# Selenium-Sulfur Analogs. Mass Spectrometric Comparison of Substituted Selenazoles and Thiazoles



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The electron impact mass spectra of a series of thiazoles and selenazoles were compared. No major differences in the mass spectral behavior between the sulfur and selenium containing compounds were observed. Isotopic labelling with deuterium permitted deconvolution of ion peaks of identical mass and composition, but arising from different fragmentation pathways.

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Because of the similarity in their chemical properties, the substitution of selenium for sulfur has been examined in a large number of naturally occurring and synthetic sulfur-containing compounds (1-3). As part of a research program currently underway in our laboratories to develop new radiopharmaceuticals we have been involved in the synthesis of selenium analogs of biomedically important sulfur-containing compounds. To this end we have synthesized a variety of new selenazoles, selenophenes, selenazolidines, as well as their corresponding sulfur analogs (4-7). Because of the potential use of mass spectrometry for the analysis of these compounds or their metabolites in a biological medium, we have undertaken the examination of their mass spectral characteristics using electron impact ionization mass spectrometry. Moreover, the availability of both the sulfur and selenium analogs allowed us to examine the relative influences of these elements on the mass spectral fragmentations.

The mass spectrometric properties of selenium-containing organic compounds have been reviewed by Agenäs (8). A feature of the mass spectra of selenium compounds is that they are rich in peaks due to the occurrence of six relatively abundant stable selenium isotopes. This feature has been used to determine the structure of compounds containing S and Se combinations based on the isotope content of fragment ions (9).

A number of studies have compared the mass spectrometric properties of organic oxygen, sulfur, and selenium compounds. Whereas it was originally believed that the mass spectra of sulfur and selenium analogs resemble each other quite closely, more recent studies have revealed some distinct variations when different classes of compounds are involved. For example, no major differences were seen in the mass spectral fragmentations of S- or Se-containing ureas (10) or 2-acylmethylbenzothia- (or selena)-imidazoles (11). Similarly, an examination of the mass spectrum of diaza-2,5-dioxa-1,6-thia-6a-thia-λ-IV--pentalene and its selenium and tellurium analogs showed fragmentation patterns independent of the nature of the heteroatom (S, Se or Te) (12). On the other hand, the lower energy of the C-Se as opposed to that of the C-S bond apparently results in major differences between the mass spectra of S and Se heteroaromatics or other S(Se)-heterocyclics. For example, loss of a neutral Se atom from the molecular ion to give an ion corresponding to $[M\text{-}Se]^+$, occurs more favorably in benzoselenazoles (13), selenaphenanthrenes (14) and 2,3-disubstituted-benzoselenophenes (15) than the loss of sulfur in the thio analogs. This type of elimination is extended to 1,6,6a-$\lambda^4$-triselenapentalenes which exhibit abundant ions corresponding to $[M\text{-}Se_3H]^+$. Analogous ions were not observed in the spectra of 1,6,6a-$\lambda^4$-trithiapentalenes. A more dramatic difference in the mass spectral behavior of sulfur and selenium compounds is observed when the heteroatoms are involved in ionically induced rearrangement reactions. Novel O and OH migrations to selenium acceptors were observed in the spectra of selenium compounds containing ortho-nitrophenyl groups (16), but the same migrations were not encountered in the spectra of the sulfur analogs (17).

In conjunction with the observed elimination of a selenium atom from the molecular ion in the mass spectra of Se-containing heteroaromatic systems, it should be noted that it is not clear whether the process is ionically or thermally induced, or perhaps both. Many Se-containing heteroaromatic systems are reported to be thermally sensitive and have been shown to undergo facile thermal expulsion of a selenium atom (8,18).

## Results and Discussion.

The compounds examined in this study can be divided into the following categories:

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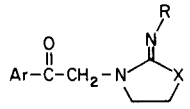
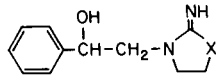
Group 1. Thiazolidines and Selenazolidines of General Formula I (Compounds Ia-Ih)



*I*

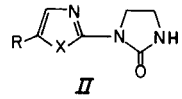
| Compound | Ar | R | X |
|---|---|---|---|
| Ia |  | H | S |
| Ib |  | H | Se |
| Ic |  | H | S |
| Id |  | H | Se |
| Ie |  |  | S |
| If |  |  | Se |
| Ig |  |  | S |
| Ih |  |  | Se |

Also included in Group I are the hydroxy analogs Ii and Ij.



