Mass Spectral Fragmentation Patterns of 3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-(*o*- and *p*-*R*-phenyl)-1*H*-dibenzo-[*b*,*e*][1,4]diazepin-1-ones. II (1)

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A study has been made of the fragmentation upon electron impact of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-phenyl-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one and fifteen of its derivatives containing chloro, bromo, methyl, methoxy, hydroxy, nitro, amino, carboxyl and carboxymethyl substituents on *ortho* and *para* positions of the 11-phenyl ring. All the spectra analyzed contain molecular ions and the principal fragmentation routes takes place either from the molecular or from (M^+-1) ion. There are, however, some deviations from the general fragmentation pattern in the case of 1,4-dibenzodiazepin-1-ones with *o*-nitro, *o*-hydroxy and *o*-carboxyl substituents caused by direct interactions of these groups with the benzodiazepine ring.

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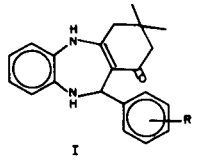
There has been scanty interest in the electron impact mass spectra of 1,5- and 1,4-benzodiazepines over the past decade in spite of the fact that they represent a series of compounds of considerable medicinal interest, mainly as tranquilizer agents (4). So, there are only two papers about the fragmentation patterns of 1,4-benzodiazepin-2-ones (5,6). Likewise, little information is available in the literature on the chemical and pharmacological properties of the 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-phenyl-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one and its derivatives (7). This induces us to report the synthesis and mass spectrometry studies of a closely related family of compounds of the general structure I (Scheme 1, *ortho*-R = Cl, Br, Me, OMe, CO_2Me, OH, NO_2, CO_2H and *para*-R = H, Cl, Br, Me, OMe, OH, NO_2, NH_2).



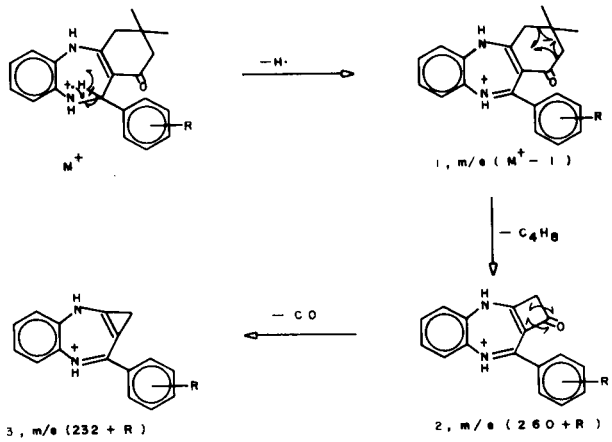
I

(o-, p-)-R = H-, Me-, -OH, -OMe, -X, NO_2-, NH_2-, -COOH, -COOMe.

Scheme I

In this paper we described the elucidation of fragmentation patterns and mechanisms of I. The relative abundances of relevant ions obtained as primary fragmentation patterns in Schemes 2 to 10. The transitions were substantiated by an appropriate metastable peak and are indicated by an asterisk in the figures. Analysis of the fragmentation patterns was aided by reference to the mass spectral data published for model compounds.

The spectra of I are essentially interesting with three dominant fragmentation patterns: (I) For compounds with a *p*-R substituent on the 11-phenyl moiety. (II) For compounds with a *o*-R substituent on the 11-phenyl moiety. (III) For compounds with a *o*-hydroxy, *o*-carboxyl or *o*-nitro substituent on the 11-phenyl moiety.



Scheme 2

Fragmentation Pattern I.

The 11-(*p*-*R*-phenyl)-1,4-dibenzodiazepin-1-ones (Table 1) are relatively stable under electron impact. The major fragmentation of the molecular ion proceeds along three pathways: (A) From $[M]^+$ to m/e 119 and m/e 104; (B) from $[M]^+$ to m/e 241 (100%) and (C) From $[M]^+$ to m/e 83.

Pathway A.

