Mass Spectra of Spiro-benzoxazin-4-one and Spiro-quinazolin-4-one Derivatives

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Mass spectra of a series of spiro-benzoxazin-4-one and spiro-quinazolin-4-one derivatives were measured by electron impact ionization, and their characteristic fragmentation patterns were discussed.

Spiro-benzoxazin-4-ones and spiro-quinazolin-4-ones were found to display different fragmentation pathways and different peak intensities. In particular, the base peak in mass spectra of spiro-benzoxazin-4-ones resulted from the molecular ion by the retro-Diels-Alder reaction with hydrogen migration. On the other hand, the base peak in mass spectra of spiro-quinazolin-4-ones resulted from the molecular ion by the cycloalkane ring decomposition. The difference in the main two processes was based on the difference in the ionization energy of the oxygen atom and the nitrogen atom at the 1-position. The difference in hydrogen migration was based on the difference in electronegativity of the heteroatom at the 1-position.

1. Introduction

The investigation of quinazoline chemistry has intensified the search for new pharmaceutical agents over the last few years. Some compounds of the spiro type are also known to exhibit inhibitory activity against histamine release from rat mastcells.⁽¹⁻²⁾ In this connection, we synthesized spiro-benzoxazin-4-ones and spiro-quinazolin-4-ones, and measured their mass spectra, as these had not been previously investigated.

In the present paper, we describe and discuss the various features of these com-

pounds revealed by the fragmentation patterns in their mass spectra, and furthermore, how differences in the heteroatom at the 1-position in these compounds affect their fragmentations. We observed that in these compounds, both cleavage of the cycloalkane ring and the retro-Diels-Alder reaction with hydrogen migration occurred.

In the mass spectra of dihydro-4(1H)-quinazolinone described in previous papers⁽³⁾ the retro-Diels-Alder reaction was observed. However, there have been no reports on the retro-Diels-Alder reaction in benzoxazin-4-one. Prominent peaks at m/z values corre-

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sponding to the molecular ions of the title compounds were observed. The fragmentation patterns of compounds **1a-1e** were found to be characterized by the appearance of peaks at $[M-43]^+$, m/z 188, m/z 174, m/z 161, m/z 121 and m/z 120. The fragmentation patterns of compounds **2a-2e**, on the other hand, were characterized by the appearance of peaks at m/z 187, m/z 173, m/z 160, m/z 120 and m/z 119.

2. Experimental

The compounds used in the present investigation are shown in Fig. 1. They were synthesized according to the published procedure⁽¹⁻²⁾, and purified by means of silica gel column chromatography and recrystallization.

The mass spectra were measured with a

Fig. 1 Compounds used in this study

Hitachi RMU-7MG double focusing mass spectrometer. The samples were introduced through a direct inlet system. The ion source was operated at a 3kV accelerating voltage, 70 eV electron energy and a pressure of approximately 3×10^{-7} torr; its temperature was maintained at approximately 180°C. Metastable ions were detected with an IKES attachment. The elemental compositions were determined using the high resolution mode.

Fig. 2 Mass spectra of compounds 1a-1e

Table 1 Intensity of the important fragment ions of the compounds 1a-1e

	M^+	$[M-43]^+$	m/z 188	m/z 174	m/z 161	$[C_nH_{2n-1}N]^+$	m/z 121	m/z 120
1a	27.6	-	-	22.3	-	50.5	100	15.1
1b	43.9	51.8	-	51.8	-	98.0	100	16.8
1c	30.6	7.4	7.4	35.3	1.6	71.2	100	18.1
1d	13.5	2.6	3.2	25.0	20.0	19.4	100	27.9
1e	20.0	5.2	1.6	42.9	16.9	24.7	100	20.6

3. Results and Discussion

The mass spectra of spiro-benzoxazin-4-ones (1a-1e) and spiro-quinazolin-4-ones (2a-2e) are shown in Fig. 2 and Fig. 4 and given in Table I and Table II, respectively. The asterisk under the arrow in Fig. 3 and Fig. 5 denotes that an appropriate metastable peak was observed in the mass spectra. The empirical formulae of the major ions were also obtained by the exact mass measurement.

