# Mass Spectrometric Intramolecular Cyclization Reactions of Some 2-*N*-Phenyliminoperhydro-1,3-oxazines



Pirjo Vainiotalo*

Department of Chemistry, University of Joensuu, P. O. Box 111, SF-80101 Joensuu, Finland

Ferenc Fülöp and Gábor Bernáth

Institute of Pharmaceutical Chemistry, University Medical School, H-6720 Szeged, Hungary

Kalevi Pihlaja*

Department of Chemistry, University of Turku, SF-20500 Turku, Finland

Received November 28, 1988

Mass spectrometric fragmentation of four monocyclic and eight condensed skeleton 2-*N*-phenyliminoperhydro-1,3-oxazine derivatives have been characterized by metastable ion analysis, collision induced dissociation measurements, exact mass measurements and ion structural studies. Extensive rearrangement reactions, best characterized in terms of intramolecular cyclizations, took place. Namely, when R = H the *N*-cyclization was almost exclusive whereas in cases where R > H steric reasons rendered the *O*-cyclization more feasible. Part of the fragmentation of the R = H compounds seemed to occur *via* the amino form. On the other hand the methane chemical ionization spectra of *cis*- and *trans*-anellated 5,6-trimethylene-2-*N*-phenyliminoperhydro-1,3-oxazines proved that at least some imino structure was present in the gas phase.

*J. Heterocyclic Chem.*, **26**, 1453 (1989).

## Introduction.

The synthesis, reactivity and conformational analysis of 2-imino-substituted 1,3-heterocycles, especially 1,3-oxazoles, 1,3-oxazines, 1,3-thiazoles, and 1,3-thiazines, have been extensively studied in recent years [1-6]. They are important both as interesting models for structural investigations and as potential pharmacons [7,8]. However, the scarcity of papers concerning the mass spectrometric behaviour of these compounds is salient.

As a continuation of our mass spectrometric studies [9,10] on different 1,3- and 3,1-oxazine derivatives we have examined mass spectrometric fragmentations of twelve 2-*N*-phenyliminoperhydro-1,3-oxazine derivatives **1-12** under electron impact. According to the ir and nmr results these compounds have the imino structure at least in condensed phase [5]. Our purpose was to find out does any imino ‖ amino tautomerism occur with these compounds and how the ring condensation and its stereochemistry affect their behaviour under the conditions of the mass spectrometer. They all showed extensive rearrangement reactions which are best rationalized in terms of intramolecular cyclizations. This was verified by ion structural studies. Fragmentation pathways have been examined with metastable ion analysis and collision induced dissociation measurements. Elemental compositions of principal ions have been confirmed using exact mass measurement.

## Results and Discussion.

The EI mass spectra of the compounds studied showed several interesting features (Table 1, Figures 1 and 2). All compounds gave rise to relatively intense molecular ion peak. For compounds **2-4** and **12** it was even the base peak in the spectrum. The principal fragmentation routes were initiated by loss of H· or $CH_3$· depending on *o*-substitution of the 2-*N*-phenyl substituent. This indicated that the eli-

