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The Mass Spectral Fragmentation of some 2,3-Dihydro-5-trifluoromethyl-7-(*p*-*R*-phenyl)-1,4-diazepines

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Summary. Electron impact mass spectra of seven 2,3-dihydro-5-trifluoromethyl/methyl-7-(*p*-*R*-phenyl)-1,4-diazepines R = H, CH_3, OCH_3, CF_3, Cl, Br) have been recorded and are discussed. These systems dissociate by scission of the C_2–C_3 bond followed by loss of H˙ to give the $[M-H]^+$ ion as the base peak. The fragmentation behaviour has been investigated using metastable scanning techniques and accurate mass measurements. The origin of some characteristic fragment ions is discussed.

Keywords. Mass spectra; 2,3-Dihydro-1*H*-1,4-diazepines.

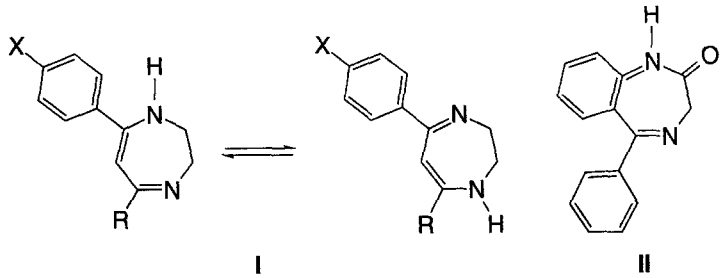
Massenspektroskopische Fragmentierung einiger 2,3-Dihydro-5-trifluormethyl-7-(*p*-*R*-phenyl)-1,4-diazepine

Zusammenfassung. Die EI-Massenspektren von 7 2,3-Dihydro-5-trifluormethyl/methyl-7-(*p*-*R*-phenyl)-1,4-diazepinen (R = CH_3, OCH_3, CF_3, Cl, Br) werden vorgestellt. Diese Verbindungen fragmentieren unter Spaltung der C_2–C_3-Bindung. Anschließende Abspaltung von H˙ führt zum Fragment $[M-H]^+$, das als Basispeak auftritt. Das Fragmentierungsverhalten wurde mittels metastabiler Methoden und genauer Massenbestimmungen untersucht. Die Herkunft einiger charakteristischer Fragmentionen wird diskutiert.

Introduction

Only few reports [1, 2] have appeared in the literature on the mass spectra of 2,3-dihydro-1,4-diazepines and their salts. *Staab* and *Wunsche* [1] have studied the mass spectra of 2,3-diaryl-2,3-dihydro-5,7-dimethyl-1*H*-1,4-diazepines. The main fragmentation process observed was the elimination of a Ar–CH=N˙ fragment. *Lloyd* and coworkers [2] have reported a similar fragmentation pattern for 2,3-dihydro-1,4-diazepinium iodides; in this case, the most intense peak is due to the ion resulting from loss of a $-C_2{=}N_1^{\cdot}$ fragment. The possibility of thermal decomposition prior to electron impact ionization and the problem of involatility make the interpretation of the mass spectra of these compounds difficult.

In connection with our previous spectroscopic studies on 2,3-dihydro-5-trifluoromethyl/methyl-7-(*p*-*R*-phenyl)-1,4-diazepine bases (**I**, Fig. 1) [3, 4], we now



I II

	R	X
1	CF_3	H
2	CF_3	CH_3
3	CF_3	OCH_3
4	CF_3	CF_3
5	CF_3	Cl
6	CF_3	Br
7	CH_3	H

Fig. 1. Structures of 2,3-dihydro- 5-trifluoromethyl/methyl-7-(*p*-*R*-phenyl)-1,4-diazepines (**I**: **1–7**) and 5-phenyl-1,4-benzodiazepin-2-ones (**II**)

report on the mass spectra of these systems. Our interest in the fragmentation mechanisms of these systems was stimulated by our observation that the base peak was due to the $[M-H]^+$ ion for all compounds investigated. In addition, these systems bear structural resemblance to the pharmocologically important 5-phenyl-1,4-benzodiazepin-2-ones (**II**, Fig. 1) which also show an abundant $[M-H]^+$ ion [5, 6]. In the present study, the proposed fragmentation pathways leading to the formation of important daughter ions have been confirmed by metastable scanning [7, 8] of their parent ion spectra and by accurate mass measurements.

