

The Mass Spectrometric Fragmentation Patterns of some Biologically Active Derivatives of 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides

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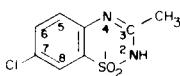
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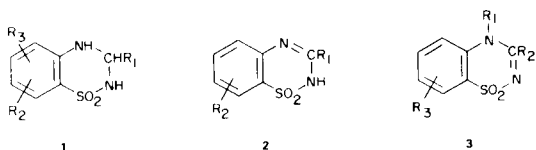
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The mass spectra of some twenty-six derivatives of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide are discussed. All compounds studied follow relatively simple fragmentation routes; as a consequence the fragmentation pattern gives a clear guide to the structure of the compound under investigation.

Analogs of the experimental antihypertensive drug, Diazoxide (3-methyl-7-chloro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide) are currently being evaluated for hyperglycemic, hypotensive and antidiuretic activity (1). The



present study of mass spectral fragmentation patterns of this compound and its derivatives indicates the value of this technique for the identification of these compounds and their metabolites, since in a majority of cases, well defined molecular ions were observed. The main groups of compounds studied were 1, 2, and 3, with the substi-



tutents on the benzene ring being H, Cl or CF_3 . In groups 1 and 2, the C-3 substituents were alkyl, aralkyl or aryl groups and in group 3, $\text{R}_1 = \text{CH}_3$. Fragmentation will be discussed in the order: group 1, 2, and 3.

Group 1. Compounds I-XIII.

The compounds studied are listed in Table I.

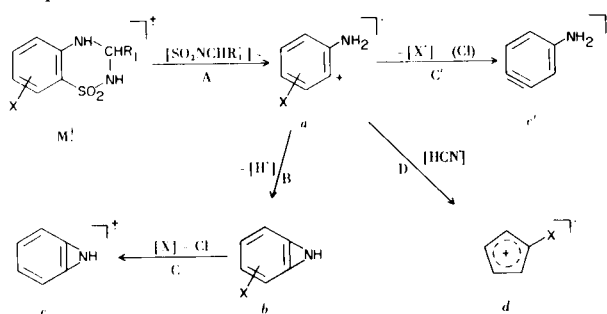
The obtained spectra will be discussed in terms of typical ions that occur in the majority of the spectra, the fragmentation routes being designated by the letters A-J, and respective fragments by a-j.

A.

Loss of $\text{SO}_2\text{-N}=\text{CHR}$ (Scheme 1). This gives rise to ions *a*, m/e 92 (I,IV), m/e 126 (II,III,V,VI,IX-XIII) and m/e 160 (VII,VIII).

B,C,D.

Ion *a* can lose H to yield *b* which further loses (2,3) Cl (when present) to yield *c*. A metastable transition (Table VI) in compound I confirms *a-b* transition. Ion *a* can also lose Cl to yield *c'* or HCl to yield *d*. Abundances are represented in Table II.



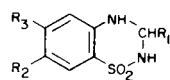
Scheme 1

A mass measurement on compound I where m/e for scheme A gives both (m-a) and *a* an equal 92 mass measurement did show 92 to correspond to 92, 0512 for $\text{C}_6\text{H}_5\text{N}$.

E.

Fragmentation corresponds to a loss of 28 in a case of $\text{R}_1 = \text{H}$ or $(27 + \text{R}_1)$ a.m.u. giving rise to peaks *e* at m/e 156 (I,IV), m/e 190 (II,III,V,VI,IX-XIII) and m/e 224 (VII, VIII).