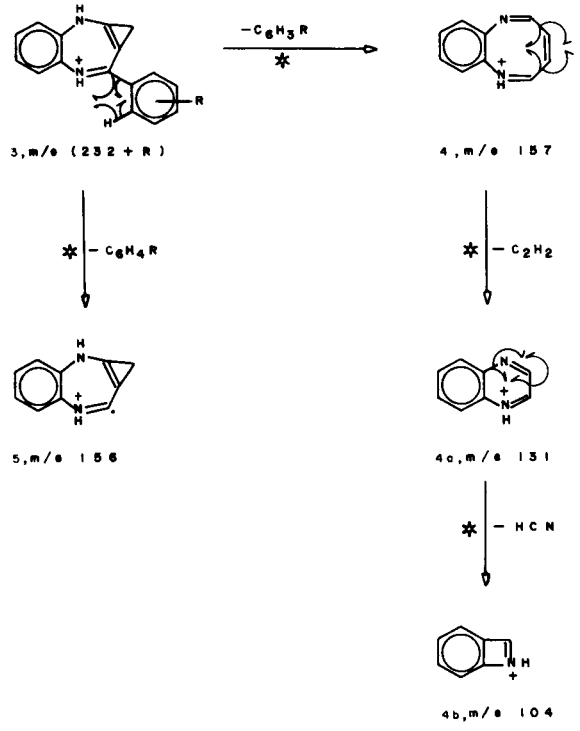
The ion 1 (M^+-1) which results from the parent ion by the loss of a benzylic hydrogen is considered to lose isobutene, *via* a retro Diels-Alder reaction (8), from the 3,3-dimethylcyclohexene-1-one moiety of 1,4-dibenzodiazepin-1-one structure yielding the species **2** (m/e 260 + R) (Scheme 2). Loss of carbon monoxide from **2** gives the ion **3** of m/e (232 + R). A similar fragmentation has been reported for 6,6-dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydrobenzofuranes (9).

Fragmentation of **3** then proceeds along three pathways (Scheme 3). In one pathway, loss of the 11-(*p*-*R*-phenyl) substituent from **3** with transfer of one *ortho*-hydrogen atom of the 11-phenyl substituent to the dibenzodiazepine ring's C-11 leads to the ion **4** of m/e 157 which is depicted

Table 1

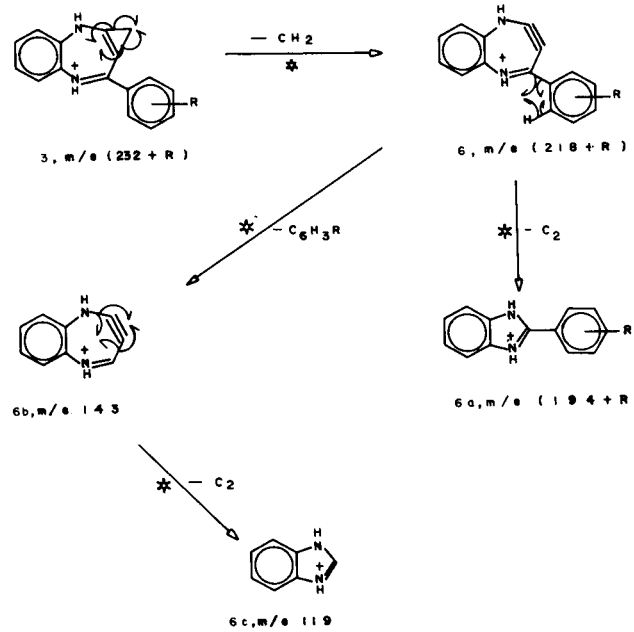
Relative Abundance of Principal Fragments
(Figures in parentheses indicate the nature of the ions)

