Benzodiazepine Analogues. Part 20.‡ Mass Spectrometric Analysis of Benzoxathiepine Derivatives†

J. Chem. Research (S), 1999, 584–585†

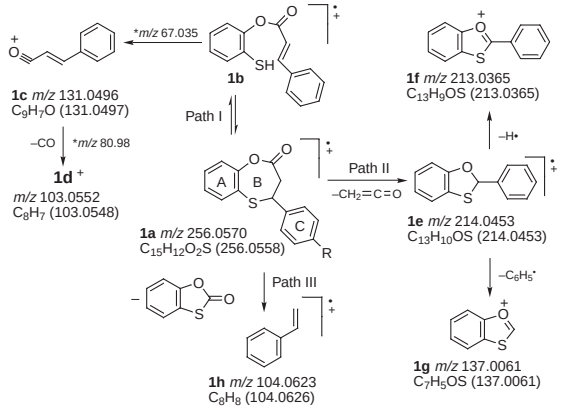
Aifheli C. Gelebe§ and Perry T. Kaye*

Department of Chemistry, Rhodes University, P.O. Box 94, Grahamstown, 6140, South Africa

Fragmentation patterns in the electron-impact (EI) mass spectra of benzoxathiepine derivatives are elucidated using a combination of high-resolution and comparative low-resolution mass spectrometric analysis.

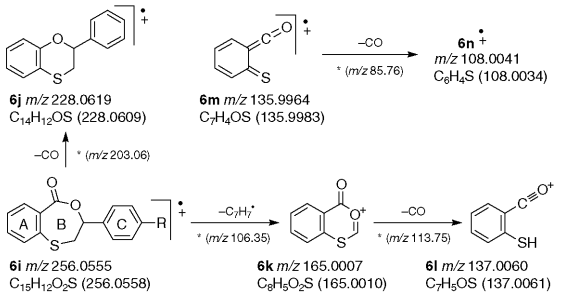
While the clinical use of benzodiazepines as anxiolytics is well established, a number of sulfur-containing analogues also exhibit useful medicinal properties. These analogues include the cardiac drug, diltiazem,[2] and the antimicrobial, 3*H*-1,5-benzoxathiepine-2,4-dione.[3] As part of an ongoing investigation of benzodiazepine analogues, we have reported the synthesis of various benzoxathiepine derivatives[4] and, here, we discuss the results of a mass spectrometric study of the latter compounds.

A combination of high-resolution, comparative low-resolution and metastable peak data was used to investigate the fragmentation of three series of benzoxathiepines, *viz*., the 4-phenyl-1,5-benzoxathiepin-2-ones **1**–**5**, the 3-phenyl-4,1-benzoxathiepin-5-ones **6**–**8** and the 3-phenyl-4,1-benzoxathiepines **9**–**12**. Selected MS data for these compounds are summarised in Table 1, while the proposed fragmentation pathways are outlined in Schemes 1–3.



Scheme 1 Mass-spectral fragmentation pathways for 4-phenyl-1,5-benzoxathiepin-2-one **1** (R = H). Accurate masses (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by the metastable peak given in parentheses.

4-Phenyl-1,5-*benzoxathiepin*-2-*ones* **1**–**5**.—Fragmentation in these systems appears to follow three major pathways. In Path I (illustrated for the parent system **1** in Scheme 1), cleavage of the heterocycle, presumably *via* radical cations of type **b**, isomeric in each case with the molecular ion **a**, affords the conjugated acylium cations **c**. Even-electron species of this type (**c**) account for the base peak for each of the compounds examined; decarbonylation then leads to the C-ring fragments **d**. Metastable peaks in the mass spectrum of the parent system **1** provide confirmation of the fragmentations **1a**/**b** (*m/z* 256) → **1c**(*m/z* 131) → **1d**(*m/z* 103).



Scheme 2 Mass-spectral fragmentation pathways for 3-phenyl-4,1-benzoxathiepin-5-one **6** (R = H). Other details as for Scheme 1.