Results and Discussion

Important features in the mass spectra of the present series of 2,3-dihydro-1,4-diazepines (compounds **1–7**) are summarized in Table 1. Intense molecular ion peaks $[M]^{+\cdot}$ of 45–56% intensity were observed for all compounds. This indicates the relatively high stabilities of the present series of 2,3-dihydro-1,4-diazepines. With the exception of the molecular ion peaks, the mass spectra of compounds **1–7** are, in general, dominated by even-electron ions.

The most striking feature of the mass spectra of these systems is the occurrence of the $[M-H]^+$ ion as the most intense peak for all compounds investigated. It is interesting that peaks of the $[M-H]^+$ ions were observed at much lower intensities in the mass spectra of 2,3-diaryl-2,3-dihydro-5,7-dimethyl-1,4-diazepines [1] and other 5,7-methyl substituted derivatives [2]. The origin of this ion has been the subject of some debate. *Lloyd et al.* [2] attributed this ion either to α-cleavage of the hydrogen from the 2,3-positions or to loss of hydrogen from the 1,4- or 6-position. However, the latter route was rejected [2] on the basis of partial deuteration at the 1,4- or 6-position. Nevertheless, the fact that the $[M-H]^+$ ions were observed at higher intensities with a phenyl group at the 5,7-position of the diazepine ring [2, 5, 6] strongly suggests the active participation of the phenyl ring in this process.

Table 1. Important ions in the mass spectra of 2,3-dihydro-5-trifluoromethyl/methyl-7-(*p*-*R*-phenyl)-1,4-diazepines (**1–7**)

Fragment ions	$R = CF_3, X = H$ **1**		$R = CF_3, X = CH_3$ **2**		$R = CF_3, X = OCH_3$ **3**		$R = CF_3, X = CF_3$ **4**		$R = CF_3, X = Cl$* **5**		$R = CF_3, X = Br$* **6**		$R = CH_3, X = H$ **7**	
	m/z	%	*m/z*	%	*m/z*	%	*m/z*	%	*m/z*	%	*m/z*	%	*m/z*	%
Molecular ion	240	45	254	57	270	53	308	47	274	50	318	47	186	50
									276	18	320	37		
$[M-H]^+$	239	100	253	100	269	100	307	100	273	100	317	100	185	100
									275	42	319	97		
$[M-R]^+$	171	1	185	2	201	1	239	5	151	2	249	<1	171	3
									153	<1	251	<1		
$[M-28]^{+\cdot}$	212	14	226	12	242	12	280	15	246	14	290	12	158	24
									248	4	292	10		
$[M-28-R]^+$	143	15	157	17	173	11	211	20	177	16	221	12	143	17
									179	8	223	10		
$[M-28-X]^+$	–	–	–	–	–	–	–	–	211	14	211	54	–	–
$[Ar-C\equiv C-CH_2]^+$	115	9	129	5	145	3	183	5	149	12	193	3	115	12
									151	7	195	2		
$[Ar-\overset{NH}{\overset{/\ \backslash}{C}}=CH]^{+\cdot}$	117	4	131	2	147	2	185	3	151	7	195	2	117	5
									153	4	197	1		
$[Ar-C\equiv NH]^+$	104	9	118	12	134	11	172	8	138	12	182	8	104	7
									140	6	184	7		
$[C_7H_6X]^+$	91	7	105	9	121	15	159	4	125	6	169	6	91	6
									127	4	171	5		
$[Ar]^+$	77	12	91	12	107	2	145	7	111	5	155	<1	77	13
									113	2	157	<1		
$[CF_3]^+$	69	4	69	2	69	3	69	8	69	3	69	10	–	–

* The second *m/z* value accounts for ions containing ^{37}Cl or ^{81}Br

Table 2. Representative parent ion spectra; the intensity (**I**) of the parent ion is given relative to a daughter ion intensity of 1000

	Molecular ion (m/z)	Daughter ion (m/z)	Parent ions (**I**) (m/z)							
1	240	115	134	(13.46)	143*	(34.02)	212	(11.34)	240	(9.28)
		143	212*	(29.85)	240	(5.60)				
		212	240*	(16.19)						
7	186	115	143*	(12.80)	158	(5.28)	186	(6.69)		
		143	158*	(131.14)	171	(6.04)	186	(9.89)		
		158	186*	(12.78)						

