Mass Spectral Fragmentation Patterns of 1,5-Benzodiazepines. I.
ortho Effects of R_2-Substituent on
2-(ortho-R_2-Aniline)-4-(para-R_1-Phenyl)-3H-1,5-Benzodiazepines

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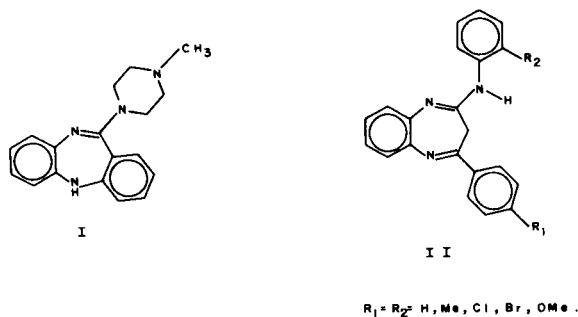Received April 17, 1981

The 70 eV electron impact mass spectra of twenty-five 1,5-benzodiazepines are discussed in detail with the aid of metastable ions and by comparison with the fragmentation patterns of known compounds. The fragmentation is markedly influenced by ortho-substituents on the aniline group.

The story of benzodiazepines as pharmacologically important agents start in 1960 when one of them was introduced as a tranquilizer under the trade name Librium (3). Since then, research in the benzodiazepine series has been very active and continues in many laboratories, leading to various modifications of the basic structure.

Some of the most interesting novel developments are derivatives with substituents at the 1 and 2 position of the diazepine nucleus. Clozapine, I, a new neuroleptic drug is particularly significant because it lacks extrapyramidal side effects in man (4). On the other hand, while the mass spectrometry of 1,4-benzodiazepines and related compounds has received widespread attention, a few studies have been published about 1,5 derivatives (5). Likewise, since the o-substituents have an appreciable influence on fragmentation patterns of many compounds (6) we would like to analyze the behaviour under electron impact of 1,5-benzodiazepines with o-substituents on their framework. As part of a program directed toward investigation of pharmacological properties of this class of compounds, 2-(o-R_2-aniline)-4-(p-R_1 phenyl)-3H-1,5-benzodiazepines of type II (Scheme 1) have been synthesized (7).

comparison with the fragmentation patterns of known compounds.

Loss of hydrogen to form the M⁺-1 ion occurs in all the mass spectra studied. The origin of the extruded hydrogen was determined from careful examination of the relative abundance listed in Table 1 which shows that: (a) For the compounds with the R_2-substituent equal to hydrogen, the relative abundance of M⁺-1 ions is the highest; (b) When the compounds have the R_2-substituent equal to Cl-, -OMe and -Br, the relative abundance of M⁺-1 ion is the smallest; (c) In the case of compounds with the R_2-substituent equal to CH_3-, the relative abundance of M⁺-1 ion is more abundant than compounds of incise b but less abundant than