Compound No.	R	M⁺	M⁺-1 (1)	260+R (2)	232+R (3)	218+R (6)	194+R (6a)	241 (7)	157 (4)	156 (5)	143 (6b)	131 (4a)	119 (6c)	104 (4b)	83 (8)
1	H	17.5	12.5	9.0	13.75	10.0	5.0	100	5.0	3.0	5.0	5.5	5.0	2.5	2.5
2	*p*-Cl	19.5	10.0	6.25	10.0	8.0	2.0	100	5.0	4.0	3.0	5.0	3.0	2.0	3.0
3	*p*-Br	15.8	10.0	5.0	5.0	5.0		100	5.0	3.0	5.0	5.0	4.0	2.0	5.0
4	*p*-Me	26.2	24.2	10.0	12.5	10.0	2.5	100	5.0	4.0	5.0	7.5	2.5	2.5	3.0
5	*p*-OMe	50.7	43.4	15.0	12.5	10.0	5.0	100	5.0	4.0	7.5	7.5	6.0	4.0	7.5
6	*p*-OH	28.9	26.3	10.0	14.0	8.0	3.0	100	2.5	3.0	5.0	8.0	7.0	2.5	3.0
7	*p*-NO_2	19.9	3.0	3.0	6.0	3.0		100	5.0	4.0	7.5	5.0	5.0	2.0	6.0
8	*p*-NH_2	37.9	65.9	22.5	5.0	10.0	5.0	100	10.0	3.0	5.0	15.0	10.0	6.0	
9	*o*-Cl	15.2	3.75	2.5	3.0	3.0	2.5	100	2.5	2.0	5.0		3.0	2.0	3.0
10	*o*-Br	8.0	2.5	2.5	2.5	5.0	3.0	100	2.5	2.0	5.0	3.0	4.0	3.0	2.5
11	*o*-Me	28.7	10.0	5.0	4.0	12.5	2.0	100	6.0	4.0	6.0	4.0	8.0	2.0	2.5
12	*o*-OMe	27.8	8.0	3.0	2.5	3.0	6.0	100	2.5	2.5	3.0	7.5	4.0	2.0	2.5
13	*o*-CO_2Me	29.7	2.5	3.0	2.5	3.0		100	3.0	3.0	7.5	6.0	6.0	2.0	3.0
14	*o*-OH	36.4	7.0	2.5	3.0	10.0	17.5	37.2	5.0	2.5	12.5	7.5	12.5	2.5	10.0
15	*o*-NO_2	76.4				10.0		13.5		3.0	13.0	7.5	5.0		
16	*o*-COOH	66.0	27.0	20.0	12.5	33.0		35.0	17.5	7.5	20.0	17.5			5.0



Scheme 3

as a benzodiazocine cation. Expulsion of acetylene from **4** leads to the formation of quinoxaline ion **4a**, of m/e 131 which further suffers the loss of hydrogen cyanide to yield the ion **4b** (m/e 104). In another pathway, elimination of the 11-(*p*-*R*-phenyl) substituent from **3** affords an ion at m/e 156, **5**. In the third pathway (Scheme 4) loss of 14 amu (CH_2) from **3** yields **6** of m/e (218 + R). Fragmentation of **6** then proceeds along two pathways. One pathway results in the loss of a carbon unit to give the 2-(*p*-*R*-phenyl)benzimidazole ion, **6a**, of m/e 194 + R; while the other results in the loss of a C_6H_3R unit with transfer of the *ortho*-hydrogen atom from the 11-phenyl substituent to the dibenzodiazepine ring to give the ion **6b** of m/e 143, which further loses molecular carbon to yield **6c** (m/e 119) which is depicted as a benzimidazole cation. It is interesting to note that Nardi (10), Hunter (11) and we (1) observed the formation of benzimidazole ions in the mass spectra of 1,5-benzodiazepines.

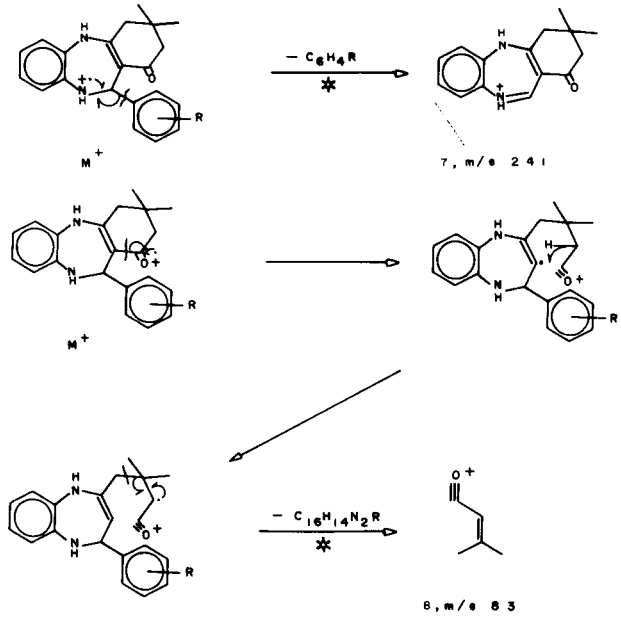


Scheme 4

Pathway B.

