Mass Spectral Study of Differently Substituted 2-Oxo- and 2-Thioxo-1,3,4-benzotriazepines

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The mass spectra of seven 2-thioxo- and four 2-oxo-1,3,4-benzotriazepines were recorded under electron ionization, and the fragmentation patterns were elucidated by exact mass measurement and metastable ion analysis. Some variations in the nature and position of the substituents greatly affected the mass spectra, allowing easy differentiation of isomeric compounds. The most characteristic feature of the mass spectral behavior of the compounds was the large number of ring contraction and complicated rearrangement reactions.

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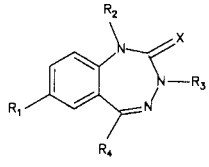
1,4-Benzodiazepines find wide use as drugs because of their powerful therapeutic activity. This importance has continually stimulated interest in bioisosteric analogues like the 1,3,4-benzotriazepines. However, the synthesis of these compounds is often complicated by the formation of five- and six-membered heterocycles in side reactions, making it necessary to prove the structure of the target compounds. In proof of the structures, compounds have been prepared by independent synthesis and a number of spectroscopic methods have been applied [1,2].

Mass spectrometry is a powerful method for the identification of isolated drugs and their metabolites. The mass spectra of some 1,3,4-benzotriazepines have been reported [3-6], but no systematic studies of fragmentation have been carried out. In this paper we describe the fragmentation analysis of some 2-thioxo- and 2-oxo-1,3,4-benzotriazepines, compounds **1-11**, under electron ionization. Our aim was to find out if the 1,3,4-benzotriazepine ring system can be unambiguously identified by mass spectrometric methods. At the same time we wished to examine the dependence of the fragmentation pathways on the nature and position of the substituents with a view to differentiating between isomeric compounds. The fragmentation pathways were verified by metastable ion analysis and collision induced dissociation measurements. Exact mass measurement was used to confirm the elemental composition of the principal fragment ions.

The structures of the compounds are given in Scheme 1 and their mass spectral data in Tables 1 and 2. All compounds were relatively stable under 70 eV electron ionization, giving rise to only a few abundant fragment ions. The molecular ion peak was always the base peak in the spectrum.

Compounds **1-5** are 2-thioxo derivatives with a methyl substituent at N(3). This methyl group strongly directed

Scheme 1



Compound	X	R_1	R_2	R_3	R_4
1	S	H	H	CH_3	H
2	S	H	H	CH_3	CH_3
3	S	Cl	H	CH_3	CH_3
4	S	H	H	CH_3	C_6H_5
5	S	Cl	H	CH_3	C_6H_5
6	S	Cl	CH_3	H	C_6H_5
7	S	Cl	H	H	C_6H_5
8	O	H	H	CH_3	H
9	O	H	H	CH_3	CH_3
10	O	Cl	H	CH_3	CH_3
11	O	H	H	CH_3	C_6H_5

Scheme 2

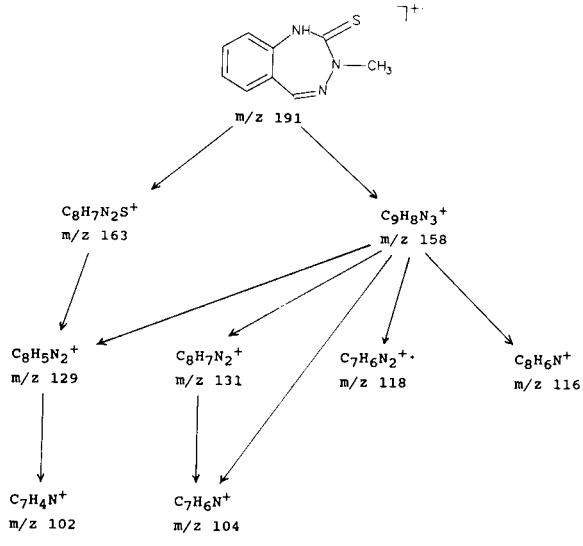


Table 1

Principal Fragment Ions (Intensity ≥8%) in the Mass Spectra of the 2-Thioxo-1,3,4-benzotriazepines Studied. Data are corrected for ^{37}Cl contribution, otherwise uncorrected. m/z (% Relative Intensities).