SCHEME 2

SCHEME 1

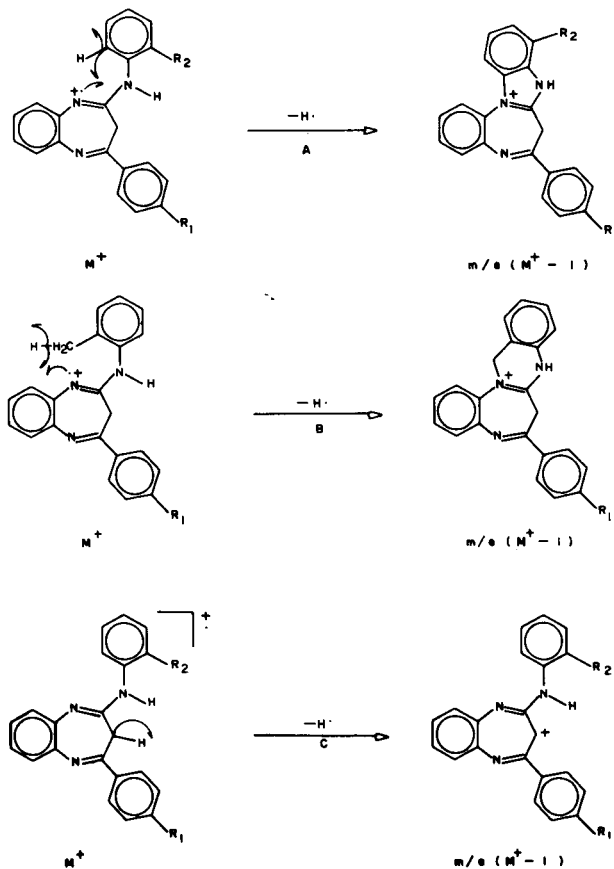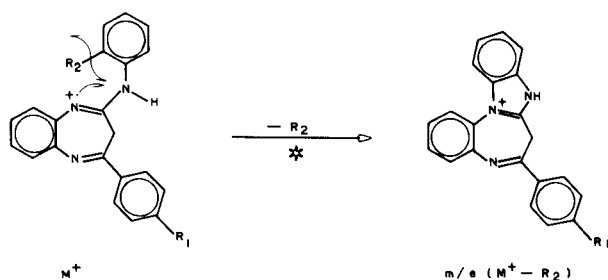$R_1 = R_2 = H, Me, Cl, Br, OMe.$

In this paper we described the elucidation of fragmentation patterns and mechanisms of 1,5-benzodiazepines II which are different from those that 1,4-benzodiazepines present (8). The relative abundances of relevant ions obtained as primary fragmentation products and discussed in this paper are reported in Table 1 and the proposed fragmentation patterns in Schemes 2-8. These latter have been justified by the existence of metastable ions and by

SCHEME 3   SCHEME 4

compounds of incise a.

Based on this data and the fact that the *o*-phenyl unit of the 2-(*o*-R_2 analine)-substituent can undergo rotation around the nitrogen atom of aniline, three pathways are feasible for the formation of M^+-1 ion from the molecular ion invoking an *ortho* interaction of the R_2-substituent on the aniline group with the 1 ring nitrogen atom of benzodiazepine.

In one pathway, loss of an *o*-hydrogen atom from the 2-(*o*-R_2 aniline)-substituent leads to the M^+-1 ion which is depicted as a benzimidazole-benzodiazepine cation (A, Scheme 2). The poor relative abundance of M^+-1 ion for compounds with R_2 = -Cl, -OMe and -Br is explained by the presence of these bulky groups which hindered the rotation of the phenyl group and the possibility of loss only one hydrogen atom.

In the second pathway, valid only for derivatives when R_2 = -CH_3, elimination of one hydrogen atom from the molecular ion, involving the hydrogen of the *o*-methyl substituent, affords the pyrimidine-benzodiazepine ion at m/e M^+-1 (B, Scheme 2). Likewise, it has been reported that rearrangements of benzodiazepines are induced by abstraction of one proton at position 3 (8). It may be assumed that elimination of the H-3 led to the ion at m/e (M^+-1) (C, Scheme 2).

Another interesting interaction of the *o*-R_2-substituent of aniline with the 1-nitrogen atom of benzodiazepine is the elimination of -Cl, -OMe and -Br from the molecular ion giving rise to a fragment at m/e (M^+-R_2) which is the base peak for the compounds with R_1 = -H, -Cl, OMe, -Br (Scheme 3).

The formation of the base peak when R_2 = CH_3- and R_1 = -H, -Cl, CH_3- involves the loss of an hydrogen of the CH_3- group leading to the (M^+-1) ion which by two β-cleavages, one of these from the 5-nitrogen atom of benzodiazepine and another from the nitrogen atom of the 2-aniline produces the ion at m/e (194 + R_1) as shown in Scheme 4. A similar *o*-methyl interaction has been reported for 1,5-benzodiazepine-2-thiones (5c).