3.1. Mass spectra of compounds 1a-1e

The mass spectra of all compounds

Fig. 3 Fragmentation routes of compounds 1a-1e

1a-1e exhibited abundant molecular ion peaks and the fragmentation patterns were rather simple. The main common decomposition routes are shown in Fig. 3. The fragmentation paths could be classified into two groups, which involved the decomposition of the spiro-cycloalkane ring and the retro-Diels-Alder reaction of the heterocyclic ring. The decomposition of the spiro-cycloalkane ring yielded ions at $[M-43]^+$, m/z 188, m/z

Fig. 4 Mass spectra of compounds 2a-2e

Table II Intensity of the important fragment ions of the compounds 2a-2e

	M^+	$[M-43]^+$	m/z 187	m/z 173	m/z 160	m/z 120	m/z 119
2a	12.5	-	-	100	8.7	6.5	12.8
2b	16.9	100	9.6	100	33.4	13.3	5.3
2c	15.8	24.3	24.3	100	19.2	8.3	-
2d	13.9	7.2	15.4	100	98.0	17.3	9.8
2e	6.4	10.9	10.8	100	63.7	19.6	9.8

m/z 174 and m/z 161, respectively. Herzig et al.⁽⁴⁾ described that compounds containing spiro-cyclohexane yielded ions corresponding to the loss of an ethyl radical, a propyl radical and cyclobutane from the molecular ion. Compounds **1a-1e** gave the intermediate which forms a 2-3 double bond by cleavage of the 1'-2' bond in the same process. This intermediate further lost its alkyl radicals and the cycloalkane molecule to give ions at m/z 188, m/z 174 and m/z 161. Although the ion at m/z 174 was shown in mass spectra of **1a-1e**, the ions at m/z 188 and m/z 161 were only shown in the mass spectra of **1c-1e**.

The ion at m/z 174 was commonly observed at an intensity of 23-53% (Table 1). Its composition was $C_{10}H_8NO_2$. Compounds **1a-1e** eliminated the alkyl radical, $C_{n-3}H_{2n-5}^{\cdot}$ ($n=7,8$ and 12), to give an ion at m/z 174 containing the double bond as a result of the spiro-cycloalkane decomposition. The ion thus formed was able to take a conjugated form between the benzoxazine skeleton and the double bond, thereby stabilizing itself considerably. In **1b-1d**, the intensities of the ion at m/z 174 decreased with increasing size of the spiro-cycloalkane ring. In the formation of the ion, hydrogen migration from the n' -position to the 2'-position becomes difficult with the increasing size of the spiro-cycloalkane ring. Although the ion at m/z 188 was not observed in the mass spectra of compounds **1a-1b**, it was apparent in the mass spectra of compounds **1c-1e** (Table 1). The composition of the ion is $C_{11}H_{10}NO_2$. This ion was formed by the same process as that responsible for formation of the ion at m/z 174 described above. The intensity of the ion decreased with increasing size of the spiro-cycloalkane ring. The

differences in the ion intensities can be explained by differences in their ability to transfer intramolecularly a hydrogen radical from the $(n-1)$ '-position to the 2'-position.

Although the ion at m/z 161 was observed in the mass spectra of compounds **1c-1e** (Table 1), such an ion was not observed in the mass spectra of compounds **1a-1b**. The composition of this ion as $C_9H_7NO_2$, and the ion was produced by loss of a corresponding cycloalkane ($C_{n-2}H_{2n-4}$) from the molecular ion. The intensity of the ion at m/z 161 was affected by the size of the spiro-cycloalkane ring. In other words, the ion intensity is affected by the stability of the cycloalkane ring.

The peak corresponding to $[M-43]^-$ is shown in Table 1. This characteristic ion was formed by loss of a propyl radical from the molecular ion. The ion intensity decreased with increasing size of the spiro-cycloalkane ring. This was due to differences in the ease with which hydrogen migration from 6'-position to 2'-position occurred during fragmentation.

On the other hand, **1a-1e** give the ions at m/z 121 and m/z 120 by the retro-Diels-Alder reaction of the heterocyclic ring. In general, benzopyran⁽⁵⁾ and chromanone⁽⁶⁾ undergo a retro-Diels-Alder reaction of the heterocyclic ring to afford intense ion peaks corresponding to the retro-Diels-Alder reaction and hydrogen migration. The benzoxazin-4-ones seemed to give the ions at m/z 121 and m/z 120 by the same process. The ion at m/z 121, $C_7H_5O_2$, was the base peak in the mass spectra of all compounds **1a-1e**. In the mass spectra of the deuterium analogue at N^3-D , the peak at m/z 121 was shifted to one mass higher. Therefore, the

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ion was considered to originate from the molecular ion as a result of the retro-Diels-Alder reaction with a hydrogen migration from the 3-position to the 1-position.