Ii, X = S
Ij, X = Se

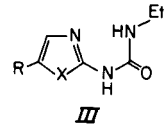
Group II. Thiazoles and Selenazoles of General Formula II (Compounds IIa-IId)



*II*

| Compound | R | X |
|---|---|---|
| IIa | H | S |
| IIb | H | Se |
| IIc | $-NO_2$ | S |
| IId | $-NO_2$ | Se |

Group III. Thiazoles and Selenazoles of General Formual III (Compounds IIIa-IIId)

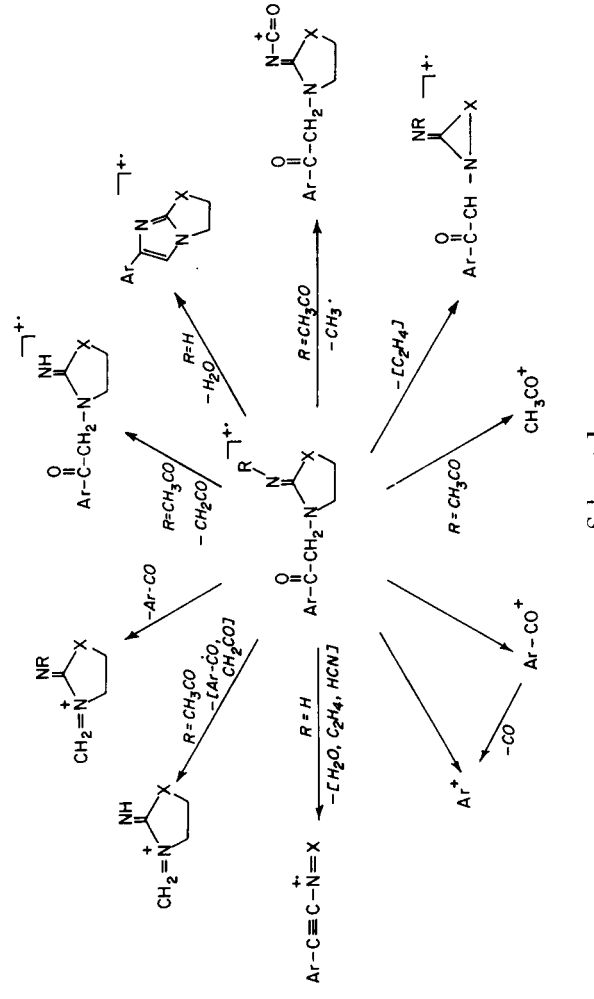


*III*

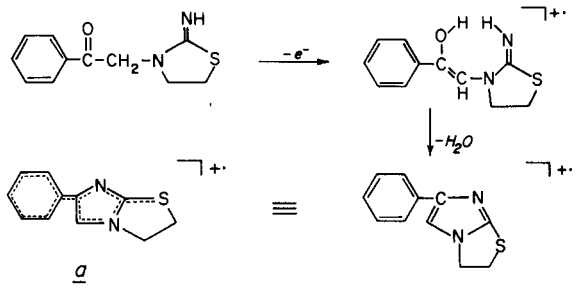
| Compound | R | X |
|---|---|---|
| IIIa | H | S |
| IIIb | H | Se |
| IIIc | $-NO_2$ | S |
| IIId | $-NO_2$ | Se |

## Mass Spectra of Compounds in Group I.

Partial mass spectra of compounds Ia-Ih are given in Table 1. A scheme summarizing the various fragmentation pathways is presented in scheme 1. The processes shown are supported by metastable evidence and deuterium labelling of the labile O-H or N-H hydrogens. The selenium isotope pattern further served as a marker to identify the portions of the molecule associated with the indicated fragment ions. Because of its somewhat unique features the complete mass spectrum of compound Ii is shown in Figure 1a along with that of its O-$^2$H, N-$^2$H labelled counterpart (Figure 1b) and that of its selenium analog Ij (Figure 1c), and disussed in more detail in this section.