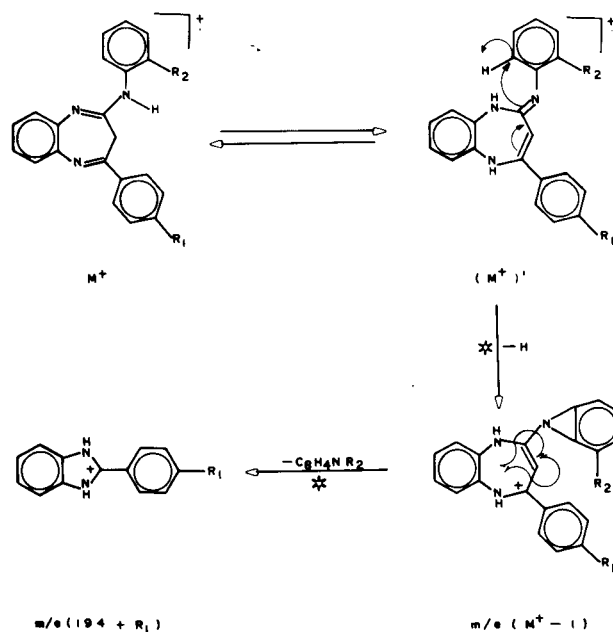In the case of compounds with the R_2-group different
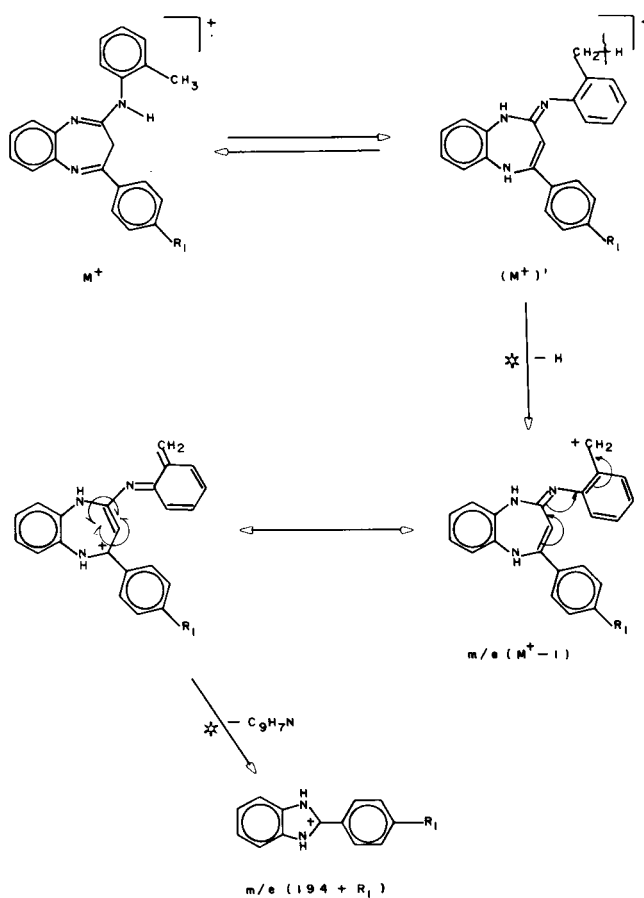
SCHEME 5

