The Mass Spectrometric Fragmentation Patterns of Some Biologically Active 1,3,4-Thiadiazoles

Alicja M. Kirkien-Rzeszotarski

Department of Chemistry, Trinity College, Washington, D. C. 20017

W. J. Rzeszotarski

Division of Nuclear Medicine, Department of Radiology,
George Washington University, Washington, D. C. 20037

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Mass spectra of some twelve derivatives of 1,3,4-thiadiazole are reported. The fragmentation scheme of the 1,3,4-thiadiazole ring is specific and indicative as to the structure. Derivatives of 5-phenyl-1,3,4-thiadiazoles show rearrangement to isothiocyanates.

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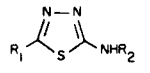
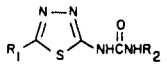
As a sequence to the study of fragmentation patterns of Diazoxide (2*H*-1,2,4-benzothiadiazine 1,1-dioxide) analogs (1), a group of 1,3,4-thiadiazole derivatives was investigated. Some of the derivatives show antihypertensive properties (2). Since in all cases, molecular ions are observed and fragmentation of the 1,3,4-thiadiazole ring follows a simple and characteristic pattern, this study might be useful as an identification technique of these compounds and their metabolites. Out of the thirty-six available compounds (2) twelve were chosen for this study. Those compounds fall into the three definite groups:

I. 5-Substituted 2-Amino-1,3,4-thiadiazoles
II. 2-Ureido and 2-Carbamoyl-1,3,4-thiadiazoles
III. 5-Substituted 2-Alkyamido-1,3,4-thiadiazoles.

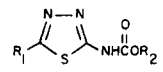


I

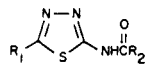


II

or

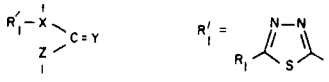


II



III

The R_1 substituents were either CH_3 or C_6H_5, R_2 substituents were NO_2, C_6H_5, *m*-C_6H_4Cl, CH_3 and C_2H_5. The objective was to determine the fragmentation patterns of the 1,3,4-thiadiazole ring as well as to confirm the previously reported fragmentation patterns of the compounds with the general formula IV,



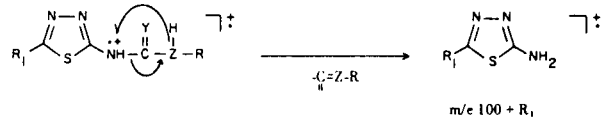
IV

where Z = X = N and Y = O in ureas (3-6), X = N and Y = Z = O in carbamates (6,7), both in group II and X = N, Y = O, Z = C in amides (8), group III.

In all the above mentioned compounds the substituent on X = N would be the thiadiazole ring (R_1'). This consideration guided us in selection of the compound studied. The results and discussion will be presented in order: Group I, II and III.

Group I. Compounds **1-4**. (Table I).

This group fully illustrates the fragmentation pattern of the heterocyclic ring. In groups II and III the fragmentation of the ring always takes place from the rearranged ion in which a 1'-3' hydrogen transfer is followed by the loss of a fragment yielding the 2-amino-1,3,4-thiadiazole ion (Group I)

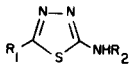


m/e 100 + R_1

which then follows the fragmentation presented in Scheme I and is characteristic for all three groups of compounds.

The fragmentation routes are denoted by letters a-d and the respective fragments by A-D. Fragments are listed in Table II and the metastable transitions are noted next to the fragments. *a*. The loss of R_1CN from the molecular ion gives rise to m/e 74 in all the cases with the exception of compound **4** where this step is preceeded by loss of R_2=NO_2 thus giving m/e 73. This elimination of R_1CN is supported by metastables in compounds **1-3** and is characteristic for a heterocyclic 5 or 6 membered ring (13) with the -C=N- configuration. It was also observed in
R