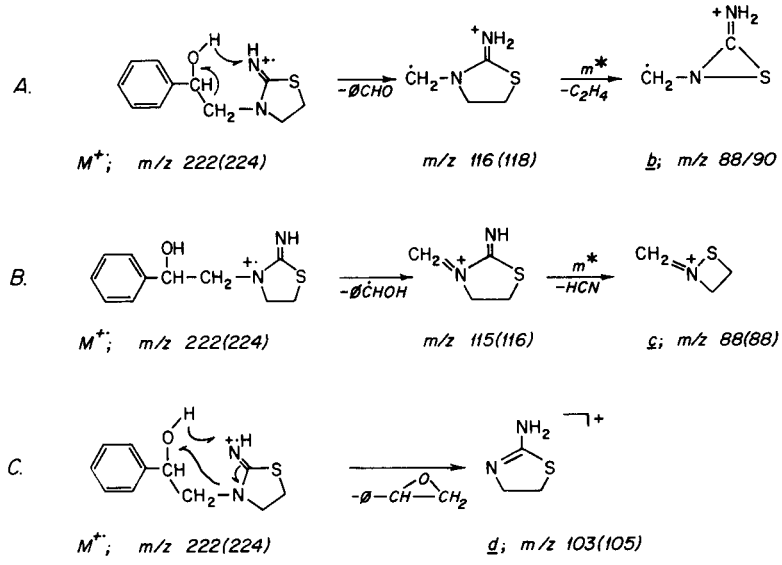


Scheme I



Scheme 2

Proposed mechanism for the elimination of water in the spectra of compounds in group I.



Scheme 3

Major fragmentation pathways (A,B,C) for compound Ii. Numbers in parenthesis refer to mass values of indicated fragment ions in the mass spectrum of the O,N-$^2H_2$ labelled analog.

In general, the mass spectra of compounds Ia-Ih are characterized by the low relative intensity of the molecular ion peaks. A common and somewhat unique feature of compounds Ia-Id is the favorable loss of a water molecule from the molecular ion, resulting in the base peak in the spectra of these compounds. The driving force for this fragmentation is probably the formation of the highly conjugated ion *a* as shown in scheme 2. Isotopic labelling of the amino nitrogen with deuterium confirmed its participation in the loss of water, presumably *via* the enolized intermediate shown in scheme 2. Formation of this intermediate should be ionically induced, as the deuterium isotope exchange reaction with $^2H_2O$ revealed incorporation of only one $^2H$ atom in the molecular ions of Ia-Id.

In comparing the spectra of the carbonyl compounds Ia-Ih to those of the hydroxy compounds Ii and Ij, it is somewhat surprising to note that the elimination of water from $M^{+\cdot}$ in the spectra of the latter compounds is considerably suppressed (Figure 1). Instead, these compounds fragment *via* three major pathways as shown in scheme 3. Of interest is the formation of two different ions (*b* and *c*) which have the same nominal mass (m/z 88) but different compositions. These ions are formed in roughly equal proportions as evidenced from the mass spectrum (Figure 1b) of the $^2H_2$-labelled analog of the sulfur compound in which the peak of m/z 88 has been deconvoluted into the doublet of m/z 88 and m/z 90. The indicated loss of ethylene leading to ion *b* has been frequently observed in the mass spectra of S or Se heterocyclic ring compounds (19,20).

Except for some minor variations in the relative intensities, the mass spectrum of the selenium analog Ij approximates very closely that of its sulfur counterpart Ii. Note for example the ion of m/z 103 (*d*, scheme 3) in the spectrum of the sulfur compound (Figure 1a) which is shifted

