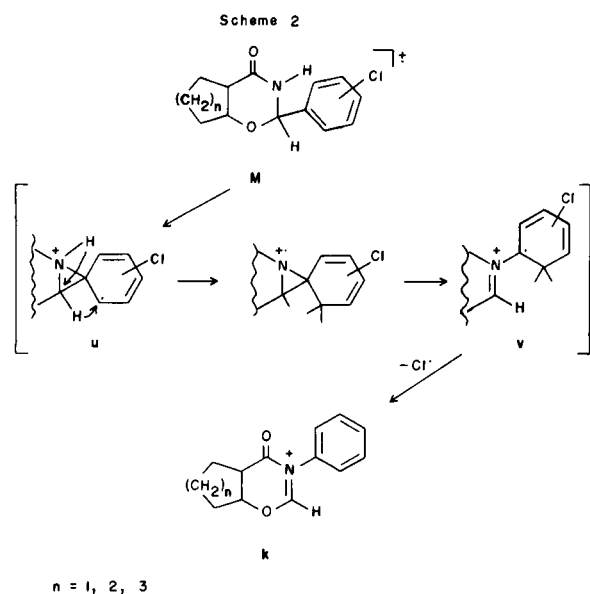
n = 1, 2, 3

Proposed mechanism for Cl· elimination from the molecular ions of **1-5**; n = 1, 2, 3.

Scheme 3
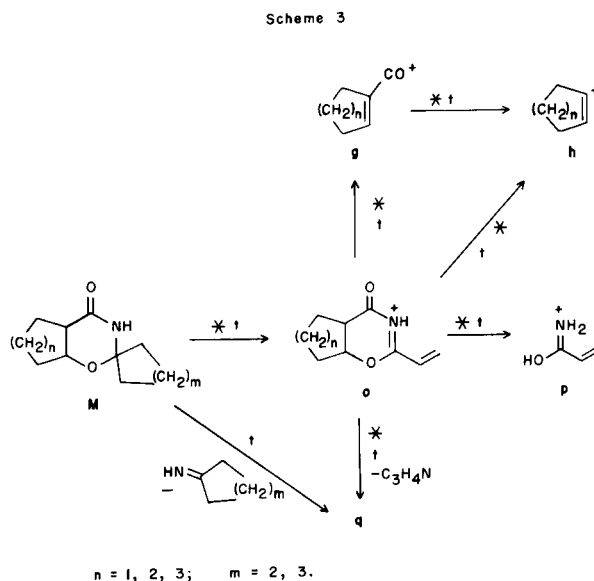
n = 1, 2, 3;   m = 2, 3.

Fragmentation routes for **11-14**; n = 1, 2, 3; m = 2, 3. * denotes 2nd, and † denotes 1st FFR metastable transitions. The latter was observed for the diastereomer pair of **12**.

Table 2

Daughter Ion Spectra (B/E scan) of the Molecular Ions (m/z 265) of **4** cis and **4** trans

	ABD %	
m/z	**4** cis	**4** trans
250	0.2	—
248	0.2	—
237	2	2
230	100	100
222	0.4	0.4
156	20	8
153	35	48
140	0.2	0.4
139	0.3	0.4
127	—	0.2
126	—	0.1
125	—	0.2
109	10	21
81	0.3	0.3

hetero atoms [8]. In this case ion **k** is practically not observable, and the formation and structure of ion **a** are different. Furthermore, the abundance of ion **e**, formed by elimination of the aryl group (cleavage β to nitrogen), increases about sevenfold as compared to those for **3** cis, **4** cis and **5** cis. This effect seems to be connected with the greater basicity of the N-methyl derivatives, leading to a significant decrease in the energy requirement of this process. (In the case of **7** cis the AE-IE value for loss of the aryl radical is 72 ± 20 kJ mol^{-1}, while for **4** cis it is 180 ± 50 kJ mol^{-1}).

Another interesting effect of the N-methyl group is that the chlorine elimination practically ceases (it is decreased about 50 times). Obviously, this is not a single substituent effect, it will be discussed below.

The observation of significant Cl· elimination of the molecular ion with a p-chlorophenyl group (formation of ion **k**) is quite striking. For example no analogue process is observable in the mass spectra of the related 1,2-di-hydro-4H-2-p-chlorophenyl-3,1-benzoxazine [6]. We therefore decided to investigate this process more thoroughly. It was found to be accompanied by a very abundant metastable peak (see Figure 2) and its energy requirement is very low (the AE-IE value is only 85 ± 20 kJ mol^{-1} for **4** cis), which suggests a rearrangement reaction.

Furthermore, a significant effect of the position of the chlorine atom was not observed (the abundance ratios for (M-Cl)/M (**k**/M) were found to be very close to one another (0.35, 0.48, 0.49) for the $ortho$ (**1** cis), $meta$ (**2** cis) and $para$ (**3** cis) isomers, respectively).

As the dauthter ion (B/E scan) spectrum of **k** revealed (**4** cis), further decomposition of ion **k** led mainly to ions **g** and **l** (see Scheme 1). This makes the participation of the carbonyl group in this rearrangement process unlikely.

It is of interest that Cl· elimination does not occur where there is no hydrogen at C-2 or at N-3, as was observed in the mass spectra of 2-(p-chlorophenyl)-5,6-tetramethylene-1,2,3,4-tetrahydro-1,3-thiazin-4-one [9] and compounds **6-8**.