TABLE I



Compound	R ₁	R ₂	R ₃	M ⁺ Molecular ion m/e %ab.		m/e	
				m/e	%ab.	m/e	a
I	H	H	H	184	36	92	a
II	H	H	Cl	218	48	126	a
III	H	Cl	H	218	43	126	a
IV	CH ₃	H	H	198	22	92	a
V	ClH ₃	H	Cl	232	66	126	a (a)
VI	CH ₃	Cl	H	232	100	232	M ⁺
VII	CH ₃	Cl	Cl	266	20	97	(C ₅ H ₂ Cl)
VIII	CH ₃	H	CF ₃	266	18	160	a
IX	C ₆ H ₅	Cl	H	294	75	126	a
X	C ₆ H ₅ CH ₂	Cl	H	308	9	217	h
XI	C ₆ H ₅ C = C	Cl	H	318	5	101	C ₆ H ₅ -C≡C
XII	n-C ₃ H ₇	Cl	H	260	11	217	h (b)
XIII	CH ₃ CH ₂ CH(CH ₃)CH(CH ₃)	Cl	H	302	0	126	a

(a) a see Table II. (b) h see Table III.

TABLE II

Compound	Fragments											
	a		b		c		c'		d			
m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	
I	92	100	91	24	n.a.	---	---	65	---	---	---	
II	126	100	125	10	90	44	91	10	99	23	23	
III	126	100	125	18	90	35	91	8	99	9	9	
IV	92	100	91	13	n.a.	---	n.a.	---	65	---	---	
V	126	100	125	15	90	46	91	20	99	22	22	
VI	126	88	125	20	90	20	91	26	99	14	14	
VII (a)	160	95	169	28	90	22	125	24	133	59	59	
VIII	160	100	159	---	n.a.	---	n.a.	---	133	---	---	
IX	126	100	125	24	90	36	91	13	99	34	34	
X	126	15	125	5	90	10	91	10	99	5	5	
XI	126	30	125	22	90	10	91	7	99	10	10	
XII	126	70	125	14	90	24	91	10	99	20	20	
XIII	126	100	125	---	90	25	91	11	99	24	24	

(a) In compound VIII, m/e 140 corresponding to a-HF 20% and m/e 132 corresponding to a-I-HCN 8% were observed.

TABLE III

Compound	Fragments											
	e		f		g		h		i			
m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	
I	156	50	108	33	119	18	n.a.	---	---	---	---	
II	190	81	142	56	153	14	n.a.	---	---	---	---	
III	190	38	142	32	153	16	n.a.	---	---	---	---	
IV	156	25	108	24	133	---	183	27	117	8	8	
V	190	78	142	46	167	---	217	62	---	---	---	
VI	190	23	142	48	167	---	217	96	151	21	21	
VII	224	21	176	55	201	---	251	22	185	4	4	
VIII	224	13	176	31	201	---	251	39	185	9	9	
IX	190	13	142	28	229	13	217	23	---	---	---	

TABLE III (Continued)

Compound	e		f		Fragments g		h		i	
	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab	m/e	%ab
X	190	6	142	13	243	---	217	100	---	---
XI	190	---	142	---	253 (a)	8	252 (a)	8	---	---
XII	190	7	142	30	195	---	217	100	---	---
XIII	190	---	142	32	237	---	---	---	---	---

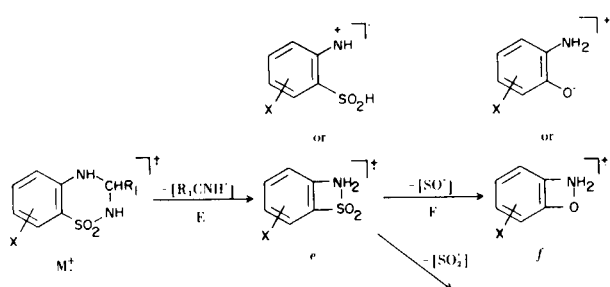
(a) Loss of H₂SO₄ occurs.