1 191 (100) $M^{+\cdot}$, 163 (27), 162 (9), 158 (40), 131 (10), 129 (43), 118 (9), 104 (9), 103 (10), 102 (8), 77 (11), 63 (9)

2 205 (100) $M^{+\cdot}$, 177 (20), 176 (9), 173 (9), 172 (47), 161 (13), 160 (12), 143 (21), 132 (9), 131 (11), 130 (9), 128 (8), 118 (20), 117 (8), 116 (10), 102 (9), 90 (9), 77 (14), 64 (10), 63 (8), 51 (8), 46 (13), 45 (9), 36 (14), 30 (14)

3 239/241 (100) $M^{+\cdot}$, 211/213 (25), 210/212 (14), 207/209 (12), 206/208 (60), 195/197 (11), 194/196 (10), 180/182 (9), 179/181 (8), 177/179 (21), 166/168 (10), 165/167 (13), 164/166 (11), 152/154 (21), 124/126 (8), 117 (9), 102 (10), 43 (10), 42 (8), 30 (15)

4 267 (100) $M^{+\cdot}$, 239 (29), 238 (15), 237 (33), 235 (14), 234 (51), 224 (14), 223 (20), 206 (8), 205 (22), 194 (8), 165 (8), 104 (9), 77 (32), 51 (12)

5 301/303 (100) $M^{+\cdot}$, 273/275 (31), 272/274 (17), 271/273 (33), 269/271 (14), 268/270 (55), 239/241 (15), 223 (32), 222/224 (10), 165 (8), 163 (8), 133 (13), 104 (8), 77 (40), 51 (14), 43 (11)

6 301/303 (100) $M^{+\cdot}$, 273/275 (12), 272/274 (11), 242/244 (12), 241/243 (56), 239 (11), 237 (92), 228/230 (42), 222 (17), 163 (9), 165 (10), 77 (29), 75 (9), 51 (15)

7 287/289 (100) $M^{+\cdot}$, 286/288 (52), 229/231 (29), 228/230 (8), 224 (10), 223 (34), 126 (18), 77 (29), 51 (14)

Table 2

Principal Fragment Ions (Intensity ≥8%) in the Mass Spectra of the 2-Oxo-1,3,4-benzotriazepines Studied. Data are corrected for ^{37}Cl contribution, otherwise uncorrected. m/z (% Relative Intensities).

8 175 (100) $M^{+\cdot}$, 147 (31), 133 (25), 132 (31), 125 (13), 118 (17), 111 (21), 109 (13), 104 (13), 97 (30), 96 (12), 95 (19), 91 (12), 85 (22), 83 (27), 82 (11), 81 (18), 77 (18), 71 (32), 70 (11), 69 (28), 67 (11), 57 (47), 56 (12), 55 (31), 51 (11) 43 (40), 41 (18)

9 189 (100) $M^{+\cdot}$, 161 (22), 147 (24), 145 (15), 132 (11), 131 (11), 128 (18), 117 (10), 97 (8), 91 (10), 90 (13), 77 (9), 71 (9), 69 (8), 63 (8), 57 (13), 55 (8), 43 (12)

10 223/225 (100) $M^{+\cdot}$, 195/197 (20), 181/183 (23), 180/182 (58), 179/181 (19), 166/168 (10), 165/167 (13), 162/164 (11), 145 (8), 124/126 (10), 117 (16), 116 (8), 90 (8), 89 (15), 63 (13), 43 (18)

11 251 (100), 250 (20), 223 (10), 221 (8), 209 (24), 208 (52), 180 (16), 152 (8), 77 (22), 51 (8)

the decompositions of the compounds, while the other substituents introduced only minor differences. The main fragmentation pathways for compound **1** are presented in Scheme 2. It is emphasized that many of the structures of fragment ions employed in this paper are assumed only.