Two distinct, intra-annular rearrangements (Fig. 1) account for the fragmentations **a** → **e** (Path II) and **a** → **h** (Path III). In the former, migration of O(1) to C(4) results in extrusion of ketene affording the ring-contracted benzoxathiolane species **e**; in the latter, migration of the sulfur to C(2) results in the loss of benzoxathiolan-2-one and detection of a styryl radical cation **h**. Loss of H· or a phenyl radical from the benzoxathiolane radical cation **e** then accounts for the resonance-stabilised fragments **f** and **g**. These intra-annular rearrangements parallel those observed in our earlier study of 1,5-benzodioxepin-2-one analogues[5] and, in fact, both series of compounds exhibit rather similar fragmentation patterns. Inspection of the mass contribution of the 4-substituents (R, Table 1) confirms that the ions of type **g** are A-ring fragments, ion-types **c**, **d** and **h** are C-ring fragments and ion-types **e** and **f** contain both A- and C-rings.¶

3-*Phenyl*-4,1-*benzoxathiepin*-5-*ones* **6**–**8**.—In spite of their structural similarity to the 1,5-benzoxathiepin-2-ones **1**–**5**, the 4,1-benzoxathiepin-5-ones **6**–**8** exhibit markedly different fragmentation patterns. In the parent system **6**, decarbonylation of the molecular ion **6i** accounts for the low-intensity peak at *m/z* 228(1%), which is attributed to

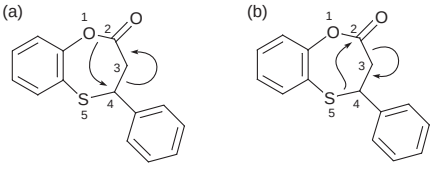


Fig. 1 Proposed intra-annular rearrangements in 4-phenyl-1,5-benzoxathiepin-2-one **1** resulting in the extrusion of: (a) ketene and (b) 1,3-benzoxathiolan-2-one.

* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡ Part 19: ref. 1.

§ Present address: Department of Chemistry, University of the North, Private Bag X1106, Sovenga, 0727, South Africa.

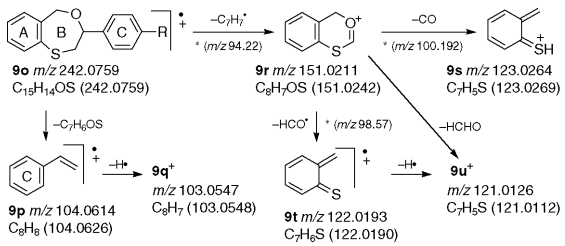
¶ See Scheme 1 for ring designations. In previous studies,[6] the designations have followed the convention used for the flavanoid precursors.

Table 1 Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from EI mass spectra of benzoxathiepines **1**–**12**, classified according to ion types **a**–**u**

Compd.	R	Ion type						
4-*Phenyl*-1,5-*benzoxathiepin*-2-*ones* (Scheme 1)		**a**/**b**	**c**	**d**	**e**	**f**	**g**	**h**
1	H	256(10)	131(100)	103(46)	214(2)	213(10)	137(9)	104(20)
2	Br[a]	334(6)	209(100)	181(9)	292(1)	291(3)	137(7)	182(10)
3	Cl[b]	290(8)	165(100)	137(23)	248(1)	247(4)	137(23)	138(12)
4	F	274(12)	149(100)	121(39)	232(2)	231(11)	137(8)	122(25)
5	OMe	286(11)	161(100)	133(19)	244(1)	243(5)	137(4)	134(24)
3-*Phenyl*-4,1-*benzoxathiepin*-5-*ones* (Scheme 2)		**i**	**j**	**k**	**l**	**m**	**n**	
6	H	256(21)	228(1)	165(93)	137(69)	136(100)	108(36)	
7	Br[a]	334(5)	306(0.5)[c]	165(100)	137(64)	136(78)	108(23)	
8	Cl[b]	290(9)	262(0.6)[c]	165(100)	137(78)	136(76)	108(22)	
3-*Phenyl*-4,1-*benzoxathiepines* (Scheme 3)		**o**	**p**	**q**	**r**	**s**	**t**	**u**
9	H	242(19)	104(10)	103(5)	151(100)	123(60)	122(96)	121(93)
10	Br[a]	320(5)	182(2)[c]	181(0.7)[c]	151(100)	123(51)	122(82)	121(76)
11	Cl[b]	276(8)	138(3)	137(3)	151(100)	123(50)	122(73)	121(67)
12	F	260(14)	122(100)[d]	121(93)	151(96)	123(69)	122(100)[d]	121(93)