TABLE IV



Compound	R ₁	R ₂	R ₃	R ₄	R ₅	M ⁺ m/e	%ab	Base Peak m/e	
XIV	CH ₃	H	H	H	H	196	32	91	a'
XV	H	H	H	H	Cl	216	100	216	M ⁺
XVI	H	H	H	Cl	H	216	50	83	
XVII	CH ₃	H	H	H	Cl	230	34	189	e'
XVIII	CH ₃	H	H	Cl	H	230	38	125	a'
XIX	CH ₃	H	Cl	H	H	230	18	189	e'
XX	CH ₃	H	H	H	CF ₃	264	46	223	e'
XXI	CH ₃	CH ₃	H	Cl	H	244	100	244	M ⁺
XXII	C ₆ H ₅	H	H	Cl	H	293	30	189	e'
XXIII	C ₃ H ₇	H	H	Cl	H	258	14	125	a'

a', e' fragments See Table V.



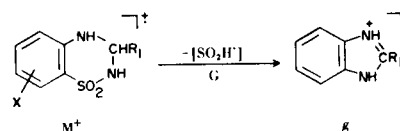
Scheme 2

F.

Loss of 48 a.m.u. (SO) to give m/e (I,IV) and m/e 142 (II,III,V,VI,IX-XIII) is observed here. Abundances of e and f ion are summarized in Table III. An alternative route to formation of fragment a in Scheme I can be loss of SO₂ from e.

G. (Scheme 3).

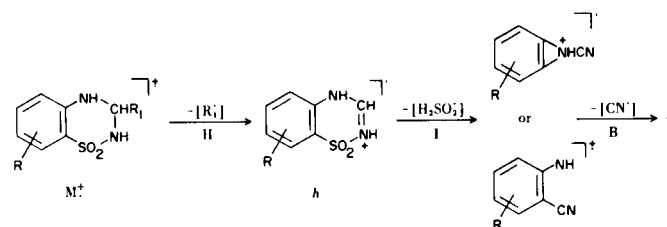
A loss of 65 a.m.u. (HSO₂) occurs giving rise to g, m/e 119 (I) and 153 (II,III) 229 (IX) (Abundances listed in Table III). A metastable transition observed in II and III confirms loss of 65 a.m.u.



Scheme 3

H,I. (Scheme 4).

These mechanisms are a useful modes to determine the nature of R₁, R₂, R₃ as it is leading to the loss of side chain R₁. The resulting fragment h, m/e 183 (IV), m/e 217 (V),



Scheme 4

TABLE V

Compounds	e'		Fragments a'		e''	
	m/e	%ab	m/e	%ab	m/e	%ab
XIV	155	81	91	100	n.a.	
XV	189	86	125	82	90	44
XVI	189	38	125	61	90	18
XVII	189	100	125	78	90	28
XVIII	189	86	125	100	90	24
XIX	189	100	125	34	90	23
XX	223	100	159 (a)	34	n.a.	
XXI	---	---	---	---	---	---
XXII	189	100	125	95	90	17
XXIII	(b)		125	100	90	33

(a) Additional loss of F ($a'-F$) m/e 140 %ab. 17. (b) Show gradual loss of the R_1 side chain ($M^+ - 15$), m/e 243, %ab. 13 ($M^+ - 26$), m/e 232, %ab. 96 ($M^+ - 67$), m/e 191, %ab. 26.

VI, X, XII) m/e 251 (VII, VIII) m/e 229 (IX) can further lose 66 a.m.u. (H_2SO_2) to yield i . A loss of CN (26 a.m.u.) offers an alternative route to fragment b . Abundances of h and i are listed in Table III.

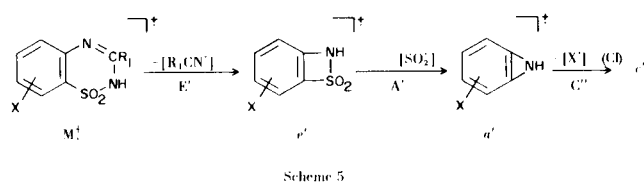
Group 2. Compounds XIV-XXIII.

The compounds studied are listed in Table IV. The presence of the additional double bond precludes some of the modes of fragmentation discussed previously. Thus only routes equivalent to or related to routes A, C, and E are observed.

E' , A' , C'' . (Scheme 5).