These findings substantially restrict the possible alternatives for the mechanism of this process. We put forward the proposal shown in Scheme 2. In intermediate ions **u** and **v** hydrogen (and Cl·) migrations can take place easily, and from ion **v** mainly Cl· will be lost, as this is energetically more favourable than H· loss. This mechanism explains the low activation energy, the abundant metastable peak, the close similarity of the mass spectra of $ortho$, $meta$ and $para$ isomers, the further decomposition routes of ion **k** and, most importantly, the necessity of C-2 and N-3 hydrogens for this process.

A comparison of the mass spectra of the cis and $trans$ isomers of group **A** (Figure 1 and Table 1) reveals significant differences in the relative abundances of several ions. The differences are also significant in the IKE spectra and in the daughter ion (B/E) spectra of the molecular ions, as can be seen in Figure 3 and Table 2, where these data for the isomeric pair **4** cis and **4** $trans$ are presented as a typical example. The largest and most characteristic differences are observed for the relative abundance of ion **g**, the formation of which involves a hydrogen migration from the cycloalkane ring to one of the ring heteroatoms which remove with the neutral fragment. Scheme 1 shows that ion **g** can be formed from M$^{+·}$ but also from ions **e** and **k**. The relative abundances of the corresponding metastable ions, as well as that of ion **g** in the normal spectra, are

significantly higher for the $trans$ isomers. No energetic reason was found which could account for this phenomenon: the energy requirement of the formation of ion **g** from the molecular ion is comparatively high and is practically the same for cis and $trans$ isomers (the AE-IE value is 290 ± 40 kJ mol^{-1} for both diastereomers of **4**).

The observed stereochemical effect can be explained by assuming easier access to a hydrogen atom of the cycloalkane ring in the case of the $trans$ isomers. From the steric structures of the stereoisomers (see, for example, those of diasteromers **4** cis and **4** $trans$, it can be concluded that the C-5 hydrogen atom migrates to the ring oxygen or nitrogen atom in this process. Besides ion **g**, its formally complementary ion **i** shows a strong, but opposite stereochemical effect: its abundance is lower for the $trans$ isomer, both as a metastable and as a normal ion. This, together with the fact that the ionization efficiency curves for **i** are very flat for both isomers, indicates the possibility of several distinct routes for the formation of **i**.

2-Alkyl Derivatives (group **B**).

The mass spectra and the fragmentation of the compounds in this group (see Figures 4 and Table 1) are much simpler and the molecular ions have much lower stability than found in group **A**. The decomposition starts almost exclusively with C_2-R^2 (C_2-R^3) bond cleavage (β to the nitrogen atom). When R^2 = R^3 = CH$_3$, the abundance of the molecular ion is only 0.1%, and nearly all the further fragments are produced from the (M-CH$_3$)$^+$ ion. For compounds having a spirocycloalkane ring, the main decomposition routes are depicted in Scheme 3. In this case the primary step is the opening of the cycloalkane ring at the spiro carbon atom, which is followed by the loss of an alkyl radical (formation of ion **o**).

For compound **14** cis, besides the main process of **o** ion formation (*i.e.* propyl radical elimination), loss of an ethyl radical takes place. The further decomposition of ion **o** (compounds **11-14**) and that of (M-CH$_3$)$^+$ (compounds **10**) consists mainly of the breakdown of the oxazinone ring *via* the processes also observed for group **A**, *i.e.* giving rise to the same or analogous ions (**g** and **h**, and **p** and **q**, respectively).

The effect of the size of the fused cycloalkane ring on the fragmentation is very similar for groups **A** and **B**.

At the same time, the stereoisomeric effects in group **B** are much less significant than for the 2-aryl derivatives. Although some stereoselectivity of the same sign is observable, especially for the formation of ion **g**, the extent of this selectivity is much smaller. (For example, in the cases of the diastereomer pairs of **4**, **10** and **12** the (**g**/M)$_{trans}$/(**g**/M)$_{cis}$ ratios are 2.5, 1.2 and 1.5, respectively). This is obviously due to the dominating role of the homolytic cleavage of a substituent at C-2 as a primary fragmentation process in the case of group **B**. Thus, in this group the forma-

tion of ion **g** takes place mostly as a secondary decomposition step, which seems to be less stereoselective than its formation *via* a direct process, *i.e.* from the intact molecular ion.

EXPERIMENTAL

Compounds.

Synthetized as stereohomogeneous *cis* and *trans* compounds by methods described in refs [2-4].

Mass spectrometry.

Mass spectrometric measurements were carried out using an AEI MS 902 double focusing mass spectrometer. Typical operating conditions were as follows: electron energy, 70 and 12 eV; accelerating voltage, 8 kV; electron trap current, 100 μA; source temperature, 130°. Samples were introduced *via* a direct inlet system, without external heating. Exact mass measurements were performed with an accuracy of at least 3 ppm, at a resolving power of 10,000. The energetic measurements were carried out using a trap current of 10 μA, with benzene (IE: 908 kJ mol⁻¹) as internal standard. The ionization and appearance energy values were determined by the semilog-plot method, with a reproducibility better than 10 kJ mol⁻¹. IKE spectra were recorded by changing the electric analyser voltage. E/E_0 values were obtained with an accuracy better than 0.2%. When required, mass analyses of the peaks were also performed. Daughter ion spectra were recorded by changing the magnetic field while keeping the B/E ratio constant.

The measured ionization and appearence energy values of some compounds (m/z (IE or AE, in kJ mol⁻¹)): **4** *cis:* 265, M (870), 230 (950), 156 (too flat to be determined), 154 (1050 ± 50, inaccurate due to the isotopic component with m/z 153), 153 (959), 109 (1139); **4** *trans:* 265, M (869), 156 (too flat to be determined), 109 (1159), **7** *cis:* 279, M (844), 168 (914), 167 (917).

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