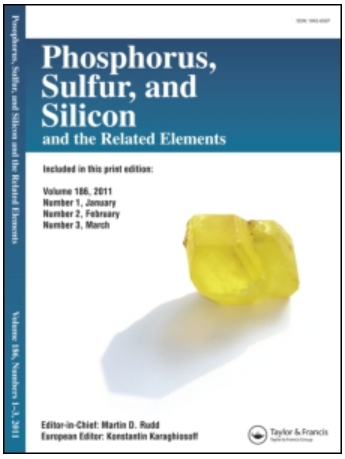

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*The mass spectrometric behavior of seven 2a,4-disubstituted 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones has been studied with the aid of mass-analyzed ion kinetic energy spectrometry and accurate mass measurements under electron impact ionization. All compounds show a tendency to eliminate a phenylketene molecule, an ethyl or benzyl radical, or a phenylketene molecule plus an SH radical. The mass spectrometric behavior of the title compounds was compared to those of 2-heteroatom-substituted analogues.*

Keywords 1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one; electron impact ionization; mass spectrometry

INTRODUCTION

Benzothiazepine and benzodiazepine tricyclic derivatives have been well-known owing to their biological importance.[1–3] Some of them with a fused four-, five-, or six-membered heterocyclic ring show effective activities as potential central nervous system depressants, antipsychotic agents, and antiinflamnatory and antiallergic agents.[4–8] Recently we performed detailed investigations on the synthesis, stereochemistry,

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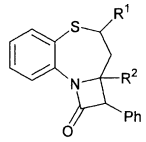
and spectral properties of a series of tricyclic benzothiazepine derivatives.[9–19] Most important, antibiotics possess a representative structure of a β-lactam fused five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms.[8,20–22] As a continuation of our studies on benzothiazepine β-lactam fused derivatives, β-lactam-fused S,N-containing seven-membered heterocyclic rings,[23–25] herein we report detailed studies on the fragmentation mechanisms under Electron Impact (EI) ionization conditions of 2a,4-disubstituted 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones. Our previous articles[26–28] reported studies of EI mass spectrometries of 2a,4-disubstituted 2-chloro-, 2-phenoxy- and 2-phthalimido-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones, but a different fragmentation mechanism was observed.

Combinatorial chemistry becomes a very important tool for the discovery of leading compounds in drug development. Mass spectral analysis will be an effective method to identify the structures of leading compounds in a screened library because of the application of LC-MS and its fast and micro properties. However, it is necessary to study the mass spectral fragmentations of known or example compounds in order to utilize effectively the mass spectral method.

The title compounds had been synthesized and characterized by EI-MS, ^{1}H NMR, IR, and elemental analysis.[29] Their structures are shown as follows (Scheme 1):



1-7

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
R_1	Me	Me	Ph	2-ClPh	4-ClPh	4-BrPh	Ph
R_2	Ph	4-MePh	Ph	Ph	Ph	Ph	4-ClPh

SCHEME 1

EXPERIMENTAL

Low-resolution 70 eV EI mass spectra of compounds **1–7** were obtained using a double-focusing mass spectrometer (VG-ZAB-HS, Micromass, Manchester, UK) coupled with a MASPEC II data system, using a direct insertion probe. Source temperature was 200°C and probe temperature was 260°C (compounds **1**, **4**, and **5**), 200°C (compounds **2** and **3**), 270°C

TABLE I EI-MS of Compounds 1–7: m/z Values (and Relative Abundances). Refer to Scheme 2 for Proposed Ion Structures

Compound	M^+	a	b	c	d	e	f	g	h	i	j	k	l
1	371	342	253	220	238	211	161	136	118	42	105	29	108
	(9.0)	(1.1)	(87)	(3.2)	(3.0)	(100)	(1.9)	(16)	(8.6)	(5.8)	(3.8)	(12)	(23)
2	385	—	267	234	252	225	175	136	118	42	119	29	108
	(6.9)		(91)	(4.2)	(1.8)	(100)	(0.5)	(9.2)	(6.3)	(5.6)	(2.2)	(9.2)	(6.2)
3	433	—	315	282	238	211	223	136	118	104	105	91	108
	(6.1)		(21)	(2.2)	(2.4)	(100)	(3.5)	(1.8)	(7.0)	(5.0)	(18)	(21)	(12)
4	467	—	349	316	238	211	257	136	118	138	105	125	108
	(5.0)		(26)	(1.2)	(2.2)	(100)	(0.4)	(2.0)	(8.4)	(2.5)	(1.0)	(5.1)	(17)
5	467	—	349	316	238	211	257	136	118	138	—	125	108
	(5.2)		(14)	(1.8)	(1.5)	(100)	(0.2)	(1.8)	(9.5)	(5.6)		(7.5)	(15)
6	511	—	393	360	238	211	301	136	118	182	—	169	108
	(2.8)		(9.6)	(1.0)	(1.0)	(100)	(0.2)	(1.2)	(7.1)	(2.4)		(3.2)	(17)
7	467	376	349	316	272	245	257	136	118	104	139	91	108
	(6.7)	(6.7)	(18)	(10)	(3.6)	(100)	(8.0)	(7.8)	(31)	(10)	(7.5)	(43)	(35)

