Mass spectrometric studies of *cis*- and *trans*-1a,3-disubstituted-1,1-dichloro-4-formyl-1a,2,3,4-tetrahydro-1*H*-azirino[1,2-*a*][1,5]benzodiazepines

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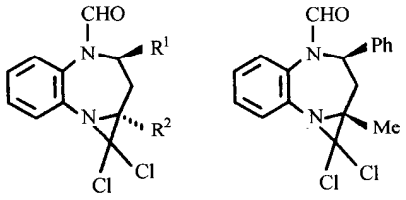
The mass spectrometric behaviour of four *cis*- and *trans*-1a,3-disubstituted-1,1-dichloro-4-formyl-1a,2,3,4-tetrahydro-1*H*-azirino[1,2-*a*][1,5]benzodiazepines has been studied with the aid of mass-analysed ion kinetic energy spectrometry and exact mass measurements under electron impact ionization. All compounds show a tendency to eliminate a chlorine atom from the aziridine ring, and then eliminate a neutral propene or styrene from the diazepine ring to yield azirino[1,2-*b*][1,3]benzimidazole ions. These azirino[1,2-*a*][1,5]-benzodiazepines can also eliminate HCl, or Cl plus HCl simultaneously to undergo a ring enlargement rearrangement to yield 1,6-benzodiazocine ions, which further lose small molecular fragments, propyne or phenylacetylene, with rearrangement to give quinoxaline ions.

Keywords 1*H*-Azirino[1,2-*a*][1,5]benzodiazepine, electron impact ionization, fragmentation mechanism, mass spectrometric studies, ring enlargement rearrangement

Introduction

Since the 1970s benzodiazepine derivatives have become well known as important therapeutic agents.[1-4] Interest has developed in correlations between the structures and properties of physiologically important benzodiazepines. Recently, it has been shown that some of their tricyclic derivatives with a fused five- or six-membered heterocyclic ring show effective activities as potential central nervous system depressants, antipsychotic agents, antiinflaminatory and antiallergic agents.[5-7] Thus, much attention has been paid to their syntheses, and structural and activity studies.[7-9] We have reported mass spectrometric studies on several series of tricyclic derivatives of benzothia/diazopine with fused five- or six-membered heterocyclic rings.[10-15]

Here we described studies on the fragmentation mechanisms under electron impact (EI) ionization conditions of four *cis*- and *trans*-1a,3-disubstituted-1,1-dichloro-4-formyl-1a,2,3,4-tetrahydro-1*H*-azirino[1,2-*a*][1,5]benzodiazepines (**1**—**4**), which had previously been synthesized and characterized by EI-MS, ^{1}H NMR, IR and elemental analysis.[16,17] Their stereo-structures, **1**—**4**, were also identified by X-ray crystal diffraction analysis.[18]



1—**3** **4**

1: R^1=Me, R^2=Ph; **2**: R^1=R^2=Ph, **3**: R^1=Ph, R^2=Me

Experimental

Low-resolution 70 eV EI mass spectra of compounds **1**—**4** were obtained using a double-focusing mass spectrometer (VG-ZAB-HS, Micromass, Manchester, UK) coupled with a PDP11-250 data system, using a direct insertion probe. The source temperature was 200℃ and the probe temperature was 220℃ for compounds **1** and

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2, 180℃ for compounds **3** and **4**, respectively. Elemental compositions of important fragment ions were determined by accurate mass determinations performed by using the same instrument at a resolution of 5,000 (10% valley), using the peak matching technique and perfluorokerosene (PFK) as a reference compound. Parent and daughter ion spectra were recorded by experiments of mass-analysed ion kinetic energy spectrometry (MIKE), in which the ZAB-HS was controlled by the MASPEC II data system.

Results and discussion

The characteristic EI fragment ions of four *cis*- and *trans*-1a,3-disubstituted-1,1-dichloro-4-formyl-1a,2,3,4-tetrahydro-1*H*-azirino[1,2-*a*][1,5]benzodiazepines (**1**—**4**) are compiled in Table 1. As an example of typical behaviour, the data from the MIKES analysis of compound **1** are listed in Table 2, and the high-resolution data are presented in Table 3. The EI spectrum of compound **1** is shown in Fig. 1.

The title compounds show low intense M^+ ions with 2—17% and moderately intense $[M^+ - Cl]$ ions with 4—50% relative abundances. Both of them show a tendency to eliminate HCl, or HCl plus Cl, to generate 1,6-benzodiazocine ions, which can further lose small molecular fragments, *i.e.* propyne or phenylacetylene, and undergo rearrangement to give quinoxaline ions. Both M^+ and $[M^+ - Cl]$ ions also show a tendency to eliminate styrene when their 3-substituents are phenyl groups, or propene when their 3-substituent is methyl group to yield azirinobenzimidazole ions.