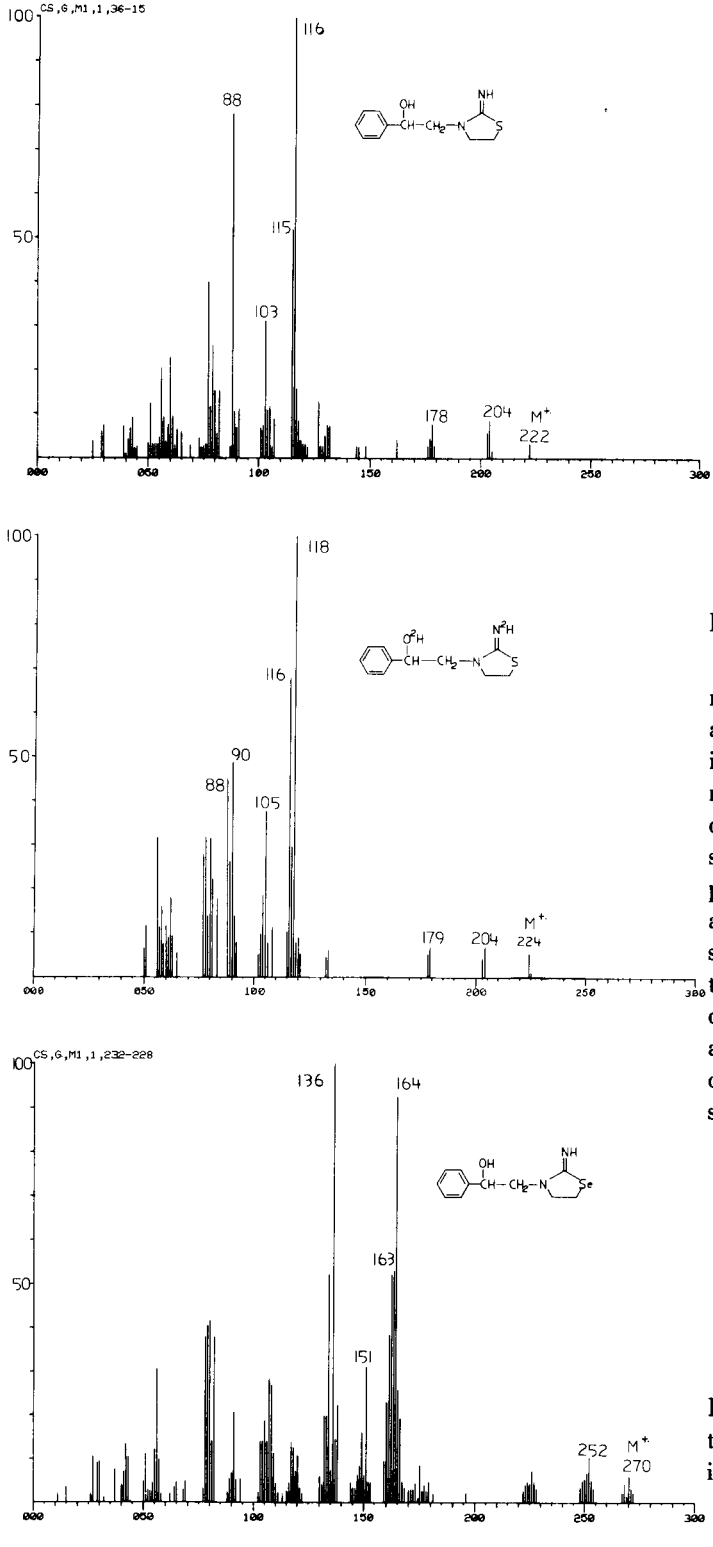


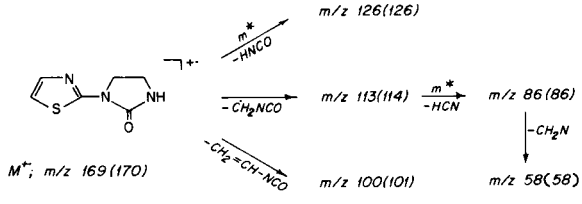

Figure 1

to m/z 151 in the spectrum of the selenium analog (Figure 1c). An additional fragmentation of interest is the loss of 44 U from $M^{+\cdot}$ in the spectra of Ii (m/z 178) and Ij (m/z 266) corresponding to the elimination of $CH_2NO$.

Contrary to some of the previous literature on related compounds (13-15,18), expulsion of Se or SeH from the molecular ion was not prevalent in the spectra of compounds of Group I. In certain instances loss of S or HS from $M^{+\cdot}$ with our compounds seemed to occur even more favorably than that of Se or SeH (*e.g.* compare Ic to Id and Ia to Ib, Table 1). However, loss of a selenium atom was considerably more prominent than that of sulfur when considering the formation of the ion $[M\text{-}H_2O\text{-}X]^+$. In addition to the latter process, the Se heteroatom may be responsible for variations in the relative abundances of ions of the type $Ar\text{-}C{\equiv}O^+$ and $[M\text{-}ArCO]^+$ when comparing the spectra of sulfur and selenium analogs. Presumably the ability of the outer electrons of selenium to undergo valence expansion and thus contribute to the stabilization of the resulting radicals and/or cations influences these fragmentations in the spectra of the Se analogs (Table 1).

## Mass Spectra of Compounds in Group II.

The mass spectra of the componds in Group II are summarized in Table 2. Fragmentation of these compounds is apparently initiated by cleavage of the C-N bond connecting the carbonyl carbon and the adjacent tertiary nitrogen, and is followed by elimination of various isocyanate containing species as shown in scheme 4 for the sulfur analog, IIa. The validity of these fragmentation pathways is supported by isotopic labelling of the labile amino hydrogen, the selenium isotope patterns in the spectrum of IIb, as well as the group labeling provided by the $NO_2$ functions in compounds IIc and IId. The spectra of the nitro compounds exhibit additional fragmentations arising from elimination of NO and/or $NO_2$, typical of compounds of this type. No major variations between the sulfur and selenium analogs were observed.