* Major precursor for the given daughter ion

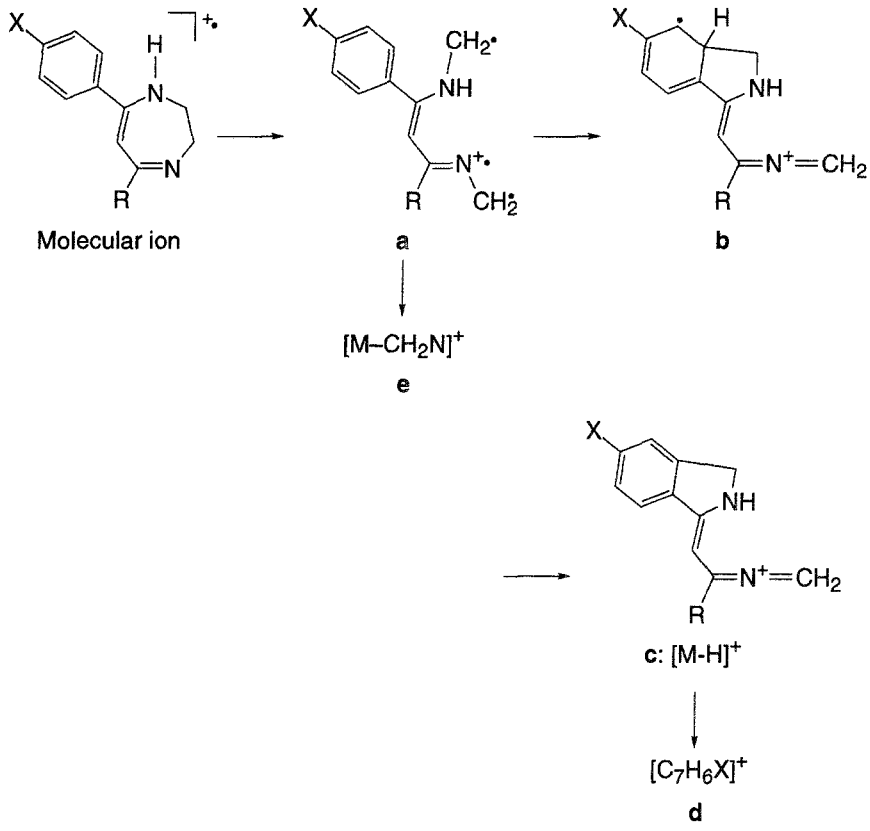
Sadee [5] was the first to suggest the loss of an aromatic hydrogen. This proposal was further confirmed by the work of *Benz et al.* [6] on 5-phenyl-1,4-benzodiazepin-2-ones (**II**, Fig. 1).

In compounds **1–7**, it is evident from metastable scanning measurements (Table 2) that the $[M-H]^+$ ion undergoes very little further fragmentation which, together with the high intensity (100%) of this ion, indicates an efficiently stabilized structure. In the present series of 2,3-dihydro-1,4-diazepines, no simple expulsion of hydrogen either from the 1,4,6-positions or from the 2,3-positions could possibly lead to such an ion. A more plausible route (Scheme 1) may involve scission of the C_2-C_3 bond to form ion **a** followed by radical attack on the phenyl ring. Subsequent expulsion of hydrogen from ion **b** to achieve rearomatization is undoubtedly the driving force for this otherwise unfavourable process.

The mass spectra of compounds **1–7** (Table 1) reveal peaks due to the substituted tropylium ions **d** ($[C_7H_6X]^+$; X = H, CH_3, OCH_3, CF_3, Cl, and Br). These ions are interesting as they provide a confirmation of the proposed structure **c** of the $[M-H]^+$ ion which is a major precursor for tropylium ions. Ion **c** contains the characteristic structural moiety required for the formation of tropylium ions, *i.e.* a methylene group attached to the aryl ring. It is worth mentioning that the relative intensities of these ions, expressed as $\log_{10}(I_X/I_H)$ where I_X and I_H are the intensities of $[C_7H_6X]^+$ ($X \neq H$) and $[C_7H_7]^+$, show a satisfactory linear correlation with *Hammett*'s substituent parameter σ_p. Similar correlations have been reported for the mass spectra of aromatic systems [11, 12]. These findings demonstrate the potential use of tropylium ions for the characterization of 5,7-aryl substituted 2,3-dihydro-1,4-diazepines. However, it should be stressed that a similar rearrangement ion at $m/z = 91$ ($[C_7H_7]^+$) has also been observed [9] in the mass spectra of 7-chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine.