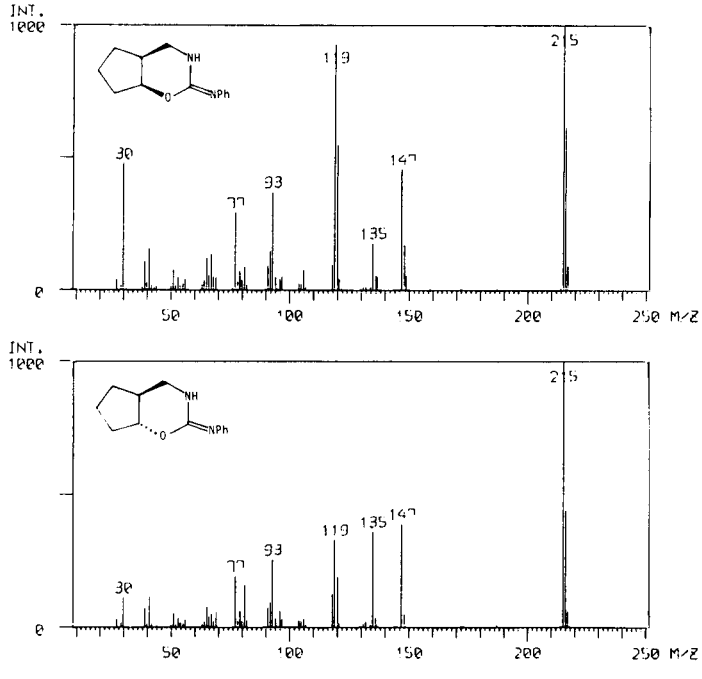



Figure 1. Electron impact mass spectra of *cis*- and *trans*-2-phenylimino-5,6-trimethylene-perhydro-1,3-oxazines **5** and **6**, respectively.

Table 1

The 70 eV Mass Spectra of the Compounds Studied. Peaks with the Relative Intensities [m/z (Rel Int)] more than 5% from the Base Peak are shown

Compound **1**

177 (5), 176 (45), 175 (100), 147 (31), 120 (26), 119 (40), 118 (5), 106 (5), 92 (14), 91 (9), 77 (24), 65 (10), 56 (8), 51 (8), 39 (5)

Compound **2**

191 (15), 190 (100), 189 (30), 176 (8), 175 (65), 161 (18), 148 (7), 147 (31), 146 (8), 145 (9), 134 (14), 133 (38), 132 (16), 131 (5), 118 (9), 107 (7), 106 (24), 104 (17), 91 (25), 79 (6), 78 (9), 77 (14), 65 (12), 58 (6), 57 (6), 56 (9), 51 (5), 41 (5), 39 (7), 30 (21)

Compound **3**

205 (15), 204 (100), 190 (13), 189 (98), 174 (6), 162 (6), 161 (52), 160 (11), 159 (13), 148 (8), 147 (35), 146 (18), 145 (8), 133 (6), 132 (12), 131 (8), 120 (17), 119 (22), 118 (12), 105 (10), 103 (6), 92 (6), 91 (14), 79 (6), 77 (15), 65 (6), 58 (9), 57 (7), 56 (7), 41 (6), 39 (6), 30 (18)

Compound **4**

191 (14), 190 (100), 189 (45), 161 (15), 149 (10), 146 (14), 132 (20), 120 (11), 119 (49), 118 (25), 106 (9), 105 (15), 104 (18), 99 (6), 92 (6), 91 (17), 86 (5), 81 (6), 77 (16), 71 (7), 70 (16), 69 (5), 64 (6), 57 (9), 56 (7), 55 (10), 51 (5), 44 (10), 42 (25), 41 (13), 39 (5), 30 (5)

Compound **9**

231 (8), 230 (53), 229 (100), 149 (6), 148 (18), 147 (40), 136 (9), 135 (20), 120 (48), 119 (74), 106 (6), 95 (9), 94 (7), 93 (40),92 (12), 91 (8), 79 (6), 77 (24), 67 (13), 65 (9), 55 (6), 54 (7), 51 (6), 41 (14), 39 (8), 30 (38)

Compound **10**

231 (6), 230 (42), 229(100), 148 (8), 147 (40), 135 (29), 120 (24), 119 (38), 118 (5), 95 (11), 94 (5), 93 (23), 92 (8), 91 (5), 77 (15), 67 (8), 65 (6), 41 (11), 39 (7), 30 (14)

Compound **11**

245 (10), 244 (57), 243 (20), 200 (6), 162 (7), 161 (15), 149 (10), 132 (6), 124 (6), 120 (14), 119 (100), 118 (11), 106 (8), 96 (9), 95 (9), 94 (7), 93 (46), 92 (6), 91 (18), 81 (6), 79 (7), 77 (12), 67 (15), 66 (10), 65 (8), 64 (6), 57 (5), 55 (7), 54 (6), 44 (85), 43 (18), 41 (15), 39 (10), 30 (5)

Compound **12**

245 (17), 244 (100), 243 (51), 200 (9), 162 (7), 161 (31), 149 (31), 132 (15), 124 (7), 120 (11), 119 (38), 118 (23), 110 (6), 106 (46), 105 (11), 104 (5), 96 (12), 95 (12), 93 (15), 91 (14), 81 (9), 79 (5), 77 (14), 68 (5), 67 (18), 57 (8), 55 (10), 44 (22), 43 (12), 42 (21), 41 (15), 39 (6), 30 (6)