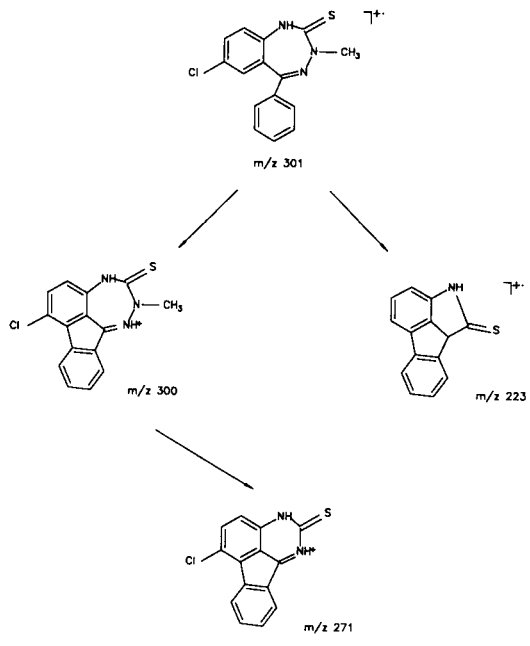
There were two important primary decomposition routes for compound **1**. One was a ring contraction reaction with loss of $CH_2N\cdot$ moiety. This led to the formation of quinazoline structure, stabilized by ring conjugation, from which H_2S was easily eliminated after a hydrogen atom migration. The other route started with the elimination of HS· and gave rise to the ion $[C_9H_8N_3]^+$ at m/z 158. In both of these primary decompositions, the most probable preliminary step was a hydrogen atom transfer from the methyl group at N(3) to the sulfur atom. This hydrogen atom migration can easily take place *via* a five membered transition state if the methyl group is in equatorial position so that its hydrogen atoms approach close to sulfur. Even if the methyl group at N(3) prefers the axial position, in analogy to some fused oxazine derivatives [7], there are no sterical factors that should prevent the existence of equatorial position as well.

The m/z 158 ion formed by elimination of HS· from the molecular ion decomposed through several routes to various ring contraction products. One of these reactions was the elimination of CH_3N, which showed that hydrogen atom in the primary migration reaction must also have originated from somewhere else than the methyl group. One possibility is that the loss of HS· took place through an enthiol form, in which case hydrogen would originate from N(1). To test the existence of this "enolization" under mass spectrometric conditions we attempted to deuterate the hydrogen atom at N(1) in compound **1**. Although only partly successful, deuteration showed that compound **1** did lose DS· to some extent. Interestingly, related enolization has not been observed for these compounds in the liquid phase [6].

Besides the fragmentation pathways mentioned, the molecular ion of compound **1** lost NH_2, CH_3N, S, CH_3N_2, CS, CHS, and CHNS, but none of these losses led to abundant fragment ions. The methyl substituent at C(5) in compound **2** did not noticeably affect the decomposition routes of 1,3,4-benzotriazepine ring. The same applied to the chlorine atom at C(6) in compound **3**.

Introduction of the phenyl group to C(5), however, caused an additional decomposition to become important, compound **4**, Table 1. This was the formal elimination of CH_4N from the molecular ion, which most probably took place in two steps ($M^{+\cdot}$-H·-CH_3N). It is possible for the phenyl substituent to approach so near the skeletal benzene ring that a new five-membered ring forms between positions 6 and 2′ of the two aromatic rings. In this process, one H· would be lost and the second H· transferred to the nitrogen atom at position 4 (*cf.* Scheme 3). Related behavior has been proposed earlier by Sadée [8] for 1,4-benzodiazepin-2-ones and by Geneste *et al.* [9] for imidazo benzodiazepines. Based on their studies on deuterium-labelled 5-phenyl-1,4-benzodiazepin-2-ones, Benz *et al.* [10] proposed that the ring-opened molecular ion is the source for hydrogen elimination and that ring closure between the 3 and 2′ carbon atoms follows this hydrogen elimination. This kind of ring-opening reaction is not, however, probable with our compounds. With the 1,4-benzodiazepines of Benz *et al.*, the $[M\text{-}H]^+$ ion is always very stable but, this was not the case with our 2-thioxo-1,3,4-benzotriazepines. Also the loss of CH_3N would hardly have taken place if the rearrangement proposed by Benz *et al.* [10] had occurred with our compounds.

Scheme 3



The spectrum of compound **5** shows yet another abundant fragment ion, namely $[C_{14}H_9NS]^{+\cdot}$ at m/z 223 (Scheme 3). The formation of this ion requires consecutive losses of CH_3N_2 and Cl, or *vice versa*, accompanied by extensive rearrangements. In addition, the product ion at m/z 223 must be very stable because it is an odd electron ion formed from an even electron ion. By contrast, the two fragment ions $[M\text{-}CH_3N_2]^+$ and $[M\text{-}Cl]^+$ are weak. The inductive effect of the chlorine atom weakens the double bond between N(4) and C(5) by driving electrons towards the aromatic ring and/or by decreasing the basicity of the nitrogen atom at position 4. This lowers the energy barrier for the elimination of CH_3N_2 from the molecular ion. With compound **5** the presence of the phenyl group at C(5) allows the rearrangements necessary for the further elimination of chlorine atom.

