Mass Spectral Fragmentation Patterns of 11-(*o*- and *p*-R-Anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines. IV [1]

E. Cortés [2], R. Martínez and A. Zarza*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510 México, D.F.

*Esc. de Ciencias Químicas, Universidad Autónoma del Estado de México

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The mass spectral fragmentation patterns of eleven 11-(*o*- and *p*-R-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines obtained by electron impact have been studied. All the spectra analyzed contain molecular ions, which are base peak for *para* isomers and the principal fragmentation routes takes place either from the molecular ion, or from ($M^+ - 1$) ion. There are, however, some deviations from the general fragmentation pattern in the case of 1,4-dibenzodiazepines with *o*-amino and *p*-methoxy substituents caused by direct interaction of these groups with the dibenzodiazepine ring.

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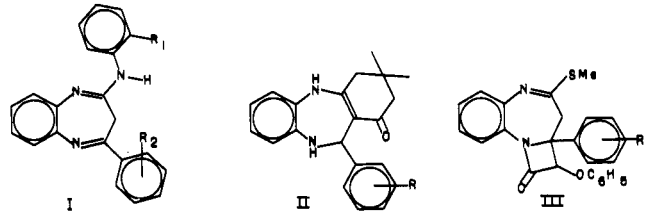
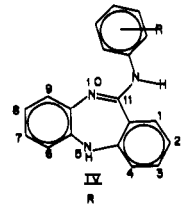
1,4- And 1,5-benzodiazepine analogs represent a series of compounds of considerable medicinal interest mainly as tranquilizer agents [4,5]. This induces us to report the synthesis and mass spectrometry studies of a closely related family of compounds of the general structure I, II and III [6,7,1]. As a part of a program directed toward investigation of pharmacological properties of this class of compounds, 11-(*o*- and *p*-R-anilino)-5*H*-dibenzo[*b*,*e*][1,4]diazepines of type IV (Scheme 1) have been synthesized [8].



I II III



IV

R

H
o-Cl p-Cl
o-Br p-Br
o-OH p-OH
o-OMe p-OMe
o-Me o-NH_2

SCHEME 1

In the present paper we wish to report the mass spectral fragmentation patterns of these compounds and to compare them with those of the analogous 1,4-benzodiazepin-1-ones II and 1,5-benzodiazepines I. 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 to 12. These latter have been justified by the existence of metastable ions and by comparison with the fragmentation patterns of known compounds.

The mass spectra of IV and I [6] compounds show some common features. They both exhibit an intense molecular

Table 1

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

Compound No.	R	M^+	M^+-1 (1)	M^+-R (5)	m/e 283 (3)	268 (3c)	207 (3a)	193 (4)	192 (3c)	181 (2)	155 (2a)	128 (2b)	102 (2c)
1	H	99.8	100.0	100.0	11.0	5.0	1.7	34.1	11.2	5.0	1.0	1.0	1.0
2	*o*-Cl	32.5	10.0	100.0	18.3	10.0	2.4	9.0	22.5	12.5	1.0	10.0	5.0
3	*o*-Br	17.5	2.5	100.0	12.7	7.5	2.4	4.5	7.5	7.5	1.0	2.5	1.0
4	*o*-Me	95.8	43.4	100.0	19.5	7.5	14.8	9.0	17.0	17.0	10.0	2.5	1.0
5	*o*-OMe	54.0	5.0	100.0	7.8	2.5	6.1	4.5	13.7	5.0	1.0	1.0	7.5
6	*o*-NH_2	89.0	36.6	33.0	7.3	3.6	10.2	12.2	17.0	—	2.5	10.0	11.0
7	*o*-OH	100.0	26.8	76.8	7.3	4.8	7.0	99.0	14.0	29.2	5.8	31.0	5.6
8	*p*-Cl	100.0	62.1	10.0	12.2	3.7	5.6	13.5	23.7	16.2	10.0	6.8	3.6
9	*p*-Br	100.0	97.8	20.3	15.8	8.9	12.0	25.0	30.3	33.0	2.4	4.8	8.5
10	*p*-OMe	100.0	53.3	5.0	7.3	2.0	4.8	25.0	35.0	7.5	2.4	9.8	3.6
11	*p*-OH	100.0	33.1	56.1	18.0	4.8	7.0	22.0	26.8	18.2	2.4	4.8	3.6

ion. The relative abundance of molecular ions of IV varies from 17.5% of the base peak to being the base peak for *para*-R isomers and the *ortho*-hydroxy compound (see Table 1). This probably reflects the stable nature of the 1,4-benzodiazepine's ring, under electron impact. The major fragmentation of the molecular ion proceeds along two pathways: (A) From $[M]^+$ to m/e 102, 207, 192 and 193; (B) From $[M]^+$ to m/e $(M^+ - R)$.