Compound **13**

114 (54), 58 (100), 57 (17), 56 (19), 55 (6), 42 (10), 30 (34), 29 (6), 28 (7), 15 (9)

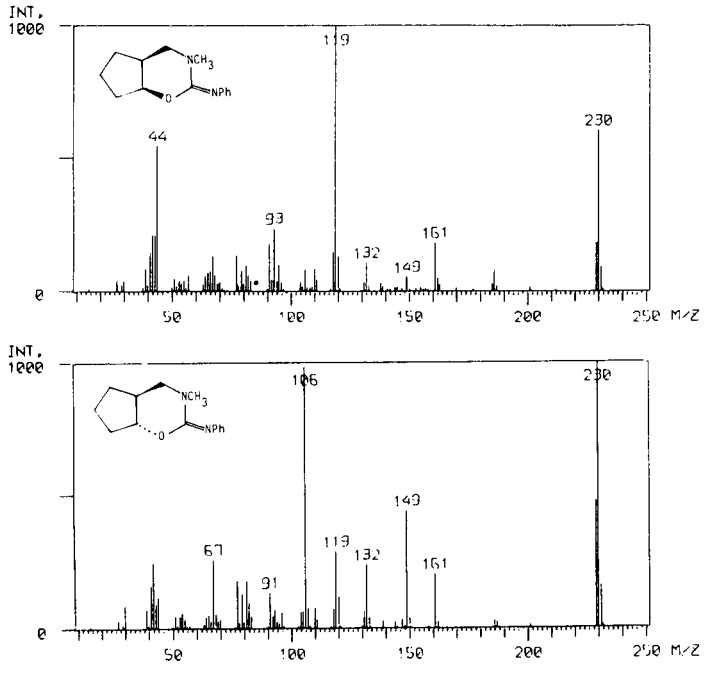
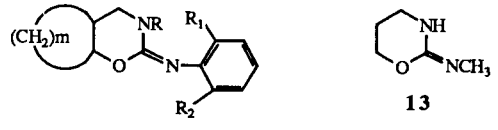



Figure 2. Electron impact mass spectra of *cis*- and *trans*-2-phenylimino-3-methyl-5,6-trimethyleneperhydro-1,3-oxazines **7** and **8**, respectively.

mination took place from the phenyl ring. The consequent fragmentation reactions of the ion so formed are best to rationalize in terms of simultaneous intramolecular cyclizations. Bujtás and Tamás [11] have proposed related cyclization reactions in connection of some 2-arylaminothiazine and -thiazoline derivatives. They suggested that the ring closure could take place either through the nitrogen or sulphur atom. With our compounds the type of cyclization seemed to depend on the substitution (R) at the nitrogen atom. For this reason the following discussion is divided into two parts.

R = H.

The main fragmentation routes for compounds **5** and **6** are presented in Scheme 1. In principle they applied to all compounds where R = H, although the importance of different routes varies. In spite of the same fragment ions *cis*- and *trans*-anellated isomers were easy to differentiate because the ion intensities differ so much. In the case of compounds **1, 5, 6, 9** and **10** the most important fragmentation channel was the loss of H· from the molecular ion. That this hydrogen atom originated from the *o*-position of the phenyl ring can be seen from the spectrum of compound **3**. It has no *o*-hydrogen atoms and in its spectrum there was practically no $[M-H]^+$ ion peak. Instead of hydrogen this compound eliminated methyl radical as its main primary fragmentation reaction. With compound **2** having both *o*-methyl and *o*-hydrogen the loss of both groups was relatively important. The ions so formed further eliminated $C_nH_{2n-2}$ and $CH_2N$ forming ion $[C_7H_5NO]^+$ at m/z 119. That the phenyl substituent played an important role within this fragmentation channel can also be seen from the spectrum of 2-*N*-methylimino derivative (compound **13**) where the lack of phenyl substituent caused the total absence of this fragmentation route.