(compound **6**), and 280°C (compound **7**). Elemental compositions of important fragment ions were determined by accurate mass determinations that were performed using the same instrument at a resolution of 5000 (10% valley), using the peak matching technique and perfluorokerosene as a reference compound. Fragment ion spectra were recorded by Mass-analyzed Ion Kinetic Energy Spectrometry (MIKES) experiments, in which the ZAB-HS instrument was controlled by the MASPEC II data system.

RESULTS AND DISCUSSION

The characteristic EI fragment ions of compounds **1–7** are compiled in Table I. Compound **7** is now taken as an example to describe the proposed fragmentation mechanism of the seven compounds. The data from the MIKES analysis of compound **7** are listed in Table II, and the high-resolution data are presented in Table III. The EI spectrum of compound **7** is shown in Figure 1.

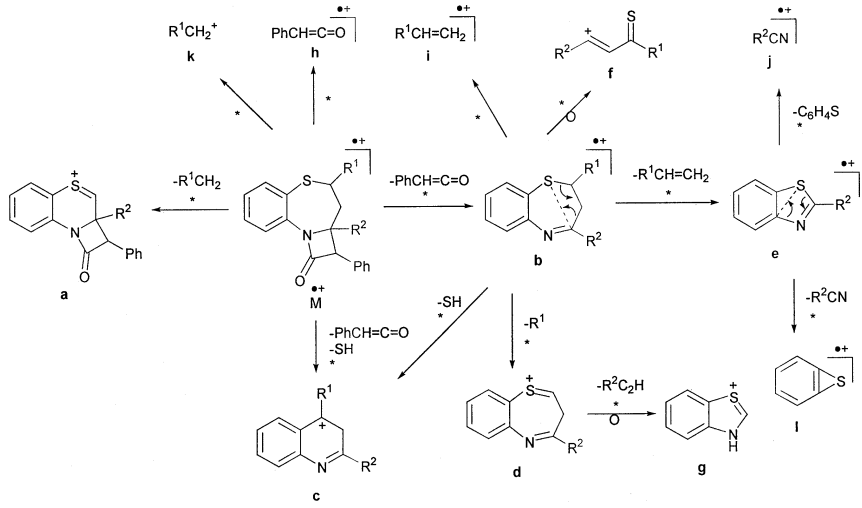
TABLE II MIKES of Compound 7

Precursor ions (m/z)	Fragment ions (m/z)
467 ($M^{+\cdot}$)	376 (a), 349 (b), 316 (c), 118 (h), 91 (k)
349 (b)	316 (c), 272 (d), 245 (e), 257 (f), 104 (i)
272 (d)	136 (g)
245 (e)	139 (j), 108 (l)

TABLE III High-Resolution Mass-Measurement Data for Ions of Compound 7

m/z	Measured value	Calculated value	Difference (mmu)	Elemental composition
467	467.1126	467.1111	1.5	$C_{29}H_{22}ClNOS(M^+)$
376	376.0568	376.0563	0.5	$C_{22}H_{15}ClNOS$ (a)
257	257.0178	257.0192	−1.4	$C_{15}H_{10}ClS$ (f)

The title compounds show low intensity M^+ ions with 2.8–9.0% relative abundances. They show a tendency to eliminate an ethyl or (substituted) benzyl radical (a, Scheme 2). They also show a tendency to undergo a reverse [2 + 2] cycloaddition (b, Scheme 2) or undergo a reverse [2 + 2] cycloaddition and eliminate SH radical simultaneously (c, Scheme 2).



SCHEME 2 Fragmentation pathways proposed for title compounds.

The fragmentation pathways of the title compounds may be proposed as shown in Scheme 2, as suggested by observations of the metastable ions (Table II) and referring to the elemental compositions of the major ions (Table III). For compounds **4–7**, some of the assigned elemental compositions of the ions containing the R^1 (compounds **4–6**) or R^2 (compound **7**) group also could be confirmed by their characteristic Cl or Br isotope patterns. The molecular ions $M^{+\cdot}$ of compounds **1** and **7** could undergo a ring contraction rearrangement to produce 2a-substituted 2,2a-dihydro-2-phenyl-azeto[2,1-*c*][1,4]benzothiazin-1-one ions (a) by a loss of an ethyl or benzyl radical (detailed mechanism shown