Table 1 EI-MS of compounds **1**—**4**: *m/z* values (and relative abundances)*

Compound	M^+	a	b	c	d	e	f	g	h
1	346	311	310	-	-	275	269	260	247
	(4)	(18)	(18)			(100)	(2)	(4)	(42)
2	408	373	372	304	276	337	269	260	309
	(2)	(4)	(7)	(5)	(4)	(100)	(4)	(2)	(49)
3	346	311	310	242	214	275	207	198	247
	(13)	(36)	(5)	(15)	(6)	(6)	(81)	(4)	(26)
4	346	311	310	242	214	275	207	198	247
	(17)	(50)	(4)	(23)	(8)	(7)	(56)	(2)	(31)
Compound	i	j	k	l	m	n	o	p	q
1	246	241	232	231	207	205	179	143	42
	(10)	(3)	(19)	(12)	(5)	(8)	(6)	(7)	(7)
2	308	241	232	231	207	205	241	205	104
	(9)	(7)	(11)	(10)	(18)	(22)	(7)	(22)	(58)
3	246	179	170	169	145	143	157	205	104
	(6)	(100)	(3)	(3)	(8)	(29)	(3)	(3)	(21)
4	246	179	170	169	145	143	157	205	104
	(6)	(100)	(9)	(5)	(9)	(31)	(3)	(7)	(35)

* See Scheme 1 for proposed ion structures.

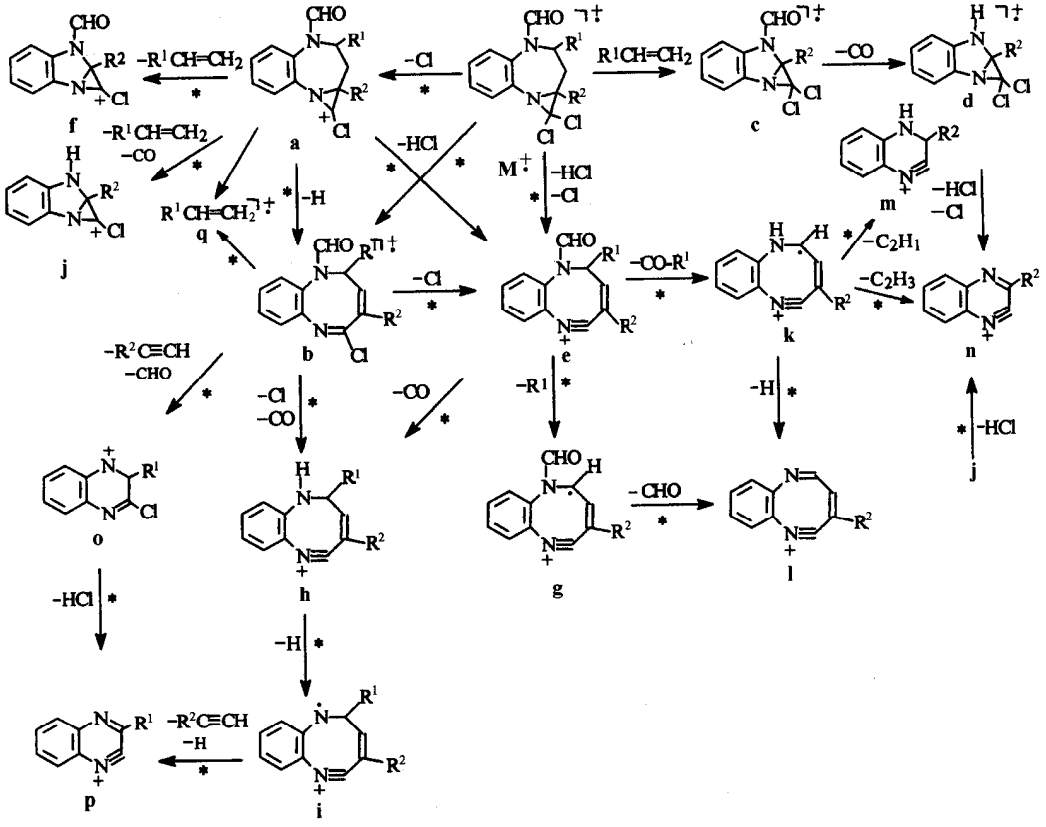
Table 2 MIKE spectra of compound **1**

Precursor ions (*m/z*)	Fragment ions (*m/z*)
346(M^+)	311(**a**),310(**b**),275(**e**)
311(**a**)	310(**b**),275(**e**),269(**f**),241(**j**),42(**q**)
310(**b**)	275(**e**), 247(**h**), 179(**o**), 42(**q**)
275(**e**)	260(**g**), 247(**h**), 232(**k**)
260(**g**)	231(**l**)
247(**h**)	246(**i**)
246(**i**)	143(**p**)
241(**j**)	205(**n**)
232(**k**)	231(**l**), 207(**m**), 205(**n**)
179(**o**)	143(**p**)