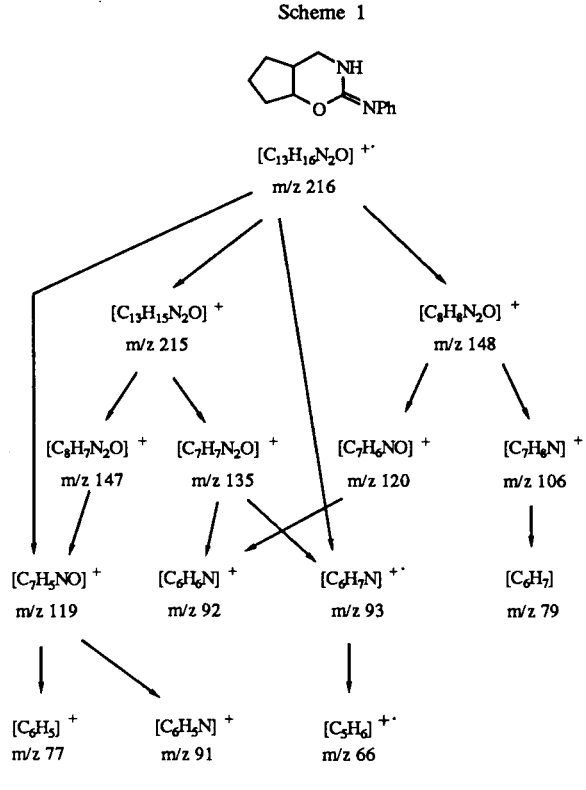




**13**

| | m | R | $R_1$ | $R_2$ | Ring fusion |
|---|---|---|---|---|---|
| **1** | 0 | H | H | H | |
| **2** | 0 | H | Me | H | |
| **3** | 0 | H | Me | Me | |
| **4** | 0 | Me | H | H | |
| **5** | 3 | H | H | H | *cis* |
| **6** | 3 | H | H | H | *trans* |
| **7** | 3 | Me | H | H | *cis* |
| **8** | 3 | Me | H | H | *trans* |
| **9** | 4 | H | H | H | *cis* |
| **10** | 4 | H | H | H | *trans* |
| **11** | 4 | Me | H | H | *cis* |
| **12** | 4 | Me | H | H | *trans* |

Scheme 1




The formation of ion $[C_7H_5NO]^+$· at m/z 119 is postulated in Scheme 2. It is an odd electron ion which is formed in large quantities from an even electron ion. This means that it has to have a very stable structure as the ion in Scheme 2 has. The formation of this structure requires the imino structure to rearrange to the amino structure before or during the cyclization process. This rearrangement reaction also explains well the consequent retro-Diels-Al-

Table 2

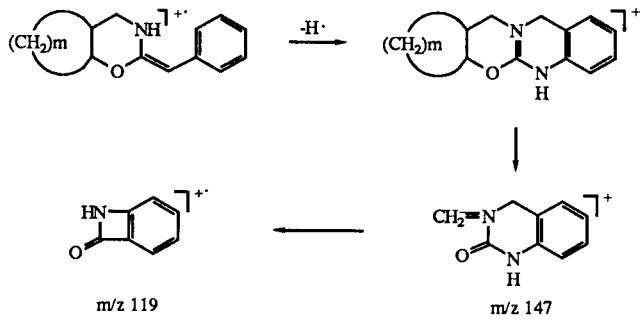
The CID Spectra of the m/z 119 Ions Generated from different precursors. Intensities are Normalized to a Total Fragment Ion Abundance = 100. The data are not corrected for Metastable Peaks (**M1** phenyl isocyanate, **M2** benzo-1,3-oxazole)