In contrast to 2,3-diaryl derivatives [1], elimination of an iminyl radical ($CH_2-N^{\cdot}$) from the molecular ions of compounds **1–7** is much less pronounced resulting in low intensity $[M-CH_2N]^+$ ions. This process also involves scission of the C_2-C_3 bond as illustrated in Scheme 1.

Whereas loss of a $CH_3^{\cdot}$ radical from the molecular ion of compound **7** is observed (Table 1) to give the ion **f** ($m/z = 171$) with 3% intensity, loss of a $CF_3^{\cdot}$ radical from

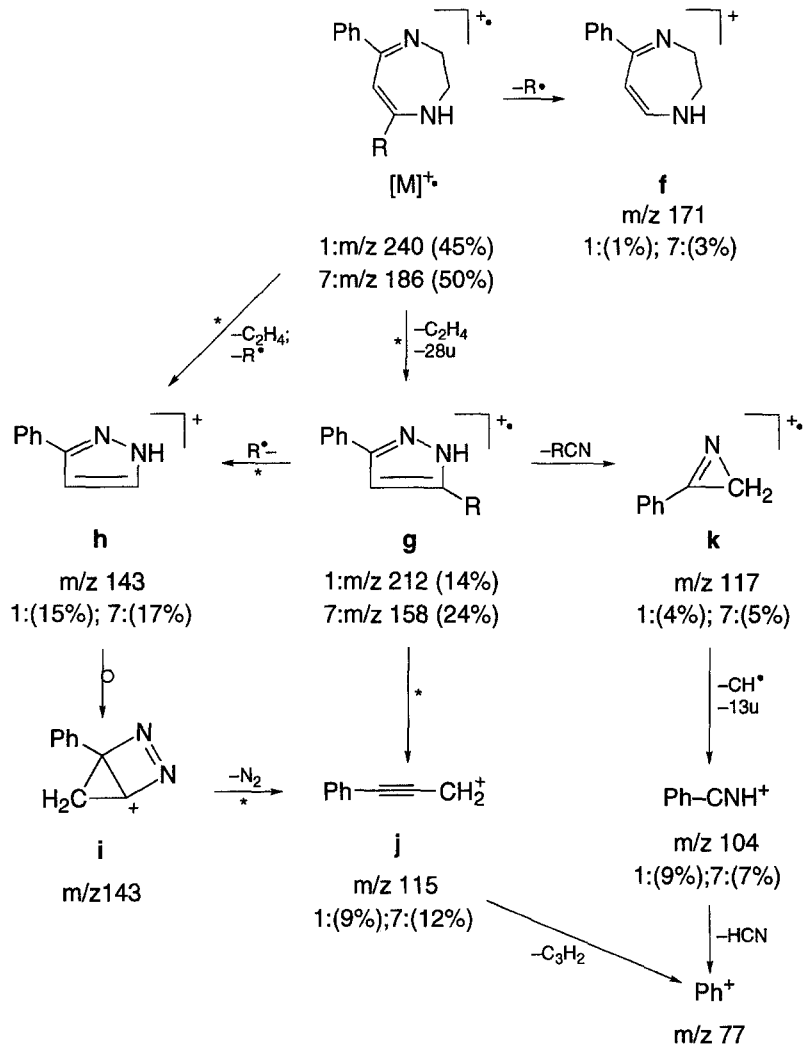


Scheme 1

the molecular ions of compounds **1–6** is not energetically favoured until an ethylene fragment is eliminated. In compound **3**, loss of $CF_3^{\cdot}$ from the aryl group appears to compete favourably with that from the 5-position of the diazepine ring resulting in the $[M-CF_3]^+$ ion ($m/z = 239$) with 5% intensity.

