The Fragmentation Behavior of Differently Substituted 2-Amino-1,3,4-benzotriazepines

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The mass spectra of eighteen 2-amino-1,3,4-benzotriazepines were recorded under electron ionization, and the fragmentation patterns were elucidated by metastable ion analysis and exact mass measurements. The most typical fragmentations were ring contraction reactions with the loss of nitrogen atoms at positions 3 and 4. Extensive rearrangement reactions took place as well. In these the substituted 2-amino group played an important role. Isomeric compounds were easily distinguished.

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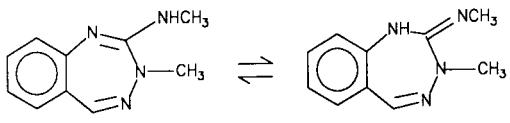
We recently reported the results of mass spectrometric studies on some 2-oxo- and 2-thioxo-1,3,4-benzotriazepines [1]. None of these seven-membered heterocycles showed any specific fragmentations that would allow unambiguous identification of the 1,3,4-benzotriazepine ring system. However, the position and nature of the substituents affected their mass spectrometric decompositions enough to allow easy identification of the isomeric compounds.

As a continuation of our studies on the mass spectrometric behavior of 1,3,4-benzotriazepines, the fragmentations of some 2-amino-substituted derivatives (compounds **1-18**) synthesized through different routes [2-7], are now discussed. These compounds are of pharmaceutical interest, since it has long been known that many compounds with aminoguanidine or amidinohydrazone structure possess biological and/or pharmacological activity [8,9].

Our aim was to find fragmentations that could assist in structure determination. The amino group at position two makes amino ⇌ imino tautomerism possible (Scheme 1). According to ir, uv and nmr results [2,10] supported by proton-catalyzed decompositions [11-14], the amino form is favored over the imino form in solid phase. We wished to ascertain whether further insight on the matter could be gained by mass spectrometry. Possible fragmentations typical of the 1,3,4-benzotriazepine ring were of special interest and comparisons were accordingly made with related 2-oxo and 2-thioxo substituted compounds [1]. Exact mass measurements and metastable studies were used to corroborate the proposed fragmentation mechanisms.

Scheme 1



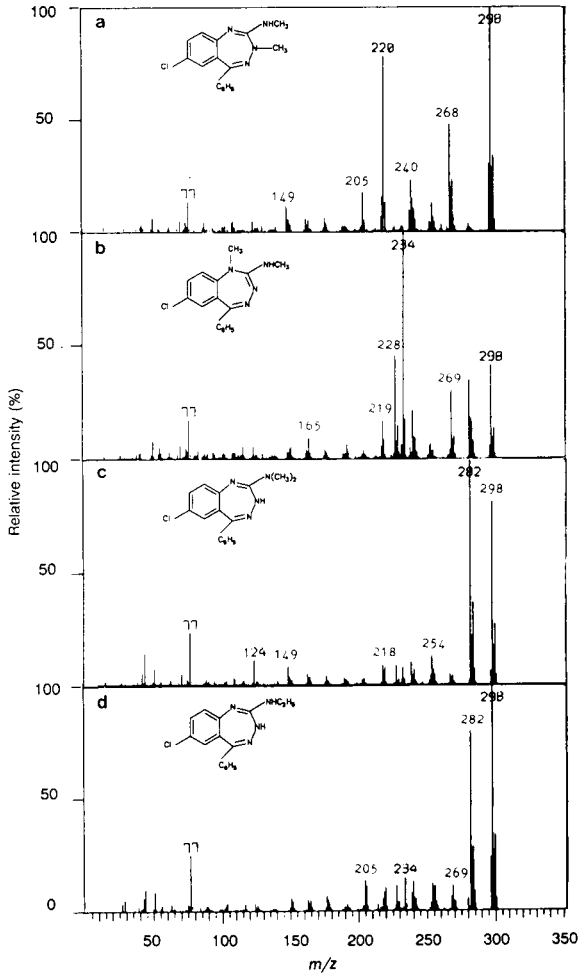
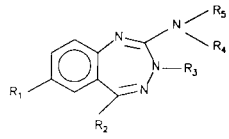


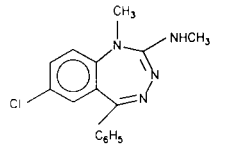
Figure 1. The 70 eV mass spectra for a) 7-chloro-3-methyl-2-methylamino-5-phenyl-3*H*-1,3,4-benzotriazepine (**4**), b) 7-chloro-1-methyl-2-methylamino-5-phenyl-1*H*-1,3,4-benzotriazepine (**12**), c) 7-chloro-2-dimethylamino-5-phenyl-3*H*-1,3,4-benzotriazepine (**10**) and d) 7-chloro-2-ethylamino-5-phenyl-3*H*-1,3,4-benzotriazepine (**7**).