| m/z | M1 | M2 | 1 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 27 | - | - | - | 0.7 | - | - | - | - | - | - | - | 0.7 | 0.8 |
| 28 | - | - | - | - | - | - | - | - | - | - | - | 0.6 | 0.7 |
| 37 | 0.9 | 1.6 | 1.3 | 1.0 | 0.8 | 1.4 | 1.4 | 1.5 | 1.3 | 1.3 | 1.3 | 1.5 | 1.3 |
| 38 | 1.6 | 1.0 | 2.2 | 2.5 | 0.9 | 2.5 | 2.2 | 2.4 | 2.2 | 2.2 | 2.2 | 2.3 | 1.9 |
| 39 | 2.2 | 1.0 | 2.8 | - | 2.0 | 3.4 | 3.0 | 3.3 | 2.9 | 3.0 | 3.0 | 3.5 | 3.5 |
| 40 | - | - | 0.5 | - | - | 0.6 | 0.6 | 0.6 | 0.6 | 0.5 | 0.6 | 0.7 | 0.7 |
| 41 | - | - | - | - | - | - | - | 0.5 | - | - | - | 1.1 | 1.7 |
| 42 | - | - | - | - | - | - | - | - | - | - | - | 1.2 | 2.1 |
| 44 | - | - | - | - | - | - | - | - | - | - | - | 0.6 | 0.8 |
| 49 | - | - | 0.7 | - | - | 0.7 | 0.8 | 0.7 | 0.8 | 0.7 | 0.7 | 0.7 | 0.8 |
| 50 | 2.3 | 3.2 | 4.0 | 2.9 | 2.5 | 4.2 | 4.1 | 3.7 | 3.9 | 4.0 | 4.0 | 3.3 | 3.6 |
| 51 | 3.8 | 3.5 | 5.0 | 1.1 | 3.6 | 5.7 | 5.2 | 4.9 | 4.9 | 5.3 | 5.2 | 4.7 | 4.6 |
| 52 | 1.9 | 2.0 | 2.1 | 2.5 | 1.5 | 2.3 | 2.3 | 2.4 | 2.2 | 2.1 | 2.2 | 2.3 | 2.1 |
| 53 | - | 1.0 | - | 1.5 | - | - | - | - | - | - | - | - | 0.7 |
| 55 | - | - | - | - | - | - | - | - | - | - | - | - | 0.6 |
| 61 | - | 1.1 | 0.7 | - | - | 0.6 | 0.7 | 0.9 | 0.9 | 0.6 | 0.7 | 0.8 | 0.9 |
| 62 | 1.3 | 3.8 | 1.5 | 1.2 | 1.3 | 1.5 | 1.7 | 2.1 | 1.9 | 1.4 | 1.5 | 2.0 | 2.1 |
| 63 | 7.0 | 15.2 | 4.7 | 3.1 | 4.5 | 5.0 | 4.9 | 6.8 | 5.4 | 4.7 | 4.8 | 6.4 | 5.4 |
| 64 | 10.9 | 11.5 | 5.3 | 1.4 | 4.9 | 6.4 | 5.3 | 8.4 | 5.7 | 5.8 | 5.5 | 7.8 | 4.8 |
| 65 | 2.4 | 1.9 | 4.1 | 5.0 | 2.5 | 3.9 | 4.0 | 2.7 | 3.4 | 3.9 | 4.0 | 2.7 | 3.0 |
| 66 | - | - | 0.5 | 1.5 | - | - | 0.6 | - | 0.5 | - | 0.5 | - | - |
| 74 | - | - | 1.0 | 0.8 | 0.6 | 0.9 | 1.1 | 0.8 | 1.1 | 0.9 | 1.0 | 0.8 | 1.0 |
| 75 | 0.8 | - | 1.1 | 1.0 | 0.7 | 1.0 | 1.2 | 1.0 | 1.1 | 1.0 | 1.1 | 0.9 | 1.0 |
| 76 | 1.2 | 1.3 | 4.0 | 1.3 | 2.1 | 3.9 | 4.0 | 1.8 | 3.3 | 4.3 | 4.3 | 1.7 | 2.4 |
| 77 | 2.4 | - | 20.6 | 8.7 | 9.8 | 19.9 | 19.4 | 5.6 | 14.1 | 21.3 | 20.1 | 5.4 | 9.2 |
| 78 | - | - | 2.1 | 2.9 | 1.4 | 1.6 | 2.1 | 0.8 | 1.9 | 1.9 | 2.0 | 0.9 | 1.6 |
| 88 | - | - | - | - | - | - | - | 0.5 | 0.5 | - | - | 0.5 | - |
| 89 | - | - | - | 4.1 | 3.9 | - | - | - | 1.8 | - | - | 2.1 | 4.3 |
| 90 | 13.1 | 10.8 | 5.3 | 3.8 | 8.1 | 6.9 | 5.9 | 11.4 | 7.1 | 6.7 | 6.3 | 11.0 | 8.1 |
| 91 | 45.1 | 33.1 | 15.5 | 21.8 | 24.2 | 16.1 | 15.6 | 29.5 | 19.8 | 15.5 | 15.5 | 28.8 | 20.3 |
| 92 | 3.1 | 8.0 | 13.9 | 9.0 | 6.5 | 10.6 | 12.6 | 3.7 | 9.5 | 11.9 | 12.3 | 3.7 | 6.1 |
| 93 | - | - | 1.2 | 4.2 | 0.6 | 0.8 | 1.2 | - | 1.2 | 0.9 | 1.1 | - | 0.7 |