Another interesting fragmentation pathway of 11-(*p*-*R*-

phenyl)-1,4-dibenzodiazepin-1-ones is the elimination of the 11-(*p-R*-phenyl) substituent from the molecular ion giving rise to a fragment at m/e 241, **7**, base peak for all the *p-R*-phenyl compounds analyzed. It is the existence of this unique species that makes the identification of the 11-(*p-R*-phenyl)-1,4-dibenzodiazepin-1-ones (I) a relatively easy matter. The abundant formation of **7** is rationalized as arising from a simple β-cleavage in the molecular ion as shown in Scheme 5.



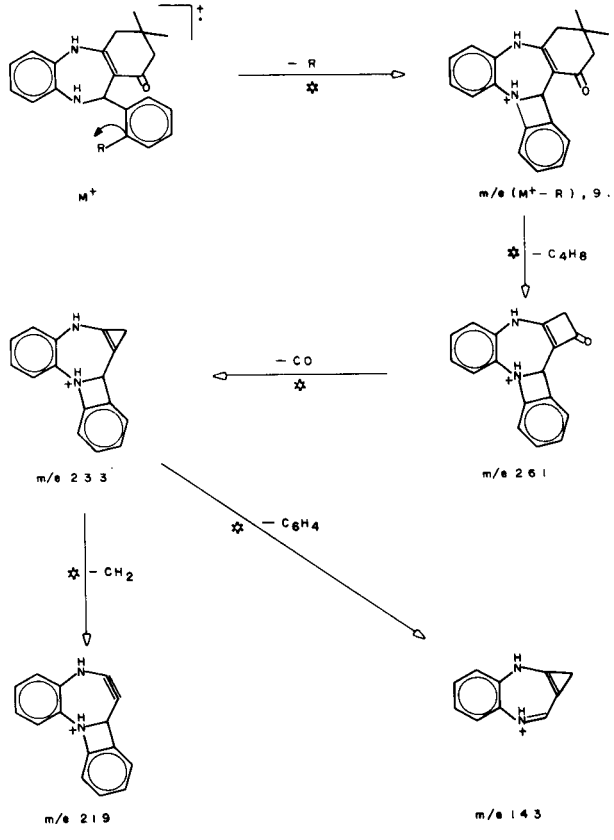
Scheme 5

Pathway C.

A typical McLafferty rearrangement of molecular ion produces an m/e 83 ion, **8**, with transfer of the α-hydrogen atom of 1,3-dimethylcyclohexene-1-one moiety to the 1,4-dibenzodiazepine ring (Scheme 5).

Fragmentation Pattern II.

The *ortho* isomers undergo fragmentation by two principal pathways. In the first the *ortho-R* group is lost in the well-known manner (12) as in Scheme 6. This leads to the ion **9** (M^+ -R), whose relative intensity is high in all the cases. This ion subsequently undergoes decomposition as the M^+ -1 ion shown in Schemes 2 and 5 leading to the m/e 261, 233, 219, 143 ions. An explanation of this difference can be found in the different structures of the (M^+ -*ortho-R*) ion. For *ortho*-isomers it is stabilized by cyclization, which is quite impossible, however for *para*-isomers.



Scheme 6

The second route, which is of equal importance, follows that of the analogous *para* isomers; the m/e 241 being the base peak, an exception of *o*-nitro, *o*-hydroxy and *o*-carboxyl derivatives.

Fragmentation Pattern III.