Table 1

Relative Abundance of Principal Fragments

Compound No.	R₁	R₂	M⁺	M⁺-1	M⁺-R₂	194 + R₁	193 + R₁	116 + R₂	102 + R₁	102	91	77
I	H	H	93.9	76.3	93.9	57.3	100	41.2	8.0	2.5	14.0	31.0
II	H	Cl	35.8	10.0	100	28.3	62.1	23.5	10.0	9.0	17.3	28.5
III	H	OMe	14.3	2.5	100	19.8	11.0	5.0	5.0	2.5	12.3	16.7
IV	H	CH₃	62.2	22.5	31.2	100	31.0	32.5	6.0	5.7	21.3	18.0
V	H	Br	21.2	8.5	100	42.5	53.3	42.5	8.0	7.5	15.0	22.5
VI	Cl	H	100	86.5	86.5	45.0	51.0	58.1	2.5	9.6	12.0	25.0
VII	Cl	Cl	39.4	9.0	100	26.0	42.9	32.5	4.0	8.0	4.3	5.0
VIII	Cl	OMe	21.5	2.5	100	18.0	6.0	11.0	3.0	7.6	6.0	8.2
IX	Cl	CH₃	86.4	28.0	69.3	100	30.0	67.0	5.0	3.4	14.3	14.2
X	Cl	Br	12.5	2.5	100	20.0	34.9	7.5	3.0	6.0	5.0	8.0
XI	OMe	H	100	94.9	94.9	49.6	15.5	5.0	8.0	4.0	1.8	28.3
XII	OMe	Cl	45.4	15.0	100	26.0	58.7	7.0	7.5	4.3	6.3	10.2
XIII	OMe	OMe	27.1	10.0	100	20.0	16.5	5.0	8.0	8.2		9.3
XIV	OMe	CH₃	100	35.3	31.1	81.3	49.9	30.0	7.5	2.3	22.8	18.3
XV	OMe	Br	20.0	4.0	100	32.0	74.7	3.0	10.0	3.8	12.3	18.7
XVI	CH₃	H	71.0	55.0	55.0	34.5	100	20.0	2.5	1.2	13.1	18.5
XVII	CH₃	Cl	37.0	9.0	100	34.9	59.5	10.0	5.0	8.0	17.6	7.2
XVIII	CH₃	OMe	29.5	2.5	100	28.3	20.0	8.0	2.8	2.0	2.1	4.3
XIX	CH₃	CH₃	68.1	30.0	38.8	100	84.0	32.5	9.1	8.2	37.3	18.2
XX	CH₃	Br	23.0	5.0	100	26.0	81.5	6.0	7.6	7.5	20.2	15.6
XXI	Br	H	76.1	57.7	57.7	28.5	50.0	100	8.3	31.2	4.2	75.7
XXII	Br	Cl	25.0	6.5	100	17.5	31.25	31.0	8.5	30.1	9.2	15.4
XXIII	Br	OMe	13.8	2.5	100	18.0	5.0	19.1	2.0	18.4	4.2	18.2
XXIV	Br	CH₃	92.1	33.8	46.6	79.2	22.5	100	4.0	23.3	33.4	23.4
XXV	Br	Br	9.0	2.5	100	28.0	51.0	20.0	7.5	38.3	21.2	55.3