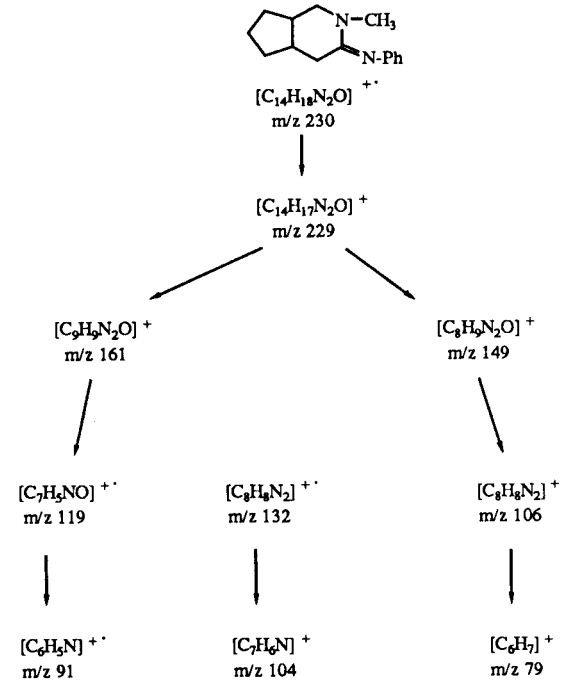
Table 2 (continued)

| m/z | M1 | M2 | 1 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 102 | - | - | - | 1.6 | 0.6 | - | - | - | - | - | - | - | - |
| 103 | - | - | - | 3.1 | 1.2 | - | - | 0.6 | 0.6 | - | - | 0.6 | 0.6 |
| 104 | - | - | - | 5.4 | 14.5 | - | - | 0.9 | 1.4 | - | - | 0.7 | 2.0 |

Scheme 2



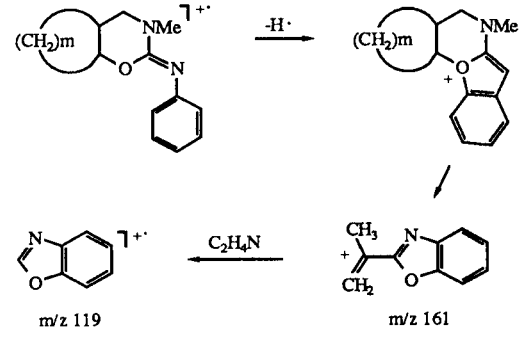

Scheme 3



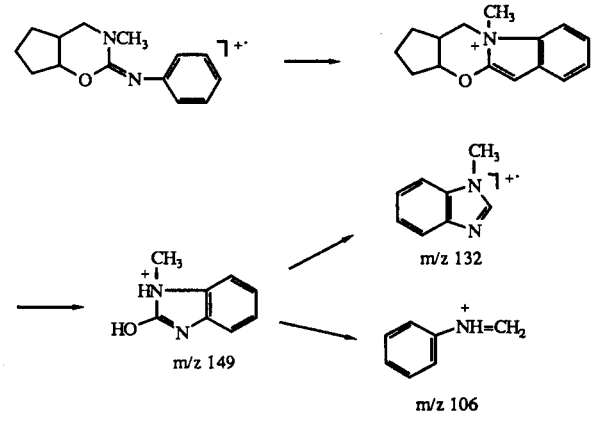

der (RDA) elimination of $C_5H_8$. The elimination was rather stereospecific favouring *cis*-isomer over *trans*-isomer, which shows that a concerted RDA process is dominant [12]. For *trans*-isomer the formation of the $[C_7H_7N_2O]^+$ ion of m/z 135 is more favourable than for the *cis*-isomer (Figure 1). Of course, it is possible that the ion of m/z 119 is formed without imino-amino rearrangement. In this case, however, the ion of m/z 147 should also eliminate hydroxyl radical (*c.f.* Scheme 5), which does not occur. Furthermore its decomposition to the ion of m/z 119 would lead to the oxazolidine structure (*c.f.* Scheme 4). However, the data in Table 2 show that this cannot be true. Although it is not possible completely to rule out oxazolidine and phenyl isocyanate structures the main contribution to the structure of the ion of m/z 119, generated from compounds **5** and **6** is something else. The direct cleavage of the N-C(2) and O-C(7a) bond would lead to the formation of phenyl isocyanate.