The introduction of a methyl group at N(1) instead of N(3) had a drastic effect on the fragmentations of 2-thioxo-1,3,4-benzotriazepines, as can be seen by comparing the mass spectra of compounds **5** and **6** (Figure 1). Although these two compounds are isomers differing only with respect to the position of the methyl group, their low resolution 70 eV mass spectra are vastly different in appearance. Almost all the fragment ions were nominally the same, but their relative intensities and ion compositions were mostly different. As can be seen from Schemes 3 and 4, the main fragmentation pathways for compound **6** were quite different from those for compound **5**.

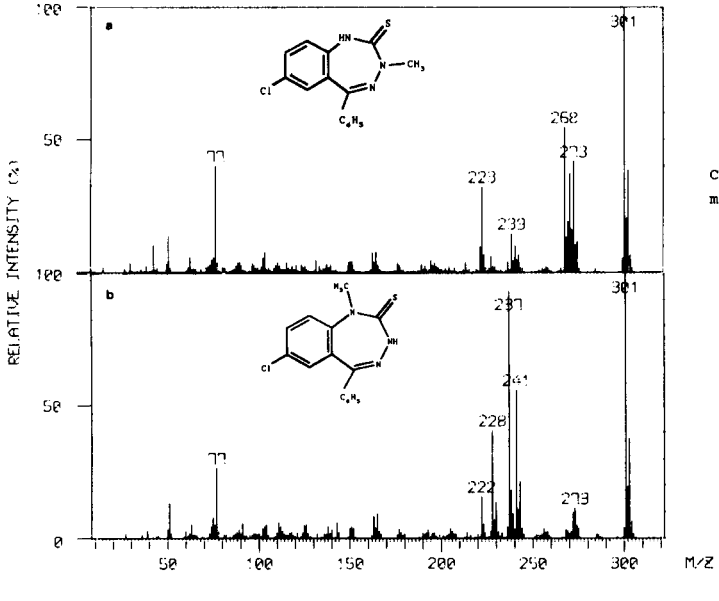
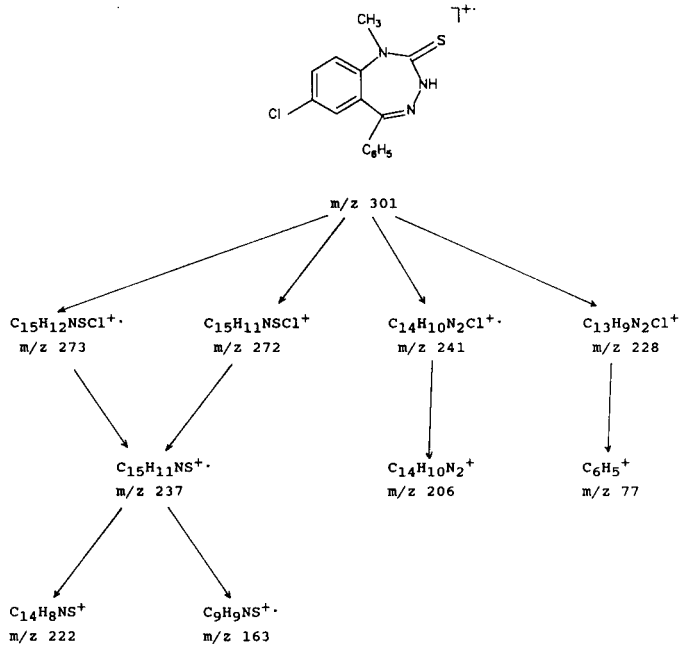


Figure 1. The 70 eV mass spectra for a) compound **5** and b) compound **6**.