Table I



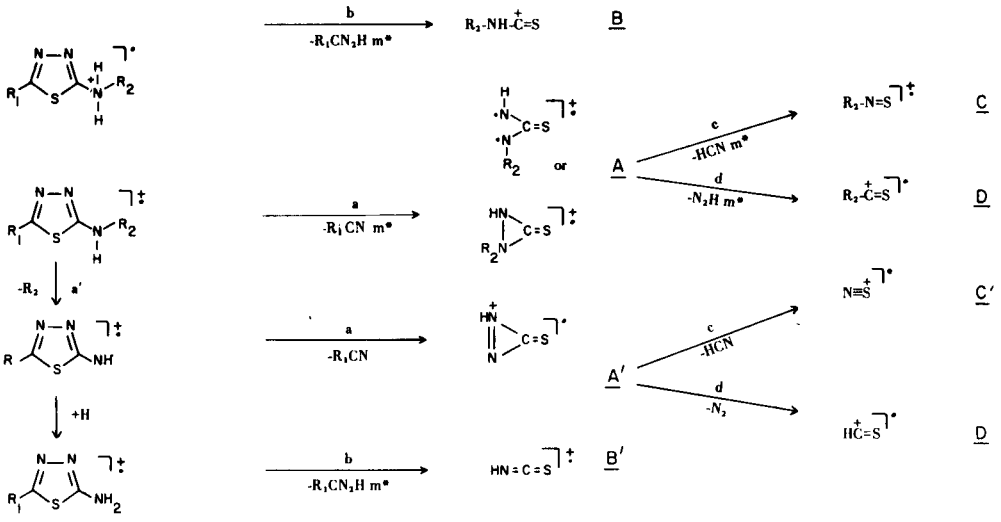
Compound	R_1	R_2	M^+ Molecular m/e	Ion % ab	Base m/e	Composition	Mechanism (a)
1	H	H	101	88	45	$S=\overset{+}{C}H$	d
2	CH_3	H	115	70	74	$HNCSNCH_3$	a
3	C_6H_5	H	177	100	M^+		
4	H	NO_2	146	54	45	$S=\overset{+}{C}H$	d

(a) See Table II.

Table II

Compound	A m/e	A % ab	B m/e	B % ab	C m/e	C % ab	D m/e	D % ab
1	74 m*	93	60 m*	45	47 m*	22	45 m*	100
2	74 m*	100	60	13	47 m*	8	45 m*	6
3	74 m*	60	60	3				
4	73 A′	18	59 B′	17	46C′ m*	25	45	100

Scheme I

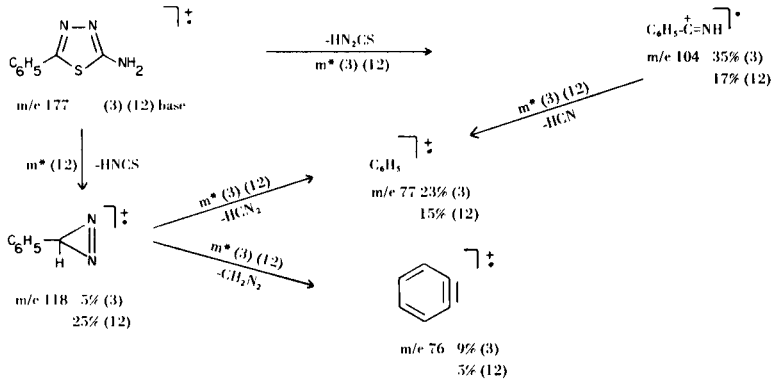


derivatives of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides (1). This step is sensitive to the nature of the heteroatom adjacent to the ring. Barnes, *et al.*, (9) reported a loss of sulfhydryl radical followed by carbon insertion in the ring in 2-amino-4-alkylthio-1,3,4-thiadiazole. No nitrile loss was observed. In 1,2,3-thiadiazoles, where the double bond is between nitrogens, loss of N_2 was predominant (10) making the loss of nitrile fragment from the ring impossible. In the case of 1,3-thiazoles which have the necessary -C(R)=N= configuration the nitrile elimination was the major step as here.