The significant mass spectral fragmentation pathway for *o*-hydroxy, *o*-nitro and *o*-carboxyl compounds are very similar. In addition to showing the characteristic fragments for *ortho*-substituted compounds, their mass spectra

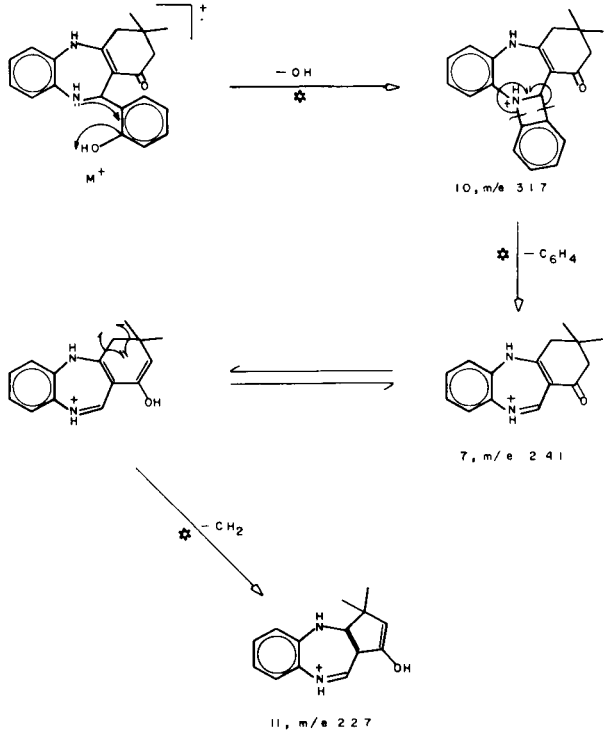
Table 2

Relative Abundance of Principal Fragments for Compounds with *o*-R = OH, NO_2, COOH
(Figures in parentheses indicate the nature of the ions)

Compound No.	R	m/e														
		M^+	M^+-17 (10)	[M^+-(R+1) (12)]	301	261	260 (13)	259	246 (14)	245 (15)	233	232	227 (11)	219	195	194
14	*o*-OH	36.4	13.0	11.0	11.0	6.0	8.0	5.0			42.5	5.0	100	5.0	3.0	3.0
15	*o*-NO_2	76.4	47.5	12.5	47.5	50.0	30.0	14.5	69.9	100	21.0	28.0	52.5	11.0		5.0
16	*o*-CO_2H	66.0	37.5	17.5	25.0	50.0	100	37.5	25.0	32.5	30.0	20.0	15.0	20.0	3.0	8.0

show other fragments which cannot be explained by the typical 1,4-dibenzodiazepin-1-ones (I) fragmentation pathways. These fragments, whose relative intensities are given in Table 3, originate directly from molecular ions, as confirmed by the presence of the appropriate metastable transition.

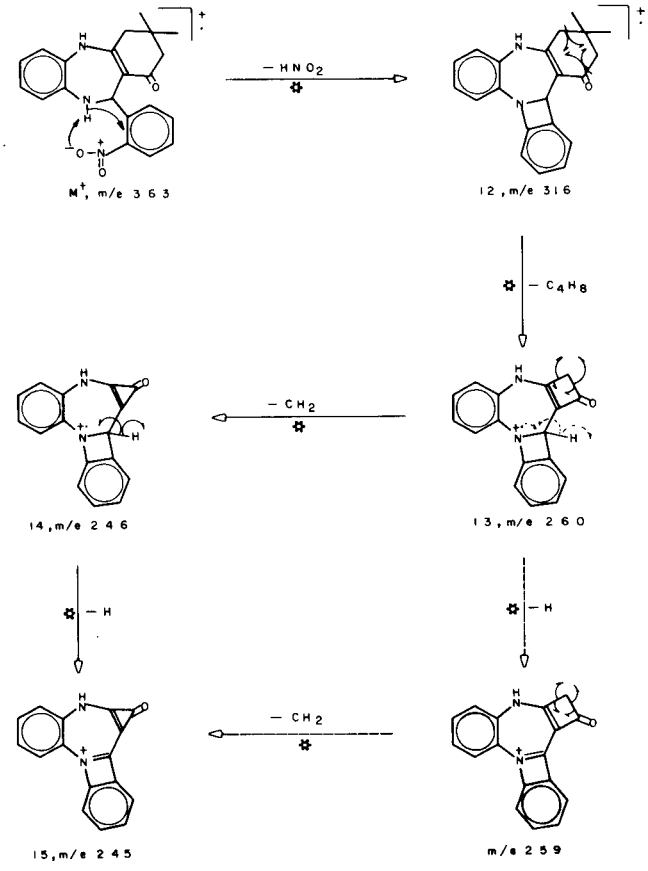
A fragment at m/e 227, **11**, is the base peak for the compound with the *o*-hydroxy substituent. This fragment is formed from the molecular ion, probably through *ortho*-interaction of the HO-substituent with dibenzodiazepine's 10-nitrogen to yield the ion at m/e 317, **10**, which further suffers the loss of the phenyl moiety to yield ion **7** of m/e 241. Elimination of a β-CH_2 unit from **7** affords the ion **11** (Scheme 7).