The structures of the compounds are given in Schemes 2 and 3 and their mass spectral data in Table 1 and Figure 1. All compounds were relatively stable under 70 eV electron ionization, giving rise to only a few abundant fragment ions. Often the molecular ion was the base peak in the spectrum. The 2-amino group and its substitution had the most salient effect on the fragmentations, although the nature and position of other substituents were also influential, allowing the different isomeric compounds to be distinguished.

Scheme 2



Compound	R_1	R_2	R_3	R_4	R_5
1	H	CH_3	CH_3	H	CH_3
2	Cl	CH_3	CH_3	H	CH_3
3	H	C_6H_5	CH_3	H	CH_3
4	Cl	C_6H_5	CH_3	H	CH_3
5	Cl	C_6H_5	CH_3	H	C_2H_5
6	Cl	C_6H_5	H	H	CH_3
7	Cl	C_6H_5	H	H	C_2H_5
8	Cl	C_6H_5	H	H	$C_4H_9(n)$
9	Cl	C_6H_5	H	H	C_2H_4OH
10	Cl	C_6H_5	H	CH_3	CH_3
11	Cl	C_6H_5	H	$-(CH_2)_5-$	



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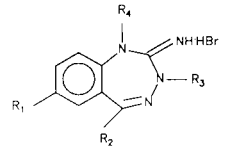
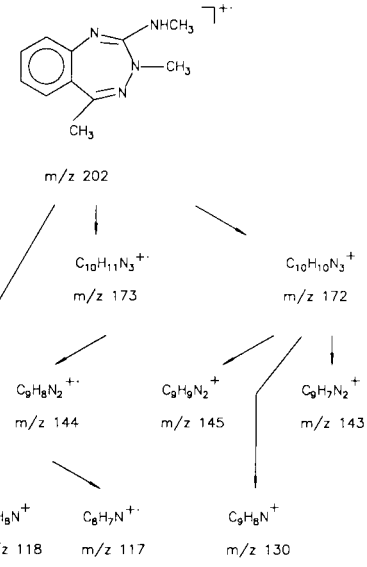
Scheme 3



Compound	R_1	R_2	R_3	R_4
13	H	C_6H_5	CH_3	H
14	Cl	C_6H_5	CH_3	H
15	Cl	C_6H_5	CH_3	CH_3
16	H	C_6H_5	H	H
17	Cl	C_6H_5	H	H
18	Cl	C_6H_5	H	CH_3

The fragmentations of compounds **1-5** were clearly directed by the methyl substituent at N(3). Almost all the primary eliminations from the molecular ions included N(3)-CH_3 in one form or another, as illustrated for compound **1** in Scheme 4. The loss of CH_2N, which requires a hydrogen migration from the 3-methyl group, most probably to the amino nitrogen, is analogous to that observed with related 2-oxo and 2-thioxo derivatives [1]. By contrast, the losses of $CH_4N^{\cdot}$ and CH_3N seem to be unique to 2-amino derivatives. With compounds **1-4** the elimination of $CH_4N^{\cdot}$ from the molecular ion could of course include the secondary 2-amino group as a consequence of α-cleavage reaction with respect to one of the ring nitrogen atoms. That this was at least not totally so is clear from the spectrum of compound **5** where, if this were the case, there would be no loss of $CH_4N^{\cdot}$. Instead, this elimination was strikingly favorable with compound **5**. We can conclude, therefore, that elimination of $CH_4N^{\cdot}$ from compounds **1-5** occurred as a hydrogen migration from the alkyl group at 2-amino nitrogen to the ring nitrogen N(3), followed by loss of this nitrogen. The possibility of a six-membered transition state with an ethyl substituent instead of a five-membered transition state with a methyl substituent was what made the hydrogen migration so favorable for compound **5**. Two consecutive CH_3N losses showed that hydrogen migration from the alkyl group at 2-amino nitrogen can occur to the ring nitrogen N(1) as well.

Scheme 4



The substituents at positions five and seven had relatively little effect on the fragmentations of compounds **1-5**. A phenyl group at C(5) prompted the elimination of hydrogen from the molecular ion, probably giving rise to a cyclic structure, as presented earlier [1]. This fragmentation seems to be relatively unimportant, however. With compounds **4** and **5**, which have both a phenyl group at C(5) and a chlorine atom at C(7), electronic effects favored the formation of the $[M-CH_3N_2-Cl]^{+\cdot}$ ions at m/z 220 and 234, respectively, analogously to the related 2-oxo and 2-thioxo derivatives [1].