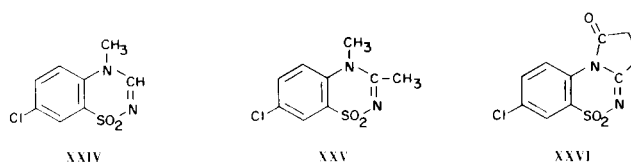
In this case, the loss is of R_1 CN (27 or 41 a.m.u.) leading to e' , the route being supported by metastables in com-

pounds XV, XVII, XVIII and XX (Table VI). This ion can further fragment by the loss of SO_2 to give a' , which in turn can lose Cl to yield e'' . Abundances of e' , a' , e'' are listed in Table V.



Group 3. Compounds XXIV-XXVI.

These are shown below and differ from Group 2 compounds in the position of the double bond. In compounds



XXIV and XXV, a retro-Diels-Adler (4) fragmentation (Scheme 6) is possible leading to e'' , m/e 203 (E''). XXIV % ab. 26, XV % ab. 88. This is confirmed by metastables in XXIV and XXV (Table VI). Both compounds show

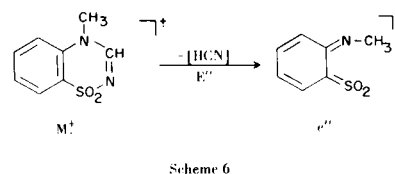


TABLE VI

Metastable Transitions

Compound	Observed	Calculated		Mechanism
I	90.1	90.0	92 = 91 + H	B scheme 1
II, III	107.8	107.4	218 = 153 - SO_2H	G scheme 3
XV	165.2	165.4	216 = 189 + HCN	E' scheme 5
XV	65	64.8	125 = 90 + Cl	C'' scheme 5
XVII, XVIII	155.2	155.3	230 = 189 + CH_3CN	E' scheme 5
XX	188.5	188.3	264 = 223 + CH_3CN	E' scheme 5
XX	227.4	227.1	264 = 245 + F	
XX	190.5	190.3	223 = 206 + F	
XX	123.3	123.5	159 = 140 + F	
XX	109.6	109.4	159 = 132 + HCN	
XXIV	179.0	179.2	230 = 203 + HCN	E'' scheme 6
	137.2	137.0	139 = 138 + H	B' scheme 1
XXV	169.0	168.9	244 = 203 + CH_3CN	E'' scheme 6
	137.0	37.0	139 = 138 + H	B' scheme 1
	110.7	110.6	139 = 124 + CH_3	
XXVI	147.5	147.6	242 = 189 + C_4H_5	

an a-type peak (Scheme 1) (m/e 139). $C_6H_3(Cl)NCH_3]^+$. This ion can lose a hydrogen atom to yield b' (supported by a metastable Table VI) $C_6H_3(Cl)NCH_2]^+$ and methyl radical to yield b'' (m/e 124). $C_6H_3ClN]^+$. Further, while XXIV shows a loss of 65 a.m.u. [SO_2H^+], XXV loses 64 a.m.u. presumably because of lack of a hydrogen on the 3-carbon atom. Both molecules show strong b' type peaks at m/e 138, and peaks due to C_6H_4Cl (m/e 111).

In the spectrum of XXVI, (m/e 205% ab. 27 is due to $(M^+ - SO_2H)$), the cyclic structure of the compound is evidenced by the fact that the molecular peak is the base peak.

Conclusions.

The appearance in the mass spectra of these compounds of reasonably intense molecular ions in most cases establishes the molecular weight. The A-type ions (normally very abundant) determine the composition of the benzenoid moiety while the substituent at C_3 is evidenced by the $(M-R_1)$ -peak (h) and confirmed by e . In the case of compounds with a 2,3 double bond, e'' represents the retro-Diels-Alder fragment.

EXPERIMENTAL

Measurements were made with a Perkin-Elmer GTC 270 instrument at a resolving power of about 900. Mass measurements when necessary, were done on an AEI MS 9. Probe temperatures of less than 100° were used and the electron beam energy was 80 e.V.

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