Scheme 7

In the case of the *o*-nitro compound we consider that the base peak **15** of m/e 245, results from molecular ion *via* the radical ion of m/e 316 (M^+ -HNO_2), **12**. Loss of isobutene unit from **12** yields **13** (m/e 260). Ion **13** then goes on to lose 14 amu (CH_2) giving **14** of m/e 246 which in turn loses a hydrogen atom giving **15** (Scheme 8). A similar fragmentation pathway may be considered in which the successive expulsion of hydrogen and CH_2 unit from **14** also gives rise to the same fragment **15**.

The formation of an ion at m/e 260, **13**, (100%) in the case of *ortho*-carboxyl compound on electron impact is also mechanistically interesting. Two fragmentation pathways are envisaged for the formation of **13** from the molecular ion, both invoking an *ortho* interaction of the



Scheme 8

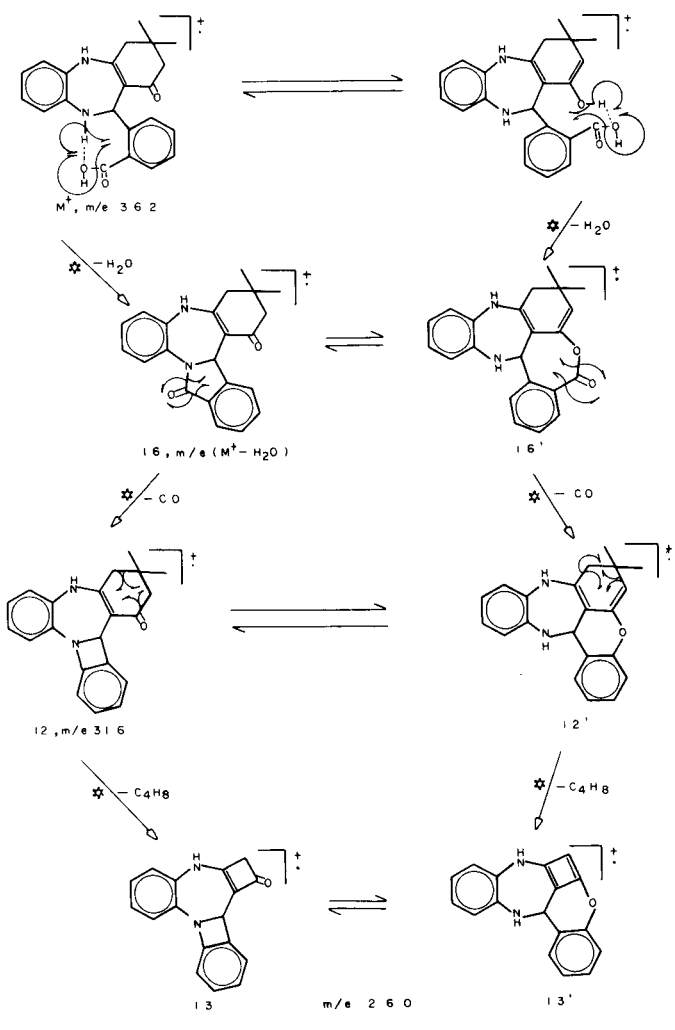
carboxyl group with the 1,4-dibenzodiazepine ring.

