Effects of *N*-Substitution on the Fragmentations of Some Cyclohexene-fused 2-*N*-phenyliminoperhydro-3,1-oxazines and Related Thiazines

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Six cyclohexene-fused 2-*N*-phenyliminoperhydro-3,1-oxazines and four related thiazines were prepared and their mass spectrometric behavior was studied by means of metastable ion analysis and exact mass measurement. In most of the fragmentations, extensive rearrangements took place. The decompositions through the retro-Diels-Alder reaction initiated by the double bond dominated in the case of the unsubstituted compounds. The effect of the double bond, however, was greatly outweighed by the effect of the substituent on the ring nitrogen atom. In comparison with the unsubstituted compounds, both electron-releasing (methyl) and electron-withdrawing (benzyl) substituents increased the contribution of the ring cleavage reactions in the heterocyclic part of the molecule; in the case of the benzyl group the loss of the substituent also became important. For isomeric compounds, the relative peak intensities were so different that such compounds were easy to differentiate. (*J Am Soc Mass Spectrom* 1991, 2, 125-129)

The mass spectrometric behavior of perhydro-1,3-oxazines depends very much on the nature and position of the substituents on the ring system [1-6]. With fused ring derivatives, the stereochemistry of the ring fusion also plays an important role in many cases. The nature of the substituents at ring positions two and three seems to be especially important. Cyclohexane-fused 2-*N*-phenyliminoperhydro-1,3- and -3,1-oxazines undergo extensive rearrangement reactions, best characterized in terms of intramolecular cyclization [2, 5, 7]. The nature and extent of these reactions depend on the *N*-substitution and stereochemistry of the ring fusion.

In this article some cyclohexene-fused 2-*N*-phenyliminoperhydro-3,1-oxazines and -3,1-thiazines were synthesized. The compounds and the synthetic route leading to them are presented in Scheme I. Their mass spectrometric behavior was studied to find out how different structural features affect their fragmentations. Special attention was paid to the effect of the

double bond of the carbocyclic ring and the effect of the substituent on the ring nitrogen on the fragmentations. Comparisons were also made with related cyclohexane fused compounds. All the fragmentation pathways were verified by metastable ion analysis, collision-induced dissociation studies, and exact mass measurement. The ion structures indicated, however, are speculative and merely meant to aid in the visualization of the fragmentation process.

Results and Discussion

From the 70-eV mass spectra of the compounds studied, some general features are easy to see (Figure 1, Table 1). All the compounds exhibited a high-intensity molecular ion peak, which in most cases was even the base peak in the spectrum. The *trans*-fused isomer was always more stable than the related *cis* isomer as regards the higher intensity of its molecular ions (Table 2) in accordance with the fact that normally *cis*-fused isomers are more strained than the *trans* forms for this type of compound [6-8]. Although the *cis* and *trans* isomers gave rise to the same

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Scheme I

fragment ions, they were easy to differentiate because the peak intensities differed adequately.

The most striking effect on the fragmentation behavior of the compounds studied was that of the substituent on the ring nitrogen atom (Figure 1). For unsubstituted compounds (1-4), the most important reaction route was a retro-Diels-Alder (RDA) reaction directly from the molecular ion with charge remaining in the heterocyclic part of the molecule. This reaction took place with both *cis*- and *trans*-fused isomers showing that a stepwise mechanism was involved. Steric reasons, however, were important because the reaction was always more favorable for the *cis* than for the *trans* isomer. For compounds 1 and 2, the $C_{10}H_{10}N_2O^+$ ion at m/z 174 thus formed decomposed by losing mainly C_3H_5N through a further RDA process, or $C_2H_4N^+$, giving rise to the $C_7H_5NO^+$ and $C_8H_6NO^+$ ions at m/z 119 and 132, respectively (Scheme II). For the thiazines (3 and 4) the secondary fragmentations of the first RDA prod-

Figure 1. The 70-eV mass spectra of compounds 2, 6 and 10.

Table 1. The 70-eV mass spectra of the compounds studied. Peaks with the relative intensities greater than 5% of the intensity of the base peak were included. The spectra are uncorrected for isotopic contributions.