Another important fragmentation route started with loss of $C_5H_8$ directely from molecular ion. This elimination can start as $\alpha$-cleavage with respect to the ring nitrogen atom or it can take place through the amino tautomer as an RDA reaction. In both cases the formation of m/z 120 ion requires a hydrogen transfer from the *endo* to the *exo* ni-

Scheme 4




Scheme 5



trogen. Formation of the aniline molecular ion, m/z 93, is also easier to explain to occur directly from the amino form of the molecular ion.

It seems to be that at least part of the fragmentations of the R = H compounds is taking place *via* the amino form. This may be due to a pure gas phase imino ⇔ amino tautomerism or isomerization caused by ionization. The methane chemical ionization spectra of compounds **5** and **6** (Figure 3) clearly show that at least some imino structure is present in the gas phase because practically the only abundant fragment the ion of m/z 98 must be formed by loss of phenyl isocyanate from the protonated molecular ion.

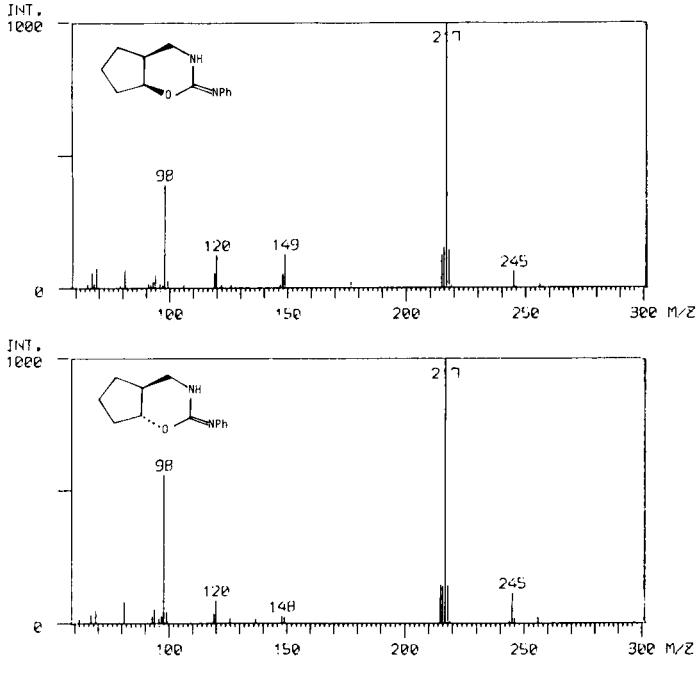



Figure 3. Methane chemical ionization spectra of *cis*- and *trans*-2-phenylimino-5,6-trimethyleneperhydro-1,3-oxazines **5** and **6**, respectively.

R = $CH_3$.

The main fragmentation routes in these cases are shown in Scheme 3 for compounds **7** and **8**. The formation of the amino structure would require a methyl transfer from the *endo* to the *exo* nitrogen which seems not to be a very favourable process. The differences between stereoisomeric compounds are even more striking than for R = H compounds mostly because of increased stereochemical control in R = $CH_3$ compounds.

The *cis*-annelated derivatives, compounds **7** and **11**, give rise to a m/z 119 ion, which also represents the base peak in the spectra (Table 1, Figure 2). This ion clearly has a different structure or mixture of structures than m/z 119 ion generated from R = H compounds (Table 2). The dominant structure is most probably oxazole (**M2**) but other structures must also be involved.