Protonated molecular ion by route *b* can form fragment B (thioformamide) m/e 60 (1-3) supported by a metastable transition in compound **1** and m/e 59 (4).

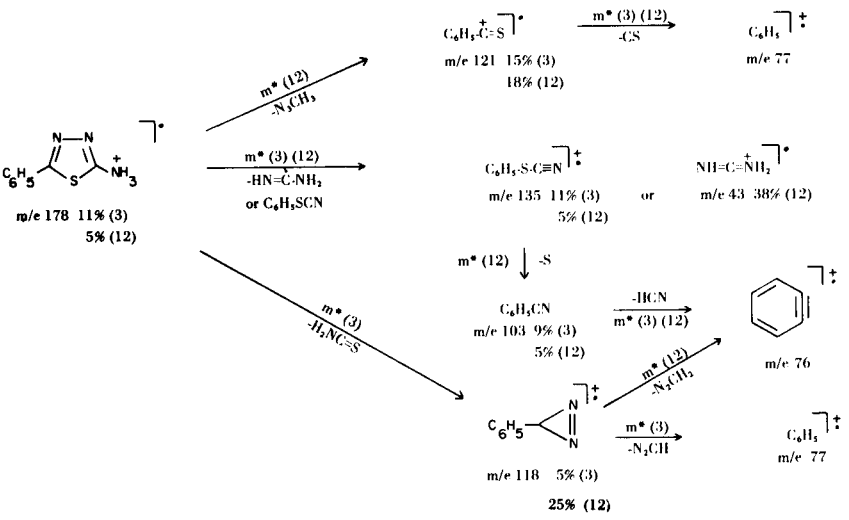
Fragment A undergoes two concurrent fragmentations by mechanisms: *c*. Loss of HCN giving rise to m/e 47 (1,2) supported by metastable and m/e 46 in compound **4** and *d*. Loss of N_2H (1-3) and N_2 (**4**) a very stable D m/e 45 supported by metastable in 1,4 where it is in the base peak.

Scheme 2



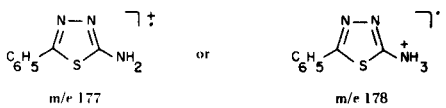
(3) (12) notation is used to indicate metastable transitions and relative abundances.

Scheme 3



(3) (12) Notation is used to indicate metastable transitions and relative abundances.

Compound **3**, the 5-phenyl substituted 1,3,4-thiadiazole is of special interest because three competing fragmentations of the ring occur here. It will be discussed together with compound **12**, a 5-phenyl substituted amide (group III) because after the 1′-3′ hydrogen transfer (equation 1) the fragmentation of the ring starts with an ion of m/e 177 or a protonated ion of m/e 178. The stability of this ion is increased by the 5-phenyl group due to the conjugated double bonds and m/e 177 is the base peak of both compounds.



Schemes 2 and 3 represent the alternative fragmentation route specific to 5-phenyl compounds as an alternative to Scheme 1.

In Scheme 2 the most important steps are losses of the fragments HNCS and HN_2CS giving rise to m/e 118 and 104.

Scheme 3 starts by postulating protonation of the basic m/e 177 (unique for 5-phenyl compounds) and its three fold decomposition into: 1. C_6H_5-$\overset{+}{C}$=S m/e 121; 2. Rearrangement into C_6H_5-S-C=N^+ m/e 135 and fragment m/e 43, both can be charge retaining, and 3. Loss of H_2NCS leading to m/e 118, this fragment also appears in Scheme 2.

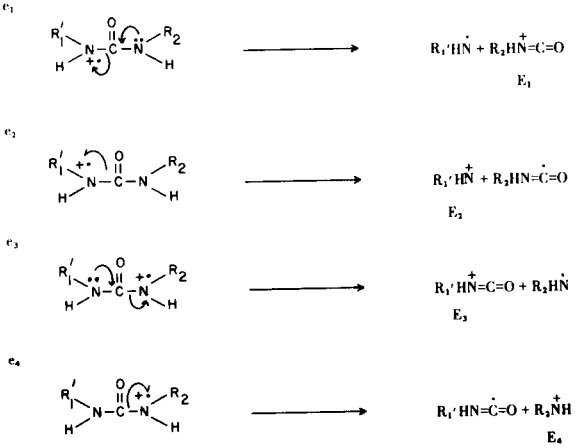
Final products of the fragmentation are the same in both schemes: m/e 77 and 76.