Table 2

Compound No.	R₁	R₂	Yield %	Mp °C	Molecular Formula	Calcd./Found C %		Analyses Calcd./Found H %		Calcd./Found N %	
I	-H	-H	42	112-114	C₂₁H₁₇N₃	81.00	81.10	5.50	5.45	13.49	13.36
II	-H	-Cl	47	215-216	C₂₁H₁₆ClN₃	72.92	72.67	4.66	4.66	12.15	12.10
III	-H	-OMe	61	220-221	C₂₂H₁₉N₃O	77.39	77.21	5.60	5.61	12.31	12.26
IV	-H	-CH₃	53	236-238	C₂₂H₁₉N₃	81.19	81.15	5.88	5.90	12.91	12.90
V	-H	-Br	50	225-228	C₂₁H₁₆BrN₃	64.62	64.40	4.13	4.10	10.76	10.69
VI	-Cl	-H	43	255-257	C₂₁H₁₆ClN₃	72.92	72.75	4.66	4.64	12.15	12.13
VII	-Cl	-Cl	51	213-215	C₂₁H₁₅Cl₂N₃	66.32	66.25	-3.97	3.95	11.05	11.00
VIII	-Cl	-OMe	60	258-260	C₂₂H₁₈ClN₃O	70.29	70.21	4.82	4.80	11.18	11.13
IX	-Cl	CH₃	51	251-253	C₂₂H₁₈ClN₃	73.42	73.40	5.04	5.00	11.67	11.60
X	-Cl	-Br	48	190-191	C₂₁H₁₃BrClN₃	59.37	59.28	3.55	3.60	9.89	9.91
XVI	-CH₃	-H	53	221-223	C₂₂H₁₉N₃	81.19	81.00	5.88	5.85	12.91	12.86
XVII	-CH₃	-Cl	60	158-160	C₂₂H₁₈ClN₃	73.42	73.50	5.04	5.10	11.67	11.54
XVIII	-CH₃	OMe	65	162-163	C₂₃H₂₁N₃O	77.71	77.68	5.95	5.91	11.82	11.79
XIX	-CH₃	-CH₃	51	182-184	C₂₃H₂₁N₃	81.38	81.25	6.23	6.20	12.38	12.33
XX	-CH₃	-Br	48	159-161	C₂₂H₁₈BrN₃	65.35	65.30	4.48	4.50	10.39	10.42
XXI	-Br	-H	48	205-206	C₂₁H₁₆BrN₃	64.62	64.51	4.13	4.12	10.76	10.71
XXII	-Br	-Cl	53	195-197	C₂₁H₁₅BrClN₃	59.37	59.31	3.55	3.50	9.89	9.90
XXIII	-Br	-OMe	67	160-162	C₂₂H₁₈BrN₃O	62.86	62.79	4.31	4.30	9.99	10.00
XXIV	-Br	-CH₃	39	215-217	C₂₂H₁₈BrN₃	65.35	65.19	4.48	4.42	10.39	10.27
XXV	-Br	-Br	38	221-223	C₂₁H₁₅Br₂N₃	53.75	53.72	3.22	3.20	8.95	8.93
XI	-OMe	-H	51	210-212	C₂₂H₁₉N₃O	77.39	77.29	5.60	5.60	12.31	12.28
XII	-OMe	-Cl	56	235-237	C₂₂H₁₈ClN₃O	70.29	70.18	4.82	4.79	11.18	11.15
XIII	-OMe	-OMe	65	205-207	C₂₃H₂₁N₃O₂	74.37	74.32	5.69	5.65	11.31	11.28
XIV	-OMe	-CH₃	49	181-183	C₂₃H₂₁N₃O	77.71	77.68	5.95	5.92	11.82	11.77
XV	-OMe	-Br	46	196-198	C₂₂H₁₈BrN₃O	62.86	62.84	4.31	4.30	9.99	9.93

from the CH_3- group, we proposed a similar mechanism to produce the ion at m/e $(194 + R_1)$ (Scheme 5).