Compounds **6-11** have no substituents on the ring

Table 1

Principal Fragment Ions (Intensity ≥ 7%) in the Mass Spectra of the Compounds Studied. Data are Corrected for ^{37}Cl and ^{81}Br Contributions, Otherwise Uncorrected, m/z (% Relative Intensities)

1 202 (100) $M^{+\cdot}$, 174 (12), 173 (18), 172 (45), 159 (13), 145 (17), 144 (36), 143 (14), 132 (7), 131 (13), 130 (13), 129 (7), 118 (11), 117 (12), 116 (7), 101 (10), 90 (9), 77 (9)

2 236/238 (100) $M^{+\cdot}$, 208/210 (13), 207/209 (24), 206/208 (59), 194/196 (7), 193/195 (20), 180 (17), 179/181 (32), 178/180 (48), 177/179 (14), 166/168 (7), 165/167 (15), 164/166 (14), 163/165 (8), 152/154 (13), 151/153 (12), 124/126 (10), 118 (11), 117 (14), 116 (9), 102 (8), 101 (7), 89 (13), 75 (12), 71 (8), 63 (9), 43 (11), 42 (11), 30 (10), 15 (10)

3 264 (100) $M^{+\cdot}$, 263 (33), 248 (7), 236 (12), 235 (24), 234 (57), 222 (8), 221 (31), 220 (24), 219 (18), 207 (18), 206 (54), 205 (26), 194 (7), 180 (7), 165 (8), 132 (12), 77 (17), 76 (7), 51 (8)

5 312/314 (96) $M^{+\cdot}$, 311/313 (17), 283/285 (24), 282/283 (100), 280/282 (7), 269/271 (15), 268/270 (18), 255 (8), 241/243 (9), 240/242 (27), 239/241 (10), 235 (9), 234 (47), 219 (16), 218/220 (8), 206 (20), 205 (24), 177/179 (9), 151 (8), 77 (21), 51 (8)

6 284/286 (100) $M^{+\cdot}$, 283/285 (59), 269/271 (10), 268/270 (42), 254/256 (7), 240/242 (16), 239/241 (12), 228/230 (8), 220 (31), 219 (16), 218 (7), 91 (8), 77 (34), 57 (10), 51 (14)

8 326/328 (100) $M^{+\cdot}$, 325/327 (36), 311/313 (12), 310/312 (41), 284/286 (14), 283/285 (47), 270/272 (32), 269/271 (47), 268/270 (19), 256/258 (26), 255/257 (24), 254/256 (25), 239/241 (8), 229/231 (11), 228/230 (48), 220 (23), 219 (12), 218 (9), 206 (20), 205 (14), 77 (37), 72 (14), 55 (11), 51 (11), 41 (13), 29 (20)

9 314/316 (100) $M^{+\cdot}$, 313/315 (9), 298/300 (18), 297/299 (7), 296/298 (16), 284/286 (28), 283/285 (98), 271/273 (21), 270/272 (76), 269/271 (50), 268/270 (11), 256/258 (16), 255/257 (29), 254/256 (30), 253/255 (7), 242/244 (9), 241/243 (17), 240/242 (7), 239/241 (12), 229/231 (9), 228/230 (30), 220 (26), 219 (18), 218 (14), 206 (14), 205 (11), 178/180 (8), 177/179 (8), 165 (9), 164 (7), 163 (9), 152 (7), 151 (8), 130 (11), 124/126 (9), 104 (7), 77 (55), 51 (17), 31 (7), 30 (8)

11 338/340 (39) $M^{+\cdot}$, 323/325 (14), 322/324 (60), 294/296 (17), 255/257 (13), 254/256 (10), 220 (10), 84 (100), 77 (17), 55 (8), 41 (10)

13 250 (100) $M^{+\cdot}$, 249 (74), 235 (8), 234 (14), 222 (19), 221 (11), 220 (27), 208 (11), 207 (24), 206 (31), 205 (12), 180 (10), 103 (9), 80/82 (18), 77 (16), 76 (7), 51 (7)

14 284/286 (100) $M^{+\cdot}$, 283/285 (69), 268/270 (10), 256/258 (13), 255/257 (9), 254/256 (11), 248 (10), 242/246 (10), 241/243 (8), 220 (14), 207 (10), 206 (53), 205 (17), 103 (8), 80/82 (27), 79/81 (9), 77 (15), 51 (7), 43 (7)