All the steps in both schemes are documented by metastable transitions. We would like to emphasize the uniqueness of the fragmentation of 5-phenyl substituted 1,3,4-thiadiazole which can concurrently occur by the three routes indicated in Schemes 1-3. Compound **4** in addition to fragments listed in Table II shows additional loss of a NO group from the M^+ ion giving a rise to m/e 116 (18%) supported by a metastable.

Group II.

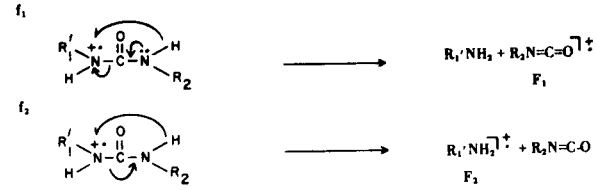
Compounds **5-8** (ureas) and **9** (carbamate) are listed in Table III. The fragmentation routes of 2-ureido-1,3,4-thiaziazoles confirm the general patterns proposed for alkyl and aryl substituted ureas (3-5), thioureas (4,11) and selenoureas (6). The interest of the ureas studied here is the unsymmetrical substitution of N^1 and N^3 atoms combined with the presence of hydrogen at each of those atoms. This results in eight predominant routes according to the fission of C-N^1 or C-N^3 bonds with or without hydrogen transfer towards or away from the nitrogen substituted by the heterocyclic ring with charge retention on either fragments.

Thus, with R_1' =  the possible routes without hydrogen transfer are:

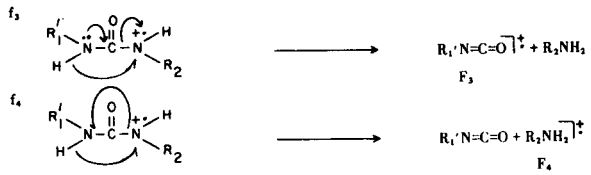


The E_{1-4} fragments are listed in Table IV and confirm the charge retaining ability of either of the N atoms (12), resulting in bond scission of either of the C-N bonds.

The next set of fragments $F_{1,2}$ results from hydrogen transfer towards the R_1' substituted nitrogen



and finally $f_{3,4}$ mechanisms with hydrogen transfer away from the R_1' substituted nitrogen resulting in F_3 and F_4 fragments.



All the fragments are listed in Table IV.

The foute f_2 yields the m/e 101 fragment, the 2-amino-1,3,4-thiadiazole which then decomposes according to Scheme 1. Fragments of this decomposition are listed in Table V. In compound **6** the additional C_6H_5N fragment is present at m/e 91 (32%) (1,6). In compound **7**, the corresponding ClC_6H_4N fragment m/e 125 is present (15%) and metastable transition shows its origin from $M^+ \rightarrow 125$ and 154 (E_1) → 125. No loss of H_2O was observed in studied compounds though it is characteristic for thio and selenoureas (loss of H_2S or H_2Se) where the charge bearing atoms are S and Se respectively (6,12). Compound **8**, Z = O, only follows the routes e_{1-4} and $f_{1,2}$ which indicate that there is no tendency to transfer hydrogen to the methoxy oxygen, suggesting that N^1 is the only charge retaining heteroatom (no F_3 observed).

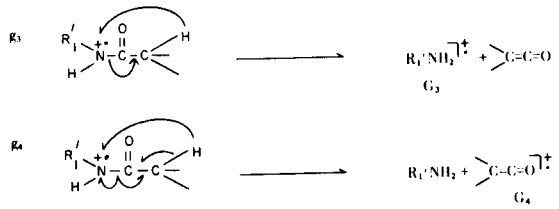
Group III. 2-Alkylamido-1,3,4-thiadiazoles (Compounds **9-12** listed in Table VI).