Compound 1
229(8) 228(M⁺, 50), 227(36), 175(12), 174(100), 173(5), 147(6), 132(33), 120(14), 119(96), 94(5), 93(14), 92(11), 91(11), 82(38), 79(7), 77(29), 67(5), 65(10), 54(8), 51(8), 41(8), 39(9).

Compound 3
246(6), 245(21), 244(M⁺, 100), 243(88), 211(10), 192(5), 191(13), 190(90), 189(30), 158(10), 157(64), 151(7), 137(5), 136(23), 135(45), 132(7), 119(23), 118(24), 110(5), 109(6), 108(6), 104(9), 98(14), 94(10), 93(32), 92(16), 91(28), 87(7), 80(8), 79(39), 78(18), 77(27), 72(6), 68(13), 67(7), 66(6), 65(15), 53(7), 51(16), 45(5), 41(13), 27(6).

Compound 4
246(6), 245(21), 244(M⁺, 100), 243(73), 211(9), 191(6), 190(46), 189(14), 177(7), 158(6), 157(32), 151(7), 150(6), 136(15), 135(19), 119(22), 118(20), 108(8), 104(7), 98(8), 94(12), 93(32), 92(15), 91(24), 80(10), 79(45), 78(16), 77(50), 72(5), 68(20), 67(6), 66(6), 65(12), 53(6), 51(12), 41(11), 39(12), 27(5).

Compound 5
243(18), 242(M⁺, 100), 241(33), 151(23), 150(6), 149(19), 133(7), 132(10), 120(11), 119(47), 108(6), 107(14), 106(31), 94(18), 93(33), 92(23), 91(38), 81(5), 79(19), 77(25), 73(6), 70(6), 69(49), 68(39), 67(5), 65(6), 53(5), 51(6), 42(46), 41(12), 39(8), 30(8).

Compound 7
260(6), 259(20), 258(M⁺, 100), 257(21), 243(16), 225(5), 204(9), 180(7), 167(11), 136(8), 135(40), 134(6), 133(62), 132(45), 131(13), 106(19), 104(8), 101(31), 100(7), 94(6), 93(20), 92(13), 91(55), 79(20), 78(9), 77(39), 69(6), 68(11), 65(7), 51(9), 42(26), 41(9), 39(7), 29(15).

Compound 8
260(7), 259(21), 258(M⁺, 100), 257(23), 225(6), 168(6), 167(30), 165(6), 136(5), 135(13), 133(34), 132(47), 131(12), 122(6), 108(6), 106(15), 104(7), 101(10), 94(7), 93(18), 92(13), 91(62), 79(20), 78(7), 77(32), 68(7), 65(6), 61(6), 51(7), 42(21), 41(7), 39(6).

Compound 9
319(25), 318(M⁺, 100), 317(13), 227(23), 226(9), 225(8), 224(10), 182(11), 145(6), 133(10), 132(88), 119(15), 107(11), 106(49), 104(7), 94(13), 93(37), 92(20), 91(100), 79(14), 77(25), 65(14), 41(6), 39(5), 30(7).

m/z (relative intensity)

uct ion differed from those of the oxazines (1 and 2). Namely, the elimination of HS^+ was energetically the most favorable process for the $C_{10}H_{10}N_2S^+$ ion at m/z 190, whereas related elimination of the hydroxy radical from oxazines was completely absent. The m/z 190 ion also gave rise to the formation of the $C_7H_5NS^+$ ions at m/z 135 formally corresponding to the formation of m/z 119 ions for compounds 1 and 2.

Another interesting feature in the spectra of compounds 1-4 was the high intensity of the peaks caused

Table 2. The intensities of the M^{+} and $[M-H]^{+}$ ions (% Σ_{10})