In the *cis*-anellated derivatives the *N*-methyl group prefers greatly the equatorial position to avoid severe *syn*-axial interactions [13]. Consequently, the imino isomer where the phenyl substituent and the ring *N*-methyl are *anti* to each other becomes more favoured than the now sterically crowded *syn* isomer. Furthermore the electron donating ability of the methyl substituent decreases the nucleophilic reactivity of the ring nitrogen atom towards the aromatic ring. For these reasons cyclization must mostly take place through the oxygen atom leading to the oxazole structure (**M2**) as shown in Scheme 4. The $[M]^+/[M\text{-}H]^+$ ratio indicates that cyclization *via* the oxygen atom does not lead to as stable an $[M\text{-}H]^+$ ion structure as that formed in the *N*-cyclization of the R = H compounds.

*trans*-Anellated compounds are not so crowded and hence their *N*-methyl group is more or less predominantly axial [13]. This allows the cyclization to take place *via* nucleophilic nitrogen atom and the formation of an analogous structure to that shown in Scheme 2. In this case, however, it is not so stable as with R = H compounds due to interactions between the methyl group and ring hydrogen atoms. Therefore the main fragmentation of the $[M\text{-}H]^+$ ion does not obey the reaction shown in Scheme 1 but that presented in Scheme 5. The N-C(4) bond is broken with simultaneous rearrangement of two hydrogen atoms. The ion so formed then eliminates CHNO giving rise to the $[C_7H_8N]^+$ ion which corresponds to the base peak in the spectrum.

It is interesting to note that *trans*-anellated isomers also show an ion of m/z 119 although its relative intensity is not very high. Its structure also differs from that generated from related *cis*-isomers. The intensities of m/z 77 and m/z 90-92 ions in the CID spectra of m/z 119 ion from compounds **8** and **12** (Table 1, Figure 2) point out that some azetidone structure (Scheme 2) must be present together with some unknown structure as indicated by the relatively high intensity of the m/z 104 ion peak especially in case of compound **4**.

## EXPERIMENTAL

The LR, HR, B/E and CID measurements were carried out on a Jeol JMS D-300 mass spectrometer equipped with a JMA-2000H data system as described elsewhere [10]. For the preparation of the compounds see Fülöp *et al.* [5].

Acknowledgements.

The authors wish to thank Dr. Geza Stájer (Szeged, Hungary) for skillful synthetic assistance, F. F. and K. P. are grateful to the Research Council for Natural Sciences, the Academy of Finland for fellowships.

## REFERENCES AND NOTES

* Authors to whom correspondence should be addressed.

[1] A. R. Katritzky, R. T. Langthorne, R. C. Patel, and G. Lhommet,

*Tetrahedron*, **37**, 2383 (1981).

[2] N. N. Guseva, L. A. Ignatova, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 270 (1981); *Chem. Abstr.*, **95**, 62089 (1981).

[3] J. Liebscher and E. Mitzner, *Tetrahedron Letters*, **26**, 4179 (1985).

[4] Y. Matsubara, T. Nakamura, M. Yishihara, and T. Maeshina, *Chem. Pharm. Bull. Japan*, **33**, 3009 (1985).

[5] F. Fülöp, G. Bernáth, and P. Sohár, *Tetrahedron*, **41**, 5981 (1985).

[6] F. Fülöp, G. Bernáth, and G. Csirinyi, *Org. Prep. Proced. Int.*, **20**, 73 (1988).

[7] A. Kleeman and J. Engel, "Pharmazeutische Wirkstoffe", Georg Thieme Verlag, Stuttgart, 1982.

[8] *Drugs Fut.*, **8**, 26 (1983); *ibid*, **8**, 671 (1983); *ibid.*, **8**, 1005 (1983).

[9] S. Kankaanpää, K. Pihlaja, G. Bernáth, and F. Fülöp, *Adv. Mass Spectrom.*, 1413 (1986).

[10] K. Pihlaja, P. Vainiotalo, F. Fülöp, and G. Bernáth, *Rapid Commun. Mass Spectrom.*, **2**, 000 (1988).

[11] Gy. Bujtás and J. Tamás, *Org. Mass Spectrom.*, **11**, 726 (1976).

[12] F. Turecek and V. Hanus, *Mass Spectrom. Rev.*, **3**, 85 (1984).

[13] F. G. Riddell and J. M. Lehn, *J. Chem. Soc. (B)*, 1224 (1968).