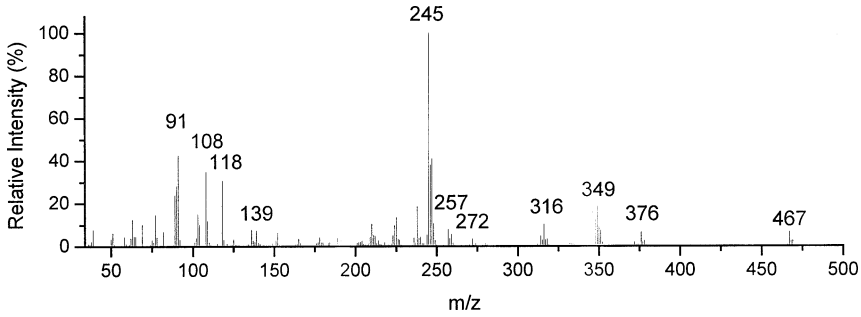
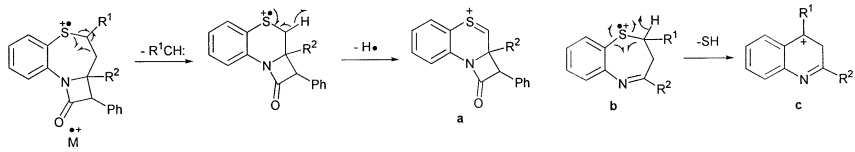


FIGURE 1 EI spectrum of 2a-(4-chlorophenyl)-2,2a,3,4-tetrahydro-2,4-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one, **7**.

in Scheme 3). The molecular ions $M^{+\cdot}$ also could undergo a reverse [2 + 2] cycloaddition to yield 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepine ions (b), or undergo a reverse [2 + 2] cycloaddition and ring contraction rearrangement to eliminate an SH radical simultaneously to give 2,4-disubstituted 3,4-dihydro-quinoline ions (c) (detailed mechanism shown in Scheme 3), which also could be formed from the ions (b) through a ring contraction rearrangement by a loss of an SH radical. The molecular ions also could give ethyl or (substituted) benzyl ions ($R^1CH_2^+$, k) and phenylketene ions (h). The 1,5-benzothiazepine ions (b) could lose a methyl or aryl radical to yield 4-substituted 3*H*-1,5-benzothiazepine ions (d), which could further form 3*H*-benzothiazole ions (g) via a complex rearrangement. It also was observed in the mass spectral studies on 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines.[30] The ions (b) also could undergo a four-membered ring rearrangement to produce propene or (substituted) styrene ions (i), or 2-substituted benzothiazole ions (e), which could further undergo a four-membered ring arrangement to yield (substituted) benzonitrile ions (j) or thiirinobenzene ions (l). The ions (b) could undergo a complex rearrangement to produce α,β-unsaturated thione ions (f), which was confirmed by the elemental composition ($C_{15}H_{10}ClS$), obtained in the accurate mass determination, of the ion (f) at m/z 257 for compound **7**.



SCHEME 3 Detailed mechanisms for the formation of the ions (a) and (c).

A characteristic fragmentation mechanism of the seven-membered heterocyclic system involves a loss of a neutral moiety R^1-CH=CH_2 from the benzothiazepine ring to produce some important ions with appreciable relative abundances.[15–18,26–28,30] However, the benzothiazepine ring in the title compounds showed better stability than others reported previously.[15–18,26–28,30] They could not eliminate directly a neutral moiety R^1-CH=CH_2 from the benzothiazepine rings before they had lost a phenylketene fragment.

Compared to the mass spectral fragmentations of 2-substituted 1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones, it has been found that 2-chloro-, 2-phenoxy-, and 2-phthalimido-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*] [1,5]benzothiazepin-1-ones reported previously[26–28] preferentially lose 2-chloro-, 2-phenoxy-, and 2-phthalimido-groups from the corresponding molecular ions first, and then fragment further. However, the title compounds, 2-phenyl-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones, can not lose a phenyl group from their azetidinone ring and preferentially undergo a reverse [2 + 2] cycloaddition. It could be rationalized that the C—C bond is more stable than the C—Cl, C—O, and C—N bonds. Furthermore, the title compounds yield relatively less abundant fragment ions than their 2-chloro-, 2-phenoxy-, and 2-phthalimido-analogues.

CONCLUSION

The mechanisms of mass spectrometric fragmentation of 2a,4-disubstituted 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones have been studied. The fragmentation mechanisms proposed in Scheme 2 have been supported by MIKES, and some key ions have been defined via their elemental compositions obtained in the high-resolution accurate mass measurements. We have discovered that all title compounds show a tendency to eliminate a phenylketene molecule or a phenylketene molecule plus an SH radical. The mass spectrometric behavior of the title compounds was compared to those of their 2-chloro-, 2-phenoxy-, and 2-phthalimido-substituted analogues.

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