The relative abundance of the 2-(p-R_1 phenyl)benzimidazole ion, m/e $(193 + R_1)$, varies from 5% of the base peak to being the base peak when $R_1 = $-H, -CH$_3$ and $R_2 = $ H. The formation of this ion is explained as arising from a molecular rearrangement as shown in Scheme 6. It is interesting to note that Nardi (9) by acid cleavage of 4-aryl-1,3-dihydro-2H-1,5-benzodiazepine-2-thiones obtained substituted 2-phenylbenzimidazoles. Also, Nardi (9) and Hunter (5a) observed the formation of benzimidazole ions in the mass spectra of some 1,5-benzodiazepines. In keeping with this structural assignment for the m/e $(193 + R_1)$ ion it fragments to a small extent by loss of a C_6H_5NH unit to form an m/e $(102 + R_1)$ ion (Scheme 6). After this fragmentation loss of the R_1-substituent produces the ion at m/e 102. The m/e $(102 + R_1)$ and m/e 102 species are also formed from the molecular ion by loss of a $C_{14}H_{11}N_2R_2$ unit (Scheme 7).
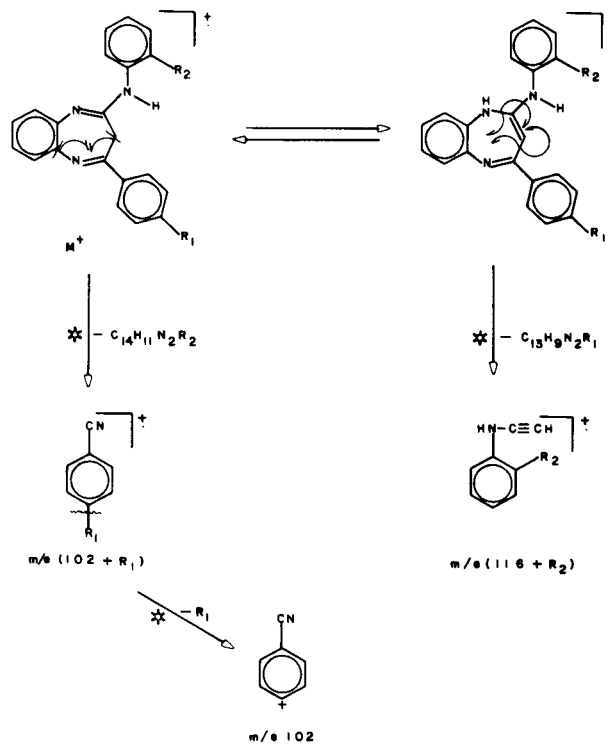
The abundant formation of an ion at m/e $(116 + R_2)$ with high relative base peak abundance, for compounds with $R_2 = $-Br and $R_1 = $-H, -CH$_3$, is rationalized as arising from simple β-cleavages in the molecular ion as shown in Scheme 7.

In conclusion, the fragments at m/e M$^+$-1, M$^+$-R$_2$, 194 + R$_1$, 193 + R$_1$, 116 + R$_2$, 102 + R$_1$ and 102 may be con-
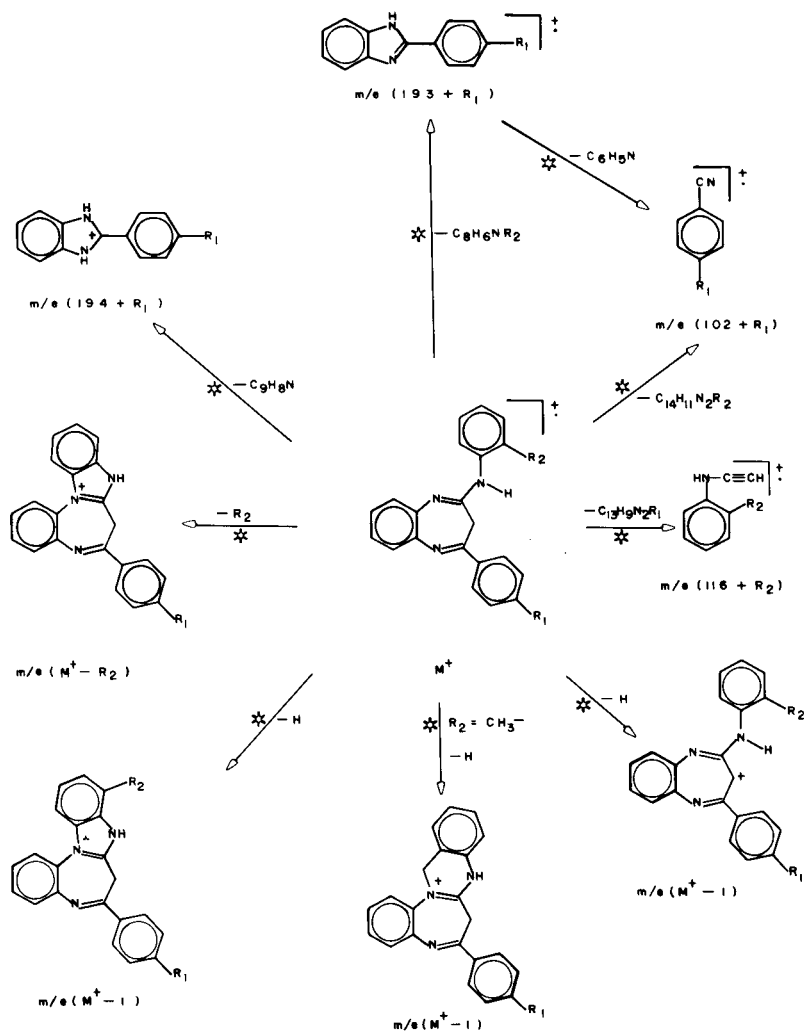
SCHEME 7
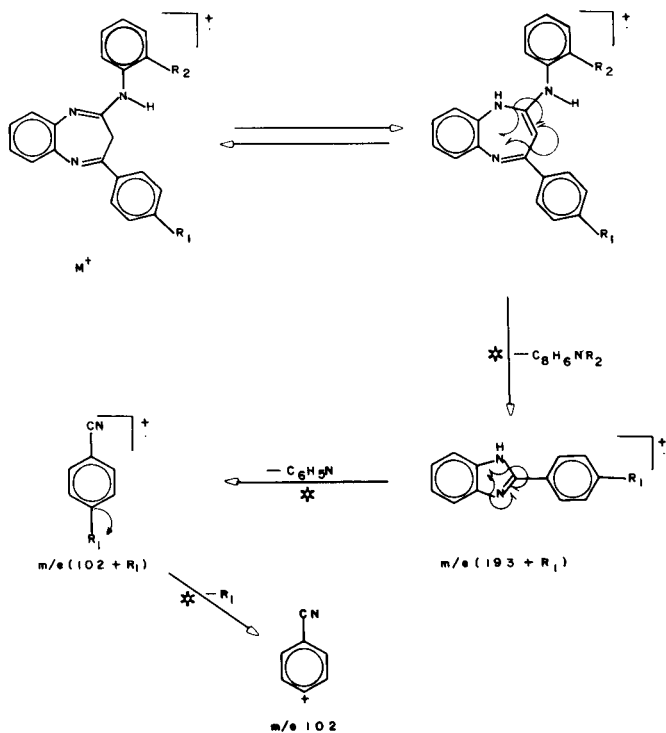
SCHEME 6