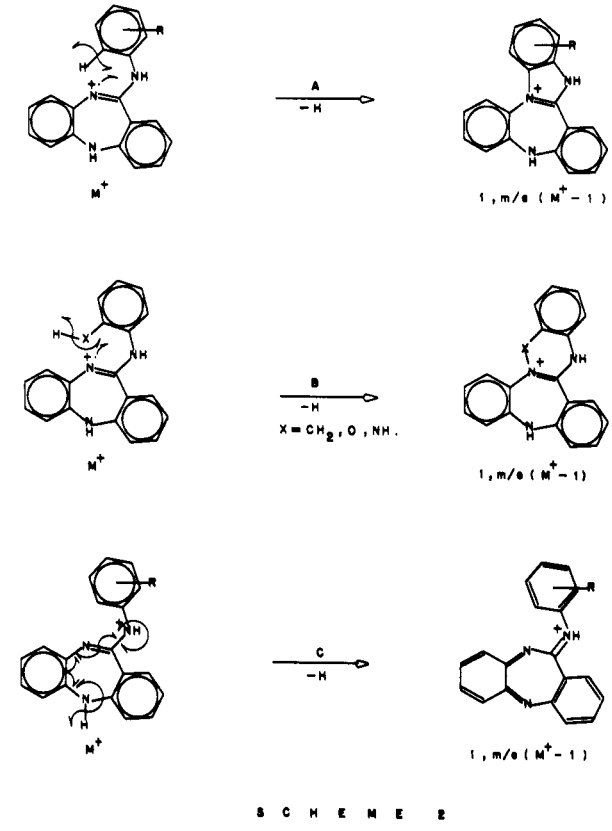
Pathway A.

A second fragmentation pattern resembling that of 1,5-benzodiazepines I [6] proceeds through the loss of a hydrogen atom from the molecular ion leading the ion **1** of m/e $(M^+ - 1)$. Based on the behaviour under electron impact of I and on the careful examination of relative abundance listed in Table 1, which show that: (a) For the compounds with the *para*-R-substituent equal to H, Cl-, Br-, OMe- and OH- the relative abundance of $M^+ - 1$ ion is the highest (for R = H, ion **1** is 100%); (b) When the compounds have the *ortho*-R-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 *ortho*-R-substituent equal to CH_3, NH_2- and OH-, the relative abundance of **1** ion is more abundant than compounds of incise *b* but less abundant than compounds of incise *a*, two pathways are feasible for the formation of the ion **1** from the molecular ion invoking an *ortho* interaction of the *o*-R-substituent on the anilino group with the 10 ring nitrogen atom of 1,4-dibenzodiazepines.

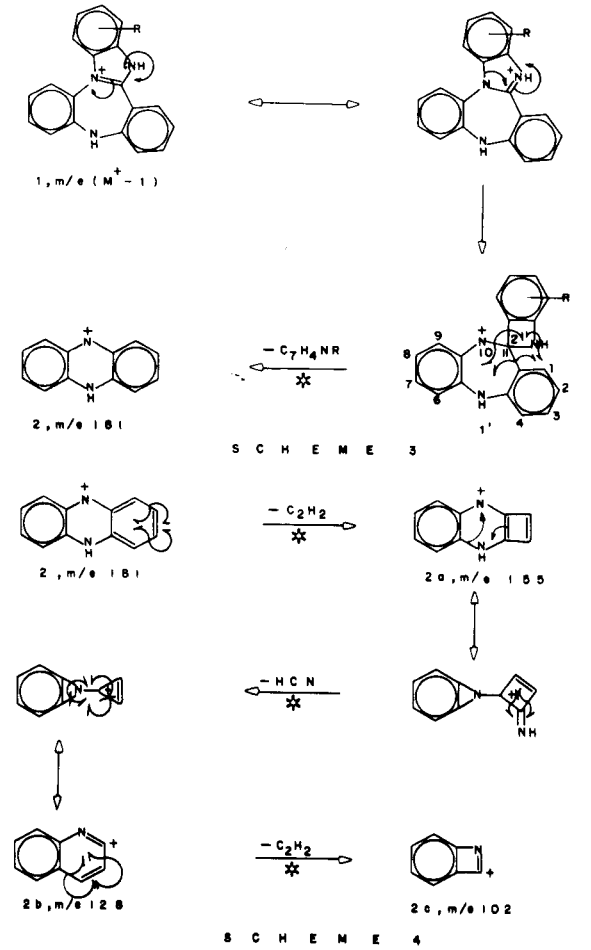
In one pathway, loss of an *o*-hydrogen from the 11-(*p*-R-anilino)-substituent leads to the $M^+ - 1$ ion which is depicted as a benzimidazole-dibenzodiazepine cation (A, Scheme 2). The high relative abundance of *para*-R compounds is explained by the presence of these groups in the *para*- position which permit the free rotation of *N*-phenyl unit of 11-(*p*-R-anilino)-substituent around the nitrogen atom of aniline and the possibility of loss easily anyone of the *o*-hydrogen.