In both pathways, elimination of H_2O from the molecule or rearrangement of the molecular ion, involving the OH of the carboxyl group and one hydrogen, affords an ion at m/e 344, whose structure may be **16** or **16'**; this ion loses carbon monoxide and isobutene successively to furnish the fragment **13** or **13'** (Scheme 9).

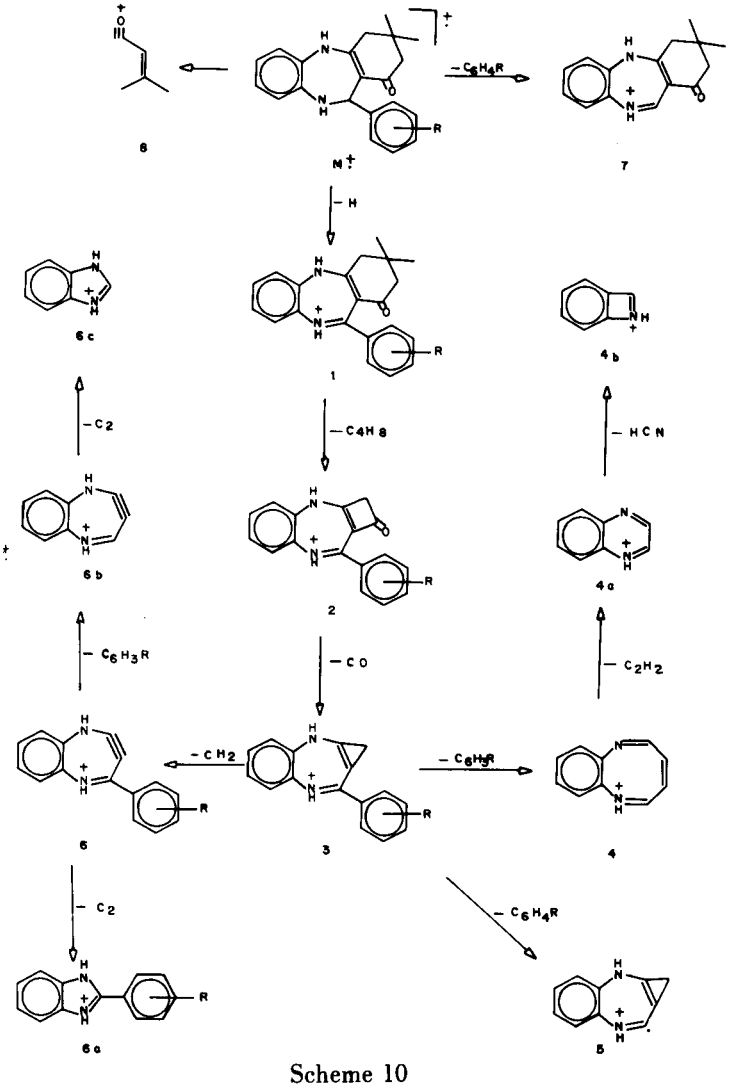
From mass spectral studies, some points can be underlined. First, the base peak of all the *ortho* and *para* isomers studied (except *o*-hydroxy, *o*-nitro, *o*-carboxyl) is the ion at m/e 241. Second, in the case of the last compounds we do not observe this strong intensity of the m/e 241 ion which represents only 37.2, 13.5 and 35.0% of their base peak. However, other fragments are very strong compared with their intensity in the mass spectra of the *ortho* and *para* compounds.

An explanation of these differences can be attributed to the common *ortho* interactions observed in the mass spectra of *o*-hydroxy (14), *o*-nitro (15) and *o*-carboxyl (16) disubstituted aromatic compounds.

In conclusion, the fragments 1,2,3,4,5,6,7 and 8 may be considered as characteristic peaks of pattern of fragmentation of 1,4-dibenzodiazepin-1-ones (I) (Scheme 10).