15 298/300 (31) $M^{+\cdot}$, 297/299 (8), 271/273 (7), 270/272 (36), 255/257 (12), 242/244 (10), 241/243 (8), 221 (18), 220 (100), 205 (13), 80/82 (19), 77 (14), 51 (8)

16 236 (100) $M^{+\cdot}$, 235 (41), 221 (15), 220 (19), 218 (9), 208 (8), 207 (43), 206 (18), 205 (21), 129 (17), 103 (8), 102 (7), 80/82 (29), 79/81 (10), 77 (22), 76 (9), 51 (10)

17 270/272 (100) $M^{+\cdot}$, 269/271 (86), 235 (10), 234 (23), 206 (27), 205 (11), 118 (14), 103 (7), 80/82 (26), 79/81 (9), 77 (19), 51 (9)

18 284/286 (73) $M^{+\cdot}$, 283/285 (47), 269/271 (7), 268/270 (9), 256/258 (8), 255/257 (7), 249 (13), 242/244 (8), 241/243 (30), 229/231 (15), 228/230 (85), 221 (18), 220 (100), 206 (15), 205 (23), 193 (13), 177/179 (7), 165 (12), 163 (7), 152 (7), 151 (8), 125 (10), 104 (7), 103 (9), 89 (7), 80/82 (35), 79/81 (12), 77 (28), 76 (8), 75 (10), 51 (14)

nitrogen atoms. When the substituents at the 2-amino group are small, as with compounds **6**, **7** and **10**, the behavior is analogous to that of compounds **1-5**. The most important primary fragmentation was the elimination of $NH_2^{\cdot}$ from the molecular ion, requiring a hydrogen transfer from the alkylamino group to the ring nitrogen. As the size of the substituent increased, the number of fragmentation routes also increased, as can be seen from the spectra of compounds **8**, **9** and **11** (Table 1). The additional fragmentations were dependent on the nature of the substituent. *n*-Butylamino and 2-hydroxyethyl groups in compounds **8** and **9** showed an α-cleavage reaction with respect to the nitrogen, leading to the elimination of $C_3H_7^{\cdot}$ and $CH_3O^{\cdot}$, respectively. The ions so formed further lost $C_2H_3N_2^{\cdot}$, giving rise to the $[C_{13}H_9N_2Cl]^{+\cdot}$ ion at m/z 228. Related fragmentations, though less intense, were observed with the 2-ethylamino derivative (compound **7**). With compounds **8** and **9** an alkene elimination, typical to amines [15], with simultaneous hydrogen migration to the nitrogen atom took place from both the $M^{+\cdot}$ and $[M-H]^+$ ions. The 2-piperidino-substituted compound (**11**) had only two important primary fragmentations: the ring contraction through the elimination of $NH_2^{\cdot}$ from the molecular ion and the formation of piperidino ion at m/z 84. This last ion even gave rise to the base peak in the spectrum (Table 1).

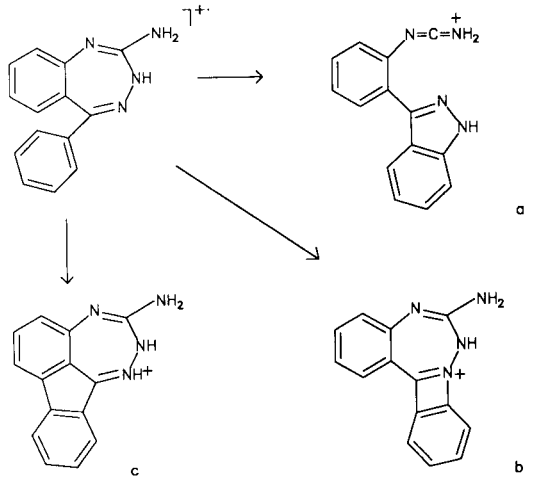
No direct evidence for the existence of amino ⇌ imino tautomerism was apparent in the spectra of compounds **1-11**. All the fragmentations can be rationalized to take place from the amino form, although many could just as well occur from the imino form. On the other hand, most of the decompositions of compound **12** (Figure 1) are best understood as taking place through the imino form, because the most important fragmentations are the same as with compounds **6-11**, which have an unsubstituted saturated nitrogen at position 3. It is noteworthy that the methyl-substituted nitrogen at position 1 does not participate in fragmentations as easily as the nitrogen at position 3. The loss of $CH_4N^{\cdot}$ is unfavorable and the losses of CH_3N and $CH_2N^{\cdot}$ are totally absent because the losses of 29 and

28 mass units representing $N_2H^{\cdot}$ and N_2, respectively, occur instead. Compared with compounds **1-11**, compound **12** had, however, one additional favorable fragmentation: namely, the elimination of $C_3H_6N_2$ directly from the molecular ion. The imino form is the natural source for this elimination, which must include N(1) adn C(2) atoms with their substituents.