R_1'-NH-C(=O)-R_2

Scission on both sides of the carbonyl group is observed leading to two fragments G_1 and G_2

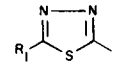
Both of those ions are analogous to the E_1 and E_3 ions in ureas. It is interesting to note that the ion corresponding to E_2 = $R_1'N^+H$ does not appear in the spectra of the amides.

As in the ureas we observe a 1'-3' hydrogen transfer to the charge bearing nitrogen by mechanisms g_3 and g_4.

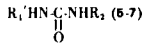


G_3 corresponds to the F_2 fragment and G_4 to the F_1 fragment in ureas fragmentation patterns. The hydrogen transfer from nitrogen (f_3 and f_4 mechanisms in the ureas) is precluded by structure of the amides. G_3, the 2-amino-1,3,4-thiadiazole further fragments according to Scheme 1 and all the fragments are listed in Table VII. Compound **11** shows an interesting metastable transition: 157 → 129 a possible loss of C_2H_4 from M^+ giving m/e 129. In compound **12** the further fragmentation of the G_3 ion was fully discussed with compound **3** in group 1.

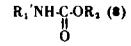
Table III



= R'1



(5-7)



(8)

Compound	R_2	m/e	M^+ ion %	Base m/e	Composition	Mechanism (a)
5	H	144	15	101	$R_1'NH_2$ m*	f_2
6	C_6H_5	220	10	93	R_2NH_2	f_4
7	C_6H_5Cl	254	6	127	R_2NH m* and $R_1'NCO$	$f_3 + f_4$
8	CH_3	159	36	45	HCS	d

(a) See Table IV.

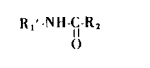
Table IV

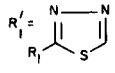
Compound	E_1 m/e	E_1 % ab	E_2 m/e	E_2 % ab	E_3 m/e	E_3 % ab	E_4 m/e	E_4 % ab	F_1 m/e	F_1 % ab	F_2 m/e	F_2 % ab	F_3 m/e	F_3 % ab	F_4 m/e	F_4 % ab
5	44	51	100	8	128m*	16			43	38	101m*	100	127	15		
6	120	8	100	11	128	19	92	20	119	36	101	73	127	10	93	100
7	154	4	100	19	128m*	36	126	6	153	32	101	76	127	100%	127	
8	59	76	100	5	128	5			58	13	101	6				

Table V

Compound	A m/e	A % ab	B m/e	B % ab	C m/e	C % ab	D m/e	D % ab
5	74 m*	27	60	19	47	5	45 m*	46
6	74 m*	17	60	20			45 m*	32
7	74	20	60	7				
8	74 m*	32	60	36	47	11	45	100

Table VI





Compound	R_1	R_2	M^+ Molecular m/e	ion % ab	Base m/e	Composition	Mechanism (a)
9	H	H	129	19	101	$R_1'NH_2$	93
10	CH_3	CH_3	157	11	43	CH_3CO	G_1
11	H	C_2H_5	157	11	57	C_2H_5CO	G_1
12	C_6H_5	CH_3	219	36	177	$R_1'NH_2$	93

(a) See Table VII.

Table VII

	G_1		G_2		G_3		G_4		A		B		C		D	
Compound	m/e	% ab	m/e	% ab	m/e	% ab	m/e	% ab	m/e	% ab	m/e	% ab	m/e	% ab	m/e	% ab
9					101m*	100			74m*	32	60	23	47	13	45	56
10	43	100	128	3	115m*	56	42	15	74m*	45	60	5			45	10
11	57	100	128	2	101	15	56	5	74	7					45	27
12	43	38	204	2	177	100	42	5	74	32	60	4			45	6

EXPERIMENTAL

The compounds were prepared as reported (2). Spectrometric measurements were made with an AEI MS 9 at the source temperature 70° using the direct inlet system with an electron beam of 70 eV. The metastable data were obtained by the defocussing technique.

Acknowledgments.

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