Scheme 4

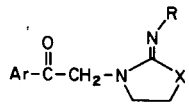
Principal fragmentation processes in the spectrum of the thiazole, IIa. Numbers in parenthesis refer to mass values in the spectrum of the N-$^2$H labelled analog.

## Mass Spectra of Compounds in Group III.

The mass spectra of compounds IIIa-IIId are summarized in Table 3. No major differences are noted between the spectra of sulfur and selenium analogs. The processes leading to the formation of the major ions in the spectrum

Table 1

Partial Mass Spectra of Compounds in Group I

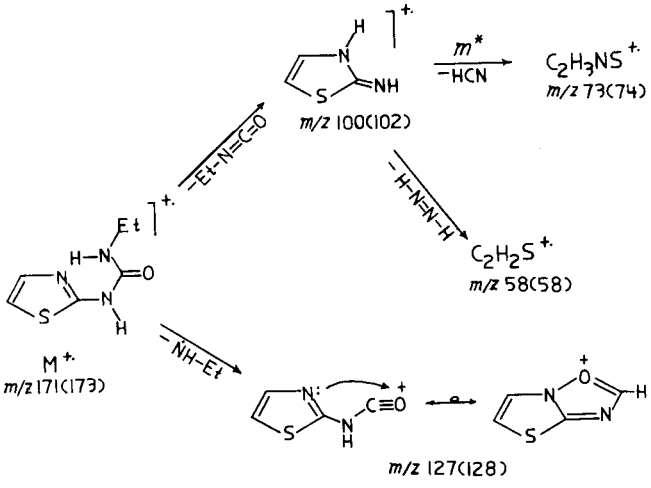


*I*

| Type of Ions | Compound 1a | 1b | 1c | 1d | 1e | 1f | 1g | 1h |
|---|---|---|---|---|---|---|---|---|
| $M^{+\cdot}$ | 220 (a,b) (17) (c) | 268 (10) | 226 (11) | 277 (17) | 262 (21) | 310 (11) | 268 (9) | 316 (21) |
| $[M-CH_3]^+$ | - | - | - | - | 247 (27) | 295 (8) | 253 (24) | 301 (9) |
| $[M-H_2O]^{+\cdot}$ | 202 (100) | 250 (100) | 208 (67) | 256 (85) | - | - | - | - |
| $[M-X]^+$ | 188 (1) | 236 (<1) | 194 (14) | 194 (<1) | 232 (<1) | 278 (6) | 236 (<1) | 236 (<1) |
| $[M-HX]^{+\cdot}$ | 187 (2) | 235 (<1) | 193 (<1) | 193 (13) | 231 (<1) | 277 (<1) | 235 (<1) | 235 (<1) |
| $[M-H_2O-X]^+$ | 170 (<1) | 170 (12) | 176 (<1) | 176 (14) | 212 (<1) | 212 (5) | 218 (<1) | 218 (<1) |
| $[M-C_2H_4]^{+\cdot}$ | 192 (20) | 240 (6) | 198 (24) | 246 (12) | 234 (7) | 282 (6) | - | 288 (4) |
| $[M-CH_2=C=O]^{+\cdot}$ | - | - | - | - | 220 (17) | 258 (6) | 226 (8) | 274 (5) |
| $[M-H_2O-C_2H_2-HCN]^{+\cdot}$ | 147 (16) | 195 (17) | 153 (20) | 201 (26) | - | - | - | - |
| $[M-(Ar(CO)CH_2)]^+$ | 101 (28) | 149 (8) | 101 (53) | 149 (50) | 143 (46) | 191 (16) | 143 (83) | 191 (72) |
| $[Ar-C\equiv O]^+$ | 105 (21) | 105 (26) | 111 (27) | 111 (95) | 105 (56) | 105 (88) | 111 (56) | 111 (100) |
| $[M-(Ar(CO))]^+$ | 115 (75) | 163 (24) | 115 (100) | 63 (67) | 157 (32) | 205 (17) | 157 (23) | 205 (18) |
| $[M-(Ar(CO))CH_2=C=O]$ | - | - | - | - | 115 (100) | 153 (62) | 115 (100) | 163 (99) |
| $C_2H_4N_2X^+$ | 88 (53) | 136 (29) | 88 (58) | 136 (100) | 88 (23) | 136 (33) | 88 (29) | 136 (44) |
| $Ar^+$ | 77 (25) | 77 (27) | 83 (4) | 83 (9) | 77 (23) | 77 (80) | 83 (5) | 88 (11) |
| $CH_3-C\equiv O^+$ | - | - | - | - | 43 (23) | 43 (100) | 43 (30) | 43 (79) |