The mass spectra of compounds **1–7** revealed other important fragment ions shown in Table 1. The origin of some key daughter ions has been investigated by metastable scanning of their parent ion spectra. The results are collected in Table 2. The proposed fragmentation pathways illustrated in Scheme 2 for compounds **1** and **7**, which account for most of these ions, have been ascertained by the existence of metastable ions and by comparison with known fragmentation patterns. Some important features are discussed below.

The $[M\text{-}28]^+$ ion is resolved into the aforementioned even-electron $[M-CH_2N]^+$ ion and the odd-electron $[M-C_2H_4]^{+\cdot}$ ion. The latter ion predominates and is shown to be the major precursor of most of the remaining fragment ions in compounds **1–7** by metastable scanning measurements. The $[M-C_2H_4]^{+\cdot}$ ions **g** dissociate predominantly by loss of odd-electron radical species. Loss of $R^{\cdot}$ ($CH_3^{\cdot}$ or $CF_3^{\cdot}$) from this ion is confirmed by metastable scanning measurements (Table 2). In compounds **1** and **7**, the ion of $m/z = 143$ (**h**; $[M\text{-}28\text{-}R]^+$) is shown to result predominantly from the $[M-C_2H_4]^{+\cdot}$ ion ($m/z = 212$ in **1** and $m/z = 158$ in **7**; Table 2). In compounds **5** and **6**, expulsion of $Cl^{\cdot}$ and $Br^{\cdot}$ from the $[M-C_2H_4]^{+\cdot}$



Scheme 2

ion is a favourable process leading to the $m/z = 211$ ion with 14% and 54% intensity, respectively.

The fragmentation processes leading to the $m/z = 115$ ion **j** (compound **1**; composition: C_9H_7) in compounds **1** and **7** are noteworthy. The parent ion spectra for this ion (Table 2) revealed two prominent pathways. The major route involves a rearrangement of ion **h** ($m/z = 143$) followed by loss of N_2. Alternatively, this ion may be formed from the $[M\text{-}28]^+$ ion, but this may involve either the $[M-C_2H_4]^{+\cdot}$ ion **g** or the $[M-CH_2N]^+$ ion **e** as possible precursors. The metastable scanning experiments [7, 8] do not allow accurate determinations of the masses of these precursors.

Elimination of cyanides is known to be a favourable process in the mass spectral fragmentation of N-heterocyclic compounds [10]. Loss of *R*CN from the $[M-C_2H_4]^{+\cdot}$ ion gave ion **k** which may be formulated as an arylaziridine structure. Ion

k dissociates by successive loss of CH$^{\cdot}$ and HCN. Since ion **k** is an odd-electron species, it is very unlikely to have arisen from the even-electron $[M-CH_2N]^+$ ion.

In conclusion, the present series of compounds dissociate under electron impact by scission of the C_2-C_3 bond followed by loss of H$^{\cdot}$ to give the $[M-H]^+$ ion as the base peak. In these compounds, this process competes favourably with the expulsion of an iminyl radical normally observed in the mass spectra of 5,7-alkyl substituted derivatives. In addition to the $[M-H]^+$ ion, the present systems exhibited characteristic peaks which are observed at $m/z = 91$ ($[C_7H_7]^+$; tropylium ion), $m/z = 117$ ($[C_8H_7N]^{+\cdot}$; phenylaziridine), and $m/z = 115$ ($[C_9H_7]^+$) for the 7-phenyl derivatives ($X \neq H$). The effects of substitutents on the relative intensities of these ions were found to correlate satisfactorily with the *Hammett* substituent parameters. Finally, the present study demonstrated the marked influence of the aryl substituents at the 5,7-position of the diazepine ring on the fragmentation behaviour of these systems.

Experimental

The compounds examined have been described previously [3, 4]. The mass spectra were determined with Varian SM-1B double focussing mass spectrometer of *Mattauch-Herzog* geometry operating at 70 eV. The ion source temperature was maintained at 200 °C. The direct inlet system was used for all samples at 50–90 °C, depending upon the volatility of these compounds. Parent ion spectra were recorded using the defocussing technique [7, 8] by scanning the ion accelerating voltage (initially 3 kV) at fixed setting of the electric and magnetic sectors.

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