Although the principal fragmentations were very similar for compounds **1-12**, isomeric compounds were nevertheless easily distinguished, as can be seen from the spectra of compounds **4**, **7**, **10** and **12** (Figure 1). Isomers differing in the position of the methyl substituent at ring nitrogen atoms (compounds **4** and **12**) were easy to distinguish because only N(3) readily participated in fragmentations. Isomers **10** and **7** differed only in their peak intensities. Especially the elimination of $NH_2^{\cdot}$ was more favorable for compound **10** than for **7**. The reason for this might be that compound **7** preferentially exist in the imino form which is prohibited in the case of compound **10**. Because of the planarity of the double bond the hydrogen atoms in the imino form are more distant from the ring nitrogen N(4) than in the related amino form explaining their smaller migration.

Compounds **13-18** were originally isolated as their hydrogen bromide salts as presented in Scheme 3. To simplify the presentation, all the compounds are drawn as existing in their imino form, although this is completely true only for compound **15**. In the gas phase they most probably existed as free bases, due to the heating in the direct insertion probe, because no peaks were observed at larger mass numbers than the molecular ion peaks. The most striking feature in the spectra of these compounds (Table 1) was the intensity of the $[M-H]^+$ peaks. This is understandable only if the ion has a cyclic structure. In analogy to the process presented by Benz *et al.* [16] for 5-phenyl-1,4-benzodiazepin-2-ones, it is possible that the ring-opened molecular ion is the source of the hydrogen elimination, and that ring closure between the 3 nitrogen and 2′ carbon atoms follows the hydrogen elimination (*cf.* compound **16** in Scheme 5, ion a). Another possibility, analogous to phthalazines containing a phenyl substituent adjacent to nitrogen [17], is that the $[M-H]^+$ ions are formed through bonding between the aromatic carbon C(2′) and ring nitrogen N(4) (Scheme 5, ion b). Yet a third possibility is that a new five-membered ring forms between positions 6 and 2′ of the two aromatic rings. In this process, one $H^{\cdot}$ would be lost and the second $H^{\cdot}$ transferred to the nitrogen atom at position 4 (*cf.* Scheme 5, ion c) [1]. Although there is no solid evidence for the structure of the $[M-H]^+$ ion, structures b and c are more probable because the decompositions of the ion were analogous to those of the molecular ion. With compounds **3-12** the tendency to form $[M-H]^+$ ions was obviously overwhelmed by the fragmentations initiated by the alkyl groups on the 2-amino nitrogen.

Scheme 5



Other fragmentations of these primary amino compounds resembled those of compounds having a secondary or tertiary amino group at position 2, although reactions associated with the alkyl amino group were of course missing. Ring contraction reactions giving rise to the loss of the N(3) and N(4) atoms were dominant. In addition, compounds **13**, **14** and **16-18** lost $NH^{\cdot}$ and $NH_2^{\cdot}$ in one or two steps. This probably means that these compounds exist at least partly in the imino form, with the result that N(1) was eliminated as $NH^{\cdot}$ from both $M^{+\cdot}$ and $[M-H]^+$.

The fragmentation behavior of the present 2-amino-1,3,4-benzotriazepines verified that, in general, these compounds are resistant toward electron ionization. The stability of the molecular ions was decreased, however, by the presence of a methyl substituent at ring nitrogen N(1) and by a large alkyl amino group at position 2. The typical fragmentations for this ring system were contraction reactions where ring nitrogen atoms at position 3 and 4 were easily lost. Extensive rearrangement reactions took place as well.

EXPERIMENTAL

A Jeol JMS D300 mass spectrometer equipped with a combined EI/CI ion source and connected to a Jeol JMA 2000H data system was utilized for obtaining low resolution and metastable data. The EI operating conditions were as follows: electron energy 70 eV; ionization current, 300 μA; source temperature, 170°; acceleration voltage, 3 kV. Samples were introduced into the instrument by a direct inlet probe at temperatures 110-190°. Fragmentation pathways were verified with metastable transitions and/or CID spectra using linked scans at constant B/E (daughter) and B^2/E (parent). Exact mass measurements were made with a Jeol JMS-HX100 mass spectrometer by repetitive scanning at a resolution of 30000. Perfluorokerosene (PFK) was used as reference compound.

The synthesis and identification of the compounds have been described elsewhere [2-7,10-14].

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