(a) Number refers to mass of indicated ion. (b) Ion masses based on $^{80}Se$ isotope. (c) Values in parentheses refer to relative intensities.

of the sulfur analog IIIa are shown in scheme 5. In all cases the base peak is formed by elimination of ethylisocyanate *via* a six-membered ring hydrogen transfer.




Scheme 5

Principal fragmentations in the spectrum of the thiazole IIIa. Numbers in parenthesis refer to m/z value in the spectrum of the N-$^2H_2$ labelled analog.

The results of this study indicate that, in general, the mass spectrometric fragmentation patterns of the selenium heterocycles can be predicted by an examination of the corresponding sulfur analog. The analysis of the mass spectrum of the sulfur compound will therefore aid in the selection of a specific ion from the selenium fragmentation pattern for use in monitoring the levels of the compound in biological fluids. The uniqueness of the selenium isotope pattern will provide the ability to discriminate the desired fragment from any coincidental ions arising from other compounds in the fluid.

Acknowledgment.

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## EXPERIMENTAL

Mass spectra were determined with a Nuclide 12-90-G magnetic mass spectrometer interfaced to a DA-CS-I data system. The ionizing voltage was 70 eV, ionizing current 50 μA, and the accellerating voltage was 4.5 kV. Samples were introduced into the ion source via the direct insertion probe.

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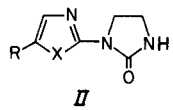
Table 2

Major Ions Recorded for Compounds of Group II



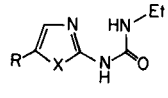
II

| Type of Ion | Compound IIa | IIb (b) | IIc | IId (b) |
|---|---|---|---|---|
| $M^{+\cdot}$ | 169 (a) (55) (c) | 217 (100) | 214 (75) | 262 (100) |
| $[M\text{-}HNCO]^{+}$ | 126 (22) | 174 (16) | 171 (13) | 219 (20) |
| $[M\text{-}(CH_2\text{-}NCO)]^{+}$ | 113 (100) | 161 (80) | 158 (100) | 206 (50) |
| $[M\text{-}CH_2\text{=}CH\text{-}NCO)]^{+\cdot}$ | 100 (22) | 148 (18) | 145 (38) | 193 (30) |
| $[M\text{-}(CH_2NCO)\text{-}HCN]^{+}$ | 86 (16) | 134 (16) | - | - |
| $[M\text{-}(CH_2NCO)\text{-}NO_2]^{+}$ | - | - | 112 (21) | 160 (10) |
| $C_2H_2X^{+}$ | 58 (33) | 106 (24) | - | - |
| $C_2HX^{+}$ | - | - | 102 | 106 |

(a) Number refers to ion mass. (b) Ion mass based on $^{80}Se$ isotope. (c) Numbers in parentheses refer to % relative intensity.

Table 3

Partial Mass Spectra of Compounds in Group III



III

| Type of Ion | Compound IIIa | IIIb (b) | IIIc | IIId (b) |
|---|---|---|---|---|
| $M^{+\cdot}$ | 171 (a) (11) (c) | 219 (15) | 216 (10) | 264 (28) |
| $[M\text{-}NHEt]^{+}$ | 127 (7) | 157 (7) | 172 | 220 |
| $[M\text{-}EtNCO]^{+\cdot}$ | 100 (100) | 148 (100) | 145 (100) | 193 (100) |
| $[M\text{-}EtNCO\text{-}HCN]^{+\cdot}$ | 73 (18) | 121 (7) | - | - |
| $[M\text{-}EtNCO\text{-}NO_2]^{+}$ | - | - | 99 (27) | 146 (42) |
| $C_2H_2S^{+\cdot}$ | 58 (27) | 106 (30) | 57 (18) | 105 (25) |

(a) Number refers to ion mass. (b) Ion mass based on $^{80}Se$ isotope. (c) Numbers in parentheses refer to % relative intensity.

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