Scheme 9



Scheme 10

Table 3
Analytical and Physical Data for I

Compound No.	R	Yield %	Mp °C	Molecular Formula	Analyses Calcd./Found C %		Calcd./Found H %		Calcd./Found N %	
1 (1)	H	32.60	250-252	$C_{21}H_{22}ON_2$	79.20	79.15	6.96	6.94	8.80	8.76
2 (1)	*p*-Cl	60.83	235-237	$C_{21}H_{21}ClON_2$	71.47	71.38	5.99	6.00	7.94	7.91
3	*p*-Br	65.97	235-237 dec	$C_{21}H_{21}BrON_2$	63.47	63.44	5.32	5.32	7.05	7.10
4	*p*-Me	83.0	134-136	$C_{22}H_{24}ON_2$	79.48	79.42	7.27	7.25	8.42	8.38
5	*p*-OMe	57.12	192-193	$C_{22}H_{24}O_2N_2$	75.83	75.80	6.94	6.94	8.04	8.00
6	*p*-OH	77.32	225 dec	$C_{21}H_{22}O_2N_2$	75.42	75.40	6.63	6.61	8.37	8.41
7 (1)	*p*-NO_2	37.51	229-231 dec	$C_{21}H_{21}O_3N_3$	69.40	69.37	5.82	5.81	11.56	11.50
8 (2)	*p*-NH_2	10.00	152-154	$C_{21}H_{23}ON_3$	75.64	75.60	6.95	6.93	12.60	12.71
9	*o*-Cl	68.72	233-235 dec	$C_{21}H_{21}ClON_2$	71.47	71.43	5.99	5.96	7.94	8.00
10	*o*-Br	85.0	223-225	$C_{21}H_{21}BrON_2$	63.47	63.41	5.32	5.32	7.05	7.10
11	*o*-Me	26.0	215-217	$C_{22}H_{24}ON_2$	79.48	79.45	7.27	7.25	8.42	8.40
12	*o*-OMe	72.35	213-215 dec	$C_{22}H_{24}O_2N_2$	75.83	75.81	6.94	6.92	8.04	7.98
13	*o*-CO_2Me	98.0	140-142	$C_{23}H_{24}O_3N_2$	73.37	73.34	6.42	6.41	7.44	7.51
14	*o*-OH	42.0	158-159	$C_{21}H_{22}O_2N_2$	75.42	75.38	6.63	6.63	8.37	8.41
15	*o*-NO_2	68.0	115-117 dec	$C_{21}H_{21}O_3N_3$	69.40	69.38	5.82	5.78	11.56	11.61
16	*o*-CO_2H	50.0	179-181	$C_{22}H_{23}O_3N_2$	79.90	79.87	6.11	6.11	7.73	7.80

(1) Synthesized by Miyano and Abe (7). (2) Prepared from **7** by tin-hydrochloric acid catalyzed reduction.

EXPERIMENTAL

The compounds were synthesized following reported procedures (7) with some modifications. The structures of compounds **1** to **16** were supported by ir and ^{1}H-nmr spectral data. The ir spectra (Nujol) for all compounds showed very strong bands at 3412, 3340, 1610, 1587, 1515 cm^{-1} (vinylogous amide) (13) and 3310 cm^{-1} secondary amine. Besides these, bands for the R substituents are also shown.

The ^{1}H-nmr spectra (deuteriochloroform) of compound **1** (R = H) had signals at 8.5 ppm (1H, s, NH-C=C-C=O), 7.2 (5H, s, C_6H_5), 7.15-6.5 (4H, Ar), 6.24 (1H, d, NH), 6.01 (H, bs, N-CH-C_6H_5), 2.58 (2H, s, CH_2), 2.26 (2H, s, CH_2), 1.14, 1.08 (2 × 3H, s, *gem* CH_3-) two (8.5, 6.24) of which were removed and one (6.01) of which changed to a singlet by deuterium oxide, in accordance with Miyano's findings for this compound (7). The ^{1}H-nmr spectra of the other compounds analyzed also showed these characteristic signals with modifications on their chemical shifts due to the *ortho* and *para-R* substituent.

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 283-B spectrophotometer. ^{1}H-nmr spectra were recorded on a Varian FT-80A spectrometer operating at 80 MHz in deuteriochloroform or DMSO-d_6 solution containing tetramethylsilane as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7H double focusing mass spectrometer and a Hewlett Packard 5985A quadropole mass spectrometer using the direct inlet system. The samples were recorded at an ionization chamber temperature of 190° and operating at 70 eV.

Analytical and physical data on the new compounds are given in Table 2.

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