Scheme 4

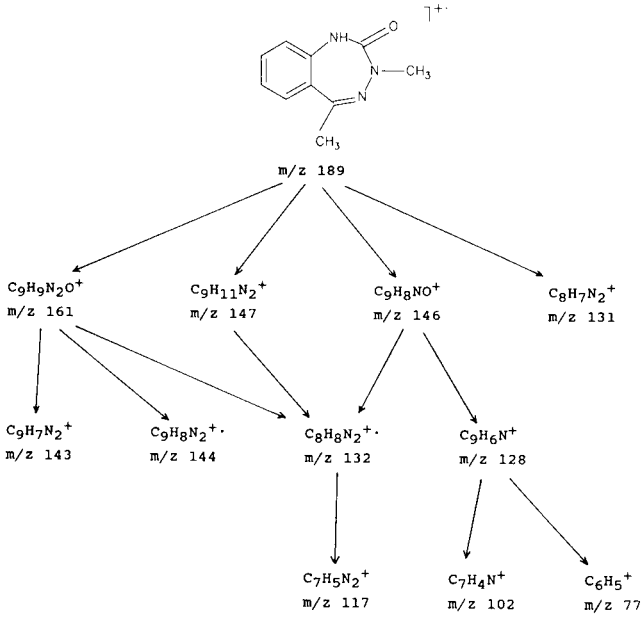


The most abundant fragment ion in the spectrum of compound **6** was $[C_{15}H_{11}NS]^{+\cdot}$ at m/z 237. The formation of this ion was analogous to the formation of the m/z 223 ion from compound **5**. The loss of two adjacent nitrogen atoms seems to be highly characteristic process for nitrogen heterocycles. Similar behavior has been observed earlier, *eq* for 1,2,3-triazoles [11,12] and 1,2,3-benzotriazines [13-15]. In contrast to compound **5**, the fragment CH_2N was not eliminated from the molecular ion of compound **6** because the loss of 28 mass units represented the loss of N_2. Likewise, the elimination of HS· was of no importance in compound **6**. These features indicated that primary hydrogen migration to the sulfur atom must be

nearly totally hindered in compound **6**. A necessary condition for hydrogen atom transfer from methyl group to sulfur atom is the equatorial position of the methyl group, and interaction between hydrogen atoms of the methyl group at N(1) and hydrogen at C(9) makes the equatorial position unfavorable. The enthiol formation was also diminished because the resulting ion would have had a planar strained structure. The fragmentations of compound **7** closely resembled those of compound **6**, although there were only two significant fragment ions, namely $[M\text{-}CNS]^+$ and $[M\text{-}N_2H\text{-}Cl]^{+\cdot}$.

Replacement of the thioxo with an oxo group at C(2) had considerable effect on the fragmentation behavior of the 1,3,4-benzotriazepine ring as can be seen in Scheme 5 where the main fragmentation pathways for compound **9** are presented. Analogously to the related thioxo compounds, the loss of CH_2N from the molecular ion was one of the most significant processes. Metastable transitions showed that the ion so formed also lost water and hydroxyl radical, although the resulting ions were of no significance in the 70 eV mass spectrum. Noticeably differing from 1,4-benzodiazepin-2-ones [8,10], the 2-oxo compounds did not lose carbon monoxide from their molecular ions. The most significant difference relative to the thioxo compounds, where the loss of HS· was the most important primary fragmentation reaction, was that the oxo compounds did not lose a hydroxyl radical from their molecular ion. Various ring contraction reactions were important instead. In this respect the oxo compounds, all of which had a methyl substituent at N(3), behaved like compounds **6** and **7** in the thioxo series. Also similarly to the thioxo compounds, the phenyl substituent at C(5) induced an additional primary fragmentation route, namely the loss of 30 mass units. Otherwise, all the 2-oxo compounds showed similar fragmentation patterns to compound **9** (Scheme 5).

Scheme 5



The 1,3,4-benzotriazepine derivatives examined did not show any specific fragmentations which would allow the unambiguous identification of this ring system. However, the position and nature of the substituents greatly affected to their mass spectrometric decompositions which made isomeric compounds easy to differentiate.

EXPERIMENTAL

Measurements were made with a Jeol JMS D300 mass spectrometer equipped with a combined EI/CI ion source and connected to a Jeol JMA 2000H data system. Samples were introduced through a direct inlet probe at temperatures 60-130°. Typical source conditions were: temperature 170°, electron energy 70 eV, accelerating voltage 3 kV and ionization current 300 μA. Accurate mass measurements were made at resolution 5000 using the data system. Fragmentation pathways were verified with metastable transitions and/or CID spectra using linked scans at constant B/E.

The preparation and identification of the compounds examined have been described elsewhere [4-6].

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