[a] ^{79}Br data cited for ions containing Br. [b] ^{35}Cl data cited for ions containing Cl. [c] Low-intensity peaks detected (for both ^{79}Br and ^{35}Cl species) in a separate experiment on a Finnigan Mat GCQ mass spectrometer. [d] Peaks for ions **12p**(*m/z* 122.0532 ≡ C_8H_7F; 30%) and **12t**(*m/z* 122.0190 ≡ C_7H_6S; 70%) overlap at *m/z* 122; ratios determined in a separate high-resolution analysis. The % relative abundance figures, however, remain based on the low-resolution data.

the benzoxathiane radical cation **6j** (Scheme 2); the corresponding peaks in the spectra of the halogenated analogues **7** and **8** are even less intense. On the other hand, loss of C_7H_7· and contraction of the heterocycle leads to a cascade of A-ring fragments having the same mass as the corresponding parent systems, *viz*., ions **k** (*m/z* 165), **l** (*m/z* 137), **m** (*m/z* 136) and **n** (*m/z* 108), the fragmentations **i** → **k** → **l** and **m** → **n** being supported by the metastable peaks indicated in Scheme 2. In the absence of metastable peak data, the origin of fragments of type **m** remains uncertain; possibilities include: (i) **l** → **m** *via* loss of H·; (ii) **k** → **m** *via* loss of H· and CO; or (iii) **i** → **m** *via* loss of a styrene oxide equivalent. The common fragment responsible for the base peak in the spectra of the halogenated derivatives **7** and **8** is the resonance-stabilised 3,1-benzoxathian-4-one cation **k**, whereas the parent system **6** affords the thione species **6m** as the base peak.



Scheme 3 Mass-spectral fragmentation pathways for 3-phenyl-4,1-benzoxathiepine **9** (R = H). Other details as for Scheme 1.

3-*Phenyl*-4,1-*benzoxathiepines* **9**–**12**.—Fragmentation of the molecular ion in these systems leads to peaks attributed to the corresponding C-ring fragments **p**, subsequent loss of H· affording the ions of type **q** (Scheme 3). Elimination of the C-ring (as RC_7H_6·) and concomitant contraction of the B-ring accounts for the formation of the resonance-stabilised cation **r** (*m/z* 151), which is common to each of the compounds examined and generally responsible for the base peak. This and the subsequent fragmentations [**r** → **s** (*m/z* 123) and **r** → **t** (*m/z* 122)] are all supported by metastable peaks in the mass spectrum of the parent system **9**. While fragmentation of cation **r** may afford, *via* loss of HCHO, the even-electron species **u** (*m/z* 121), the alternative pathway **t** → **u** is also possible. Not surprisingly, the fragments **r** and **t** correspond to the equally abundant ions **k** and **m**, observed in the mass spectra of the 5-oxo analogues **6**–**8**, respectively (Scheme 2).

Experimental

The synthesis and characterisation of the benzoxathiepine derivatives **1**–**12** have been reported previously.[4] Low-resolution mass spectra were obtained on Hewlett-Packard 5988A and Finnigan Mat GCQ mass spectrometers. High-resolution data were collected on a Kratos double-focussing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit) using the following protocol: ionisation by electron impact; sample introduction by direct insertion probe; and accurate mass determination by peak matching. Metastable peak data were acquired on a graphic recorder using a Kratos high-resolution mass spectrometer.

We thank the Deutscher Akademischer Austauschdienst (DAAD) for a bursary (A.C.G.), Rhodes University and the Foundation for Research Development for generous financial support, and Mr A. Sonemann (Rhodes University) for collecting low-resolution MS data and Dr P. Boshoff (Cape Technikon) for high-resolution data.

Received, 29th March 1999; Accepted, 15th June 1999
Paper E/9/02499I

References

1 Part 19. J. M. Mphahlele and P. T. Kaye, *Magn. Reson. Chem., submitted.*
2 D. M. Floyd, R. V. Moqui, K. S. Atuval, S. Z. Ahmed, S. H. Spergel, J. Z. Gougoutas and M. F. Malley, *J. Org. Chem.,* 1990, **55**, 5572.
3 L. Bonsignore, G. Loy, D. Secci, A. DeLogu and G. Palmieri, *Farmaco*, 1990, **45**, 1245.
4 A. C. Gelebe and P. T. Kaye, *Synth. Commun.*, 1996, **26**, 4459.
5 A. C. Gelebe and P. T. Kaye, *S. Afr. J. Chem.*, 1992, **45**, 109.
6 See, for example, P. T. Kaye and J. M. Mphahlele, *J. Chem. Res.,* 1994, (*S*) 62; (*M*) 0367.