Also the ion at m/z 120, $C_7H_4O_2$, was formed by the simple retro-Diels-Alder reaction of the heterocyclic ring. The intensity of the ion increased with increasing size of the spiro-cycloalkane ring in **1a-1d**.

The characteristic peaks corresponding to $[C_nH_{2n-1}N]^+$ ($n=5,6,7,8$ and 12) are shown in Table I. This ion was the counter-

Fig. 5 Fragmentation routes of compounds **2a-2e**

part of the ion at m/z 120. All compounds **1a-1e** exhibited this ion with marked intensity. In particular, compounds **1a-1c** which had a small spiro-cycloalkane ring exhibited this ion at an intensity of more than 50%. The metastable peaks for all processes were observed for these derivatives (**1a-1e**).

3.2 Mass spectra of compounds **2a-2e**

The molecular ions were commonly observed at an intensity of 6.5-17% (Table

II). The main common decomposition routes are shown in Fig. 5. These fragmentation paths could be classified into two groups, those showing the spiro-cycloalkane decomposition and those showing the retro-Diels-Alder reaction, as in the case of compounds **1a-1e**.

The spiro-cycloalkane decomposition formed ions at $[M-43]^+$, m/z 187, m/z 173 and m/z 160 from the molecular ion. The formation of these ions was thought to be explained by fragmentation analogous to that described for spiro-benzoxin-4-ones.

The fragment ion at m/z 187 was observed for some derivatives **2a-2d** (Table II) and its composition was $C_{11}H_{11}N_2O$. The ion was formed by loss of an alkyl radical, $C_{n-4}H_{2n-7}^{\bullet}$ ($n=6,7,8$ and 12), from the molecular ion. Since the alkyl radicals are small and unstable in **2a** and **2b**, the relative intensities of the ions were very small. In **2c-2e** the relative intensities of the ions decreased with increasing size of the spiro-cycloalkane ring. The differences in the ion intensity was based on the ease with which hydrogen migration could occur from the $(n-1)$ -position to $2'$ -position during fragmentation.

The base peak in the spectra of compounds **2a-2e** is the ion at m/z 173 which was due to loss of an alkyl radical, $C_{n-3}H_{2n-5}^{\bullet}$ ($n=5,6,7,8$ and 12), from the molecular ion. The high intensity shows the stability of the quinazolinone skeleton which contains the 2-3 double bond of the quinazoline ring though cleavage of the $1'-2'$ bond. These results were supported by the presence of a number of ions which arise by the decomposition of the spiro-cycloalkane ring.

The fragment ion at m/z 160 was found in the mass spectra of **2a-2e** and was commonly observed at an intensity of 9-98%

(Table II). The composition of this fragment ion was confirmed to be $C_9H_8N_2O$. The common intermediate ion was formed by loss of cycloalkane molecule, $C_{n-2}H_{2n-4}$ ($n = 5, 6, 7, 8$ and 12), from the molecular ion. This ion showed a strong intensity when the number of carbons in the spiro-cycloalkane were even. The relative intensity of the ion is based on the stability of the cycloalkane which is the counterpart of the ion at m/z 160. For instance, when the total heat of formation between the common intermediate ion and its counterpart was lower, the relative intensity of its common intermediate ion was strong.

Although no ion at $[M-43]^+$ was found in the mass spectrum of **2a**, this ion was observed in the mass spectra of **2b-2e**. The ion at $[M-43]^+$ corresponds to the ions at m/z 173 and m/z 187 in the mass spectra of **2b** and **2c**, respectively. The ion was formed by loss of a propyl radical containing a hydrogen migration from the 6'-position to the 2'-position in the molecular ion. The fragmentation process is influenced by the competing processes of the spiro-cycloalkane decompositions.