Compound	M^{+}	$[M-H]^{+}$	$M^{+}/[M-H]^{+}$
1	8.0	5.8	1.37
2	10.1	11.2	0.90
3	9.0	7.9	1.14
4	11.3	8.3	1.36
5	12.0	4.0	3.04
6	14.5	7.1	2.06
7	11.3	2.3	4.84
8	13.7	3.1	4.39
9	13.7	1.8	7.75
10	14.7	4.7	3.15

by the $[M-H]^{+}$ ions (Table 2). Most probably this was due to an intramolecular cyclization reaction in which a hydrogen atom was lost from an *ortho*-position of the benzene ring (Scheme II) in analogy to the case of the related 2-*N*-phenylimino-perhydro-1,3-oxazines [5]. For the last mentioned compounds, this cyclization is the most important process and it is followed by the RDA reaction. In the present case, however, the related RDA reaction would lead to the ion with the same mass number as the parent ion, due to the position of the newly formed double bond. As a consequence, no remarkable fragment ions were observed. In every case, formation of the $[M-H]^{+}$ ion was more favorable for the *trans* than for the *cis* isomer. Cyclization through the oxygen or sulfur atom, of course, cannot be ruled out completely. The *N*-cyclization, however, better explains the stereochemical effect observed, because in the predominant *N*-in conformation of the *cis*-fused derivatives [9] (Scheme III), the substituent on the ring nitrogen atom, even if it is only a hydrogen atom, probably favors the equatorial position to avoid *syn*-axial interactions [10], making the cyclization more difficult.

For the *N*-methyl-substituted compounds (5-8) the fragmentation patterns differed essentially from those

for the unsubstituted compounds. First of all, the RDA reaction had lost its predominance. In all the cases, the abundance of the primary reaction products, the $[M-C_4H_6]^{+}$ ions, was very low; practically only the secondary fragment ions at m/z 119 and m/z 135 for oxazines and thiazines, respectively, were present. This means that the charge was not able to localize to the carbon-carbon double bond as effectively as in the case of compounds 1-4, probably due to the fact that the methyl group, as an electron-donating substituent, increases the ability of the ring nitrogen atom to lose its nonbonding electron in the ionization process more easily than the unsubstituted nitrogen does, making the charge preferentially localized on the nitrogen instead of on the double bond. As a consequence, the spectra of compounds 5-8 resembled to a surprisingly large extent those of the related saturated compounds (cf. Figure 2a) [7], although in the present case the spectra of the isomeric compounds differed enough to allow isomeric differentiation as mentioned above.

The abundance of $[M-H]^{+}$ ions formed from com-

Figure 2. The 70-eV mass spectra of (a) 1-methyl-2-*N*-phenylimino-*trans*-perhydro-3,1-benzoxazine and (b) 1-benzyl-2-*N*-phenylimino-*trans*-perhydro-3,1-benzoxazine.

pounds 5-8 was also greatly diminished in comparison with compounds 1-4 (Table 2). This is analogous to the situation for the 2-*N*-phenyliminoperhydro-1,3-oxazines studied earlier because the methyl substituent decreases the electrophilic reactivity of the ring nitrogen atom towards the aromatic ring. The most important fragmentations for oxazines (5 and 6) are presented in Scheme IV. The largest difference in the spectra of these two compounds was caused by the fact that the RDA reactions were more favorable for the *cis* than for the *trans* isomer, manifested as a greater abundance of the *m/z* 119 ion in the case of the *cis* isomer. Besides the related reactions presented in Scheme IV, the elimination of $C_7H_9S^+$ from the M^+ and $[M-H]^+$ ions of 3,1-thiazines (7 and 8) was especially important because it displayed stereochemical specificity (Table 1). The fragmentation through the $[M-H]^+$ ion was more favorable for the *trans* than for the *cis* isomer. For the cyclization to occur it is necessary that the *N*-substituent is *axial* and that the ring nitrogen atom and the phenyl group are *syn* to each other. The *cis* isomer exists as a mixture of *N*-in and *N*-out conformations (Scheme III) of which the *N*-out form becomes the more favored the bigger the *N*-substituent [9]. Cyclization, however, is turned difficult in both of them because, in the *N*-in form, the *N*-methyl cannot be axial because of severe *syn*-axial interactions, and steric crowding in the *N*-out form makes the *syn* orientation of the phenyl and the ring nitrogen atom very unfavorable. In the *trans* isomer these burdens do not exist.