Table 3 High-resolution mass-measurement data for ions of compound **1**

m/z	Measured value	Calculated value	Difference (mmu)	Elemental composition
346	346.0630	346.0640	-1.0	$C_{18}H_{16}N_2Cl_2O$
275	275.1179	275.1184	-0.5	$C_{18}H_{15}N_2O$
247	247.1222	247.1235	-1.3	$C_{17}H_{15}N_2$
246	246.1149	246.1157	-0.8	$C_{17}H_{14}N_2$
241	241.0526	241.0533	-0.7	$C_{14}H_{10}N_2Cl$
207	207.0925	207.0922	0.3	$C_{14}H_{11}N$
205	205.0775	205.0766	0.9	$C_{14}H_9N_2$
179	179.0378	179.0376	0.2	$C_9H_8N_2Cl$
143	143.0609	143.0609	0.0	$C_9H_7N_2$

Scheme 1 Fragmentation pathways proposed for title compounds



* Fragmentation pathway confirmed by MIKES spectrum.

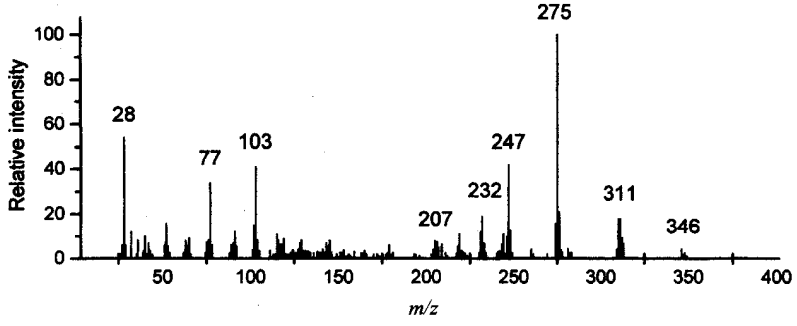


Fig. 1 EI spectrum of 1,1-dichloro-4-formyl-3-methyl-1a-phenyl-1a,2,3,4-tetrahydro-1*H*-azirino[1,2-*a*][1,5]benzodiazepine (**1**).

The fragmentation pathways of the title compounds can be proposed as shown in Scheme 1, as suggested by observations of the metastable ions and referring to the elemental compositions of the major ions (Table 3). The molecular ions M^+ can undergo α-cleavage to produce ions (**a**) by loss of chlorine atom. Both of them can eliminate HCl to give *N*-formyl-1, 6-benzodiacine ions (**b**) and (**e**), respectively, by *i*-cleavage, and, in the cases of **2-4**, eliminate styrene $R^1CH=CH_2$ to yield *N*-formyl-azirino[1,2-*a*]benzimidazole ions (**c**) and (**f**), and ions (**c**) can further eliminate CO to generate azirino [1,2-*a*] benzimidazole ions (**d**) by *i*-cleavage. Note that the molecular ion of compound **1** do not eliminate propene. The molecular ions M^+ also yield ions (**e**) by consecutive loss of HCl and Cl. $[M^+ - Cl]$ ions can also eliminate H atom from azirinobenzodiazepine rings by *i*-cleavage processes to yield formyl dihydro-1,6-benzodiazocine ions (**b**), which can further form 1,6-benzodiazocine ions (**e**) by *i*- and α-cleavage processes to lose Cl, form 1, 6-benzodiazocine ions (**h**) by *i*-cleavage processes to lose consecutively CO and Cl atom, and form quinoxaline ions (**o**) by rearrangements to lose CHO and propyne or phenylacetylene, which can further eliminate HCl to give quinoxaline ions (**p**).

The $[M^+ - Cl]$ ions (**a**) can undergo *i*- and α-cleavage processes to give azirino[1,2-*a*]benzimidazole ions (**j**) and propene or styrene ions (**q**). The ions (**h**) can undergo α-cleavage processes to lose H to give ions (**i**), which can also undergo rearrangement to yield quinoxaline ions (**p**). The ions (**e**) can undergo *i*, *i*-cleavage processes to give ions (**h**) by loss of CO. The ions (**e**) can undergo α-cleavage processes to give ions (**g**) by loss of R^1, which can further lose CHO to yield 1,6-benzodiazocine ions (**l**). The ions (**e**) can also undergo *i*, *i*, α-cleavage processes to give ions (**k**) by consecutive loss of CO and R^1, which can further yield 1,6-benzodiazocine ions (**l**) by loss of H, or yield quinoxaline ions (**n**) or dihydroquinoxaline ions (**m**) by loss of C_2H_3 or C_2H, respectively. Both of ions (**d**) and (**j**) can also yield ions (**n**) by loss of HCl plus Cl and HCl, respectively. The ions (**c**) can undergo *i*-cleavage processes to give dichloroazirino[1,2-*a*][1,3]benzimidazole ions (**d**) by loss of CO.