On the other hand, the retro-Diels-Alder reactions in compounds **2a-2e** yielded ions at m/z 120 and m/z 119. Their compositions were confirmed to be C_7H_6NO and C_7H_5NO , respectively. In the mass spectra of the deuterated analogue at N^1-D and N^3-D , the peak at m/z 120 was shifted to two masses higher. Therefore, this ion resulted from the retro-Diels-Alder reaction containing the hydrogen migration from N-3 to N-1. The relative intensity of the ion at m/z 120 was observed to be 6.5-19.6%, while that of the ion at m/z 119 exhibited an intensity of

less than 13% (Table II). Moreover, the intensity of the ion at m/z 120 was more abundant than that of the ion at m/z 119 in all compounds except **2a**. In general, 2,3-dihydro-4(1H)-quinazolinone derivatives⁽³⁾ gave the ions formed by the simple retro-Diels-Alder reaction and that with a hydrogen rearrangement. Compounds **2b-2e** as well as compounds **1a-1e** showed the ions formed by both the retro-Diels-Alder reaction with a hydrogen rearrangement and the simple retro-Diels-Alder reaction. Although in 2,3-dihydro-4(1H)-quinazolinones a hydrogen at the 2-position migrated to the heteroatom at the 1-position, a hydrogen at the 3-position migrated to that position in **2a-2e**. Furthermore, comparison of the ion intensities at m/z 120 and m/z 119 in the mass spectra of **2a-2e** showed that hydrogen migration occurred very easily.

For all derivatives, metastable peaks were observed in all processes.

3.3 Comparison of the spiro-benzoxazin-4-ones (**1a-1e**) with the spiro-quinazolin-4-ones (**2a-2e**)

The main fragmentation pathway of **1a-1e** is the retro-Diels-Alder reaction with hydrogen migration of the benzoxazin-4-one skeleton and that of **2a-2e** is the decomposition of the spiro-cycloalkane. The differences between the main processes seem to be based on the difference in ionization energy between an oxygen atom and a nitrogen atom at the 1-position. In other words, since the ionization energy of a nitrogen atom is generally lower than that of an oxygen atom, the effect of a nitrogen atom on the cycloalkane ring is greater than that of an oxygen atom.

In the mass spectra of **1a-1e**, the ratios

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of the intensities of m/z 120 and m/z 121 were about 1:4-6, but the ratios in the mass spectra of **2a-2e** were about 1:2. The differences in the ratios are affected by the ease of hydrogen migration on the basis of the difference in electronegativity between an oxygen atom and a nitrogen atom at the 1-position: The electronegativity of an oxygen atom is larger than that of a nitrogen atom. In other words, the electron density of an oxygen atom is higher than that of a nitrogen atom. From these facts, when the ionization of a heteroatom at the 1-position occurs, the charge density of an oxygen atom is higher than that of a nitrogen atom.

On the other hand, compounds **1a-1e** and **2b-2e**, except for **2a**, showed that the fragment ion intensities of the retro-Diels-Alder reaction with a hydrogen migration were more abundant than those of the simple retro-Diels-Alder decomposition.

From these results, the hydrogen at the 3-position of the heterocyclic ring containing the γ^3 -H becomes easily rearranged to the heteroatom at the 1-position.

4. Conclusion

In the mass spectral characterization of spiro-benzoxazin-4-ones and spiro-quinazolin-4-ones, the two main fragmentations occurring are the cleavage of a spiro-cycloalkane ring and the retro-Diels-Alder decomposition.

Mass spectra of spiro-benzoxazin-4-ones show common ions at $[M-43]^+$, m/z 188,

m/z 174, m/z 161, m/z 121, m/z 120 and $[C_{n+1}H_{2n-1}N]^+ \cdot$ ($n=5,6,7,8$ and 12). Mass spectra of spiro-quinazolin-4-ones show common ions at $[M-43]^+$, m/z 187, m/z 173, m/z 160, m/z 120 and m/z 119.

The difference ionization energy between the oxygen atom and the nitrogen atom at the 1-position affected the main two processes (the retro-Diels-Alder decomposition with hydrogen migration and the cycloalkane ring cleavage). In addition, although spiro-benzoxazin-4-ones give the cycloalkylideneamine radical cation, the ion is not observed in the spiro-quinazolin-4-ones. Moreover, the hydrogen at the 3-position of compounds containing N^3 -H migrates to the heteroatom at the 1-position. This is due to the electronegativity of the heteroatom at the 1-position.

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Keywords

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