The benzyl group on the ring nitrogen atom totally dominated the fragmentations of compounds 9 and 10 (Scheme V). Their spectra bore an even more salient resemblance to the spectra of the related saturated compounds (*cf.* Figure 2b) [7] than in the case of the methyl substituted compounds 7 and 8. In spite of the bulkiness of the benzyl group some cyclization certainly took place: peaks corresponding to the $C_{14}H_{14}N_2O^+$ at *m/z* 226 and $C_{14}H_{12}N_2O^+$ ions at *m/z* 224 formed from the $[M-H]^+$ ion were totally absent in the spectra of the related *N*-methyliminoperhydro-3,1-oxazines, where this kind of cyclization is not possible [11]. This can be explained as due to the electron-withdrawing character of the benzyl group, which made the ring nitrogen atom more reactive towards the aromatic moiety. The bulkiness of the

substituent makes the small abundance of the $[M-H]^+$ ions understandable (Table 2).

Conclusion

The nature of the substituent on the ring nitrogen atom had the most striking effect on the fragmentation behavior of the compounds studied. With the unsubstituted compounds the RDA reaction was the most important primary reaction of the molecular ions. Due to the electronical effects of the substituent, this reaction lost its predominance in the case of the substituted compounds so that with the benzyl substituted compounds the substituent totally dominated their fragmentations.

All the compounds studied formed the $[M-H]^+$ ions through the intramolecular cyclization with the simultaneous elimination of *ortho*-hydrogen from the 2-*N*-phenyl group. Both the nature of the substituent and the stereochemistry of the ring fusion had effect upon the abundance of these ions. Stereochemistry also played an important role in other fragmentations. As a consequence, although the *cis* and *trans* isomers gave rise to the same fragment ions, they were easy to differentiate because the peak intensities differed adequately.

Experimental

Synthesis (Scheme I)

Aminoalcohols. The starting aminoalcohols **1A**, **2A**, and **9A** were prepared as described earlier [12, 13]. Aminoalcohols **5A**, **6A**, and **10A** were prepared as described for cyclohexane derivatives [14]; starting from ethyl *cis*- and *trans*-2-amino-4-cyclohexene-1-carboxylate [12]. The thin layer chromatography pure oily products were used without further purification.

Thiourea derivatives. To 5 mmol of an aminoalcohol in 20 mL of ether, 0.6 mL (5 mmol) of phenyl isothiocyanate was added. After standing 3 h at room temperature, the crystalline products were filtered off and recrystallized. **1B**: 149-152°C; **2B**: 120-123°C (EtOH);

5B: 133–136°C (MeOH); **6B:** 195–196°C (MeOH); **9B:** 130–132°C (EtOAc) (lit. [13] mp 129–131°C); **10B:** 149–151°C.

Cyclohexene-fused 2-phenyliminoperhydro-1,3-oxazines. To 0.3 mmol of thiourea in 10 mL of methanol, 1 mL of methyl iodide was added and the solution was stirred for 2 h. After evaporation the residue was stirred with 20 mL of 3 M methanolic KOH for 3–4 h. After evaporation the residue was dissolved in water and extracted with chloroform (3 × 30 mL). After drying and evaporation the desired oxazines were obtained: **1:** 137–138°C (hexane); **2:** 170–173°C (diisopropyl ether); **5:** oil (mp of HCl salt 163–166°C); **6:** 95–98°C (hexane); **9:** 95–96°C (hexane) (lit. [13] mp 89–91°C); **10:** 129–130°C (hexane).

Cyclohexene-fused 2-phenyliminoperhydro-1,3-thiazines. Thiourea derivatives (3 mmol) were refluxed for 1 h in ethanol containing 10% of dry HCl. After evaporation to dryness, 10 mL of saturated aqueous sodium carbonate was added and the desired thiazines were extracted in chloroform (3 × 30 mL): **3:** 170–173°C (EtOAc); **4:** 192–194°C (EtOAc); **7:** 107–109°C (hexane); **8:** 152–155°C (EtOAc).

Mass Spectrometry

Measurements were carried out with a JEOL JMS D300 mass spectrometer (JEOL U.S.A., Peabody, MA) equipped with a combined electron ionization/chemical ionization ion source and connected to a Jeol JMA 2000H data system. Samples were introduced through a direct inlet probe at temperatures of 40 to 170°C.

Typical source conditions were: temperature, 170°C; electron energy, 70 eV; accelerating voltage, 3 kV, and ionization current, 300 μ A. Accurate mass measurements were made at resolution 5000 using the data system. Fragmentation pathways were verified via metastable transitions and/or collision-induced dissociation spectra by means of linked scans at constant B/E.

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