It is usually a characteristic fragmentation mechanism that the seven-membered heterocyclic system loses a neutral R^1-$CH=CH_2$ molecule from the benzodiazepine ring to produce ions (**c**). However, the compound **1** in this kind of compound with methyl group in 3-position does not undergo this cleavage. As shown in Table 1, the ions (**e**) of compounds **1** and **2** (R^1 = Me or Ph, R^2 = Ph) show the highest relative abundances, as base peaks. However, the ions (j) of the compounds **3** and **4** (R^1 = Ph, R^2 = Me, *trans* and *cis* isomers) are base peaks. These phenomena indicate some of meaningful correlations of the fragmentation mechanism with structural parameters, 1a- and 3-substituents. *Cis* and *trans* isomers show no difference except relative abundances.

Conclusion

The mechanisms of mass spectrometric fragmentation has been clarified for the *cis*- and *trans*-1a,3-disubstituted-1, 1-dichloro-4-formyl-1a, 2, 3, 4-tetrahydro-1*H*-azirino[1, 2-*a*][1, 5]benzodiazepines. The fragmentation mechanism shown in Scheme 1 is supported by MIKES spectra and some key ions have been defined via their elemental compositions obtained in the high-resolution spectra. We have proven that these title compounds can undergo α-cleavage to produce $[M^+ - Cl]$ and $[M^+ - HCl - Cl]$ ions, and can also lose neutral styrene to yield azirino[1,2-*a*][1,3]benzimidazole ions when R^1 = Ph. Both of M^+ and $[M^+ - Cl]$ ions in turn tend to eliminate HCl to produce 1, 6-benzodiazocine ions by rearrangements. These rearrangements are very interesting ring enlargement phenomena in electron impact spectra. 1, 6-Benzodiacine ions can further lose alkyne to give quinoxaline ions.

References

1. Sternbach, L.H., *Prog. Drug Res.*, **22**, 229(1978).
2. Roma, G.; Grossi, G.C.; Di, B.M.; Ghia, M.; Mattioli, F., *Eur. J. Med. Chem.*, **25**, 489(1991).
3. Xu, J.X.; Jin, S., *Chin. Chem. Lett.*, **3**, **181(1992)**.
4. Xu, J.X.; Jin, S., *Heteroatom Chem.*, **10**, 35(1999).
5. Hester, J.B.; Rudzik, Jr. A.D.; Framdas, B.V., *J. Med. Chem.*, **14**, 1078(1971).
6. Bliwise, D., *Curr. Therap. Res.*, **34**, 1009(1983).
7. Xu, J.X.; Jin, S., *Chin. Chem. Lett.*, **5**, 557(1994).
8. Aversa, M.C.; Ferlazzo, A.; Glannetto, P.; Kohnke, F.

H., *Synthesis*, 230(1986).
9. Xu, J.X.; Wu, H.T.; Jin, S., *Chin. J. Chem.*, **17**, 84(1999).
10. He, X.R.; Lin, X.Y.; He, M.Y.; Yu, Z.P.; Xu, J. X., *J. Chinese Mass Spectrom. Soc.*, **14**, 26(1993).
11. Xu, J.X.; He, M.Y.; Jin, S., *Rapid Commun. Mass Spectrom.*, **12**, 1115(1998).
12. Xu, J.X.; Wu, H.T.; Jin, S., *Rapid Commun. Mass Spectrom.*, **13**, 908(1999).
13. Xu, J.X.; Wu, H.T.; Jin, S., *Rapid Commun. Mass Spectrom.*, **13**, 963(1999).
14. Xu, J.X.; Lan, R.X.; Jin, S., *Rapid Commun. Mass Spectrom.*, **13**, 1506(1999).
15. Xu, J.X.; Lan, R. X.; Jin, S., *Rapid Commun. Mass Spectrom.*, **13**, 1511(1999).
16. Zhang, X. Y.; Jin, S.; Liao, R. A., *Chin. Chem. Lett.*, **3**, 179(1992).
17. Zhang, X.Y.; Xu, J.X.; Jin, S., *Chin. J. Chem.*, **17**, 404(1999).
18. Xu, J.X.; Zhang, X.Y.; Jin, S., *Chin. J. Struct. Chem.*, **18**, 152(1999).

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