sidered as characteristic peaks of pattern fragmentation of 2-(o-R_2-aniline)-4-(p-R_1-phenyl)-3H-1,5-benzodiazepines (Scheme 8).

EXPERIMENTAL

The compounds were synthesized following reported procedures (7) with some modifications. The structures of compounds I to XXV were supported by ir spectral data. The ir spectra for all compounds exhibited very strong bands at 3300-3400 (-NH-); 1648, 1610 (-C=N-); 1590, 1510, 750-730 (C=C) and 1370-1340, 1250-1230 (C-N-C) cm^{-1}. In addition, bands for the -R$_2$ and R$_1$-substituents are also shown. All the compounds investigated gave satisfactory elemental analyses. In Table 2, chemical and physical data for the new compounds are recorded. The ^{1}H nmr data for these compounds are not given due to their insolubility in solvents normally used in these analyses.

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 283-B spectrophotometer. The mass spectra were measured on a Hitachi-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 70eV.

SCHEME 8

m/e $(193 + R_1)$

$- C_6H_5N$

$- C_8H_6NR_2$

CN

R_1

m/e $(102 + R_1)$

m/e $(194 + R_1)$

$- C_9H_8N$

$- C_{14}H_{11}N_2R_2$

HN—C≡CH

R_2

$- C_{13}H_9N_2R_1$

m/e $(116 + R_2)$

$- R_2$

M^+

m/e $(M^+ - R_2)$

$R_2 = CH_3$
$- H$

$- H$

$- H$

R_2

m/e $(M^+ - 1)$

m/e $(M^+ - 1)$

m/e $(M^+ - 1)$

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(1) To whom correspondence should be addressed.

(2) Contribution 581 from Instituto de Química.

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