Contrary to what has been observed in the *para*-R compounds, IV, the loss of an *o*-hydrogen atom from the molecular ion of *ortho*-R compounds with R = Cl-, OMe- and Br- appears to be of lesser importance. The poor relative abundance of $M^+ - 1$ ion for these compounds is explained by the presence of these bulky groups which hindered the rotation of the phenyl group and the possibility of loss only one *o*-hydrogen atom. This indicates that the major part of $M^+ - 1$ ion are due to the elimination of an *ortho*-hydrogen and support the fragmentation pattern mechanisms proposed for this loss on the 1,5-benzodiazepines I [6].

In the second pathway, applicable only for derivatives



SCHEME 2



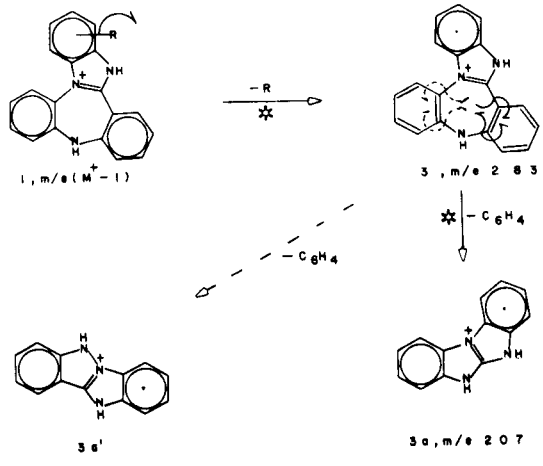
SCHEME 3

SCHEME 4

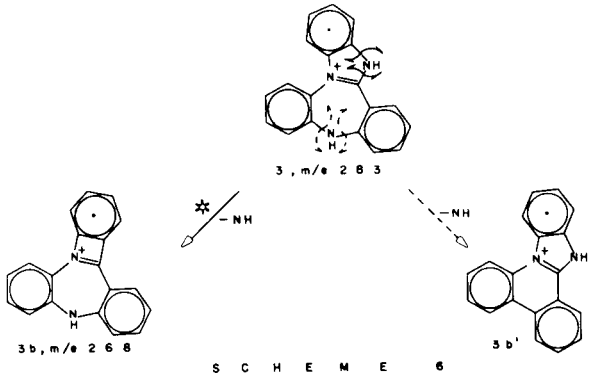
when *ortho*-R = CH_3-, NH_2- and OH-, elimination of one hydrogen atom from the molecular ion, involving one hydrogen of the *o*-methyl, *o*-amine or *o*-hydroxy substituent, affords the ionic species **1** consisting of a six membered ring fused to the 1,4-dibenzodiazepine ring (B, Scheme 2). On the other hand, elimination of 5-hydrogen atom of 1,4-benzodiazepine moiety (C, Scheme 2) cannot be excluded.

Fragmentation of **1** then proceeds along three pathways. In one pathway, loss of a benzazetine unit from **1**, probably through the [*b*,*e*][1,4]dibenzodiazepine-11-spiro-2'-benzoazetidine intermediate **1'**, leads to the ion **2** of m/e 181 which is depicted as a benzoquinoxaline cation (Scheme 3). Expulsion of acetylene from **2** leads to the formation of ion **2a** of m/e 155 which suffers the loss of hydrogen cyanide to yield the ion **2b** (m/e 128). The latter then loses acetylene yielding the already known ion **2c** [9] of m/e 102 (Scheme 4).

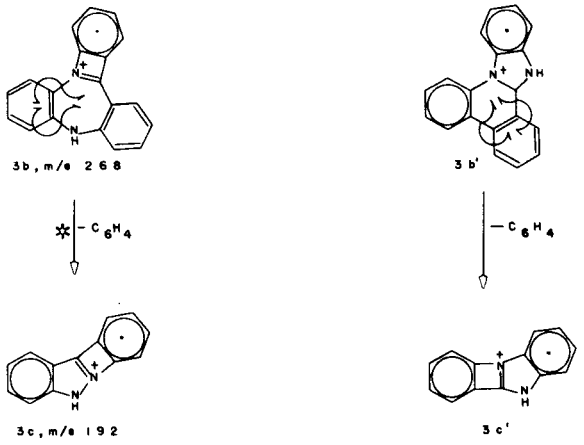
In another pathway, the *ortho* or *para*-R group is lost in the well-known manner [10] from **1** yielding an ion at m/e 283, **3** (Scheme 5). Fragmentation of **3** then proceeds along two pathways. One pathway results in the loss of a C_6H_4 unit to give the indolebenzimidazole or the indolebenzopyrazole ion radical **3a** or **3a'**, of m/e 207 (Scheme 5); while the other results in the loss of 15 mass units to give the ion **3b** or **3b'** of m/e 268. Most probably this signifies a loss of NH either directly from the 1,4-dibenzodiazepine ring or from the benzimidazole ring as shown in Scheme 6. Loss of a C_6H_4 unit from **3b** gives the ion of m/e 192. It is difficult to establish the structure of this species we propose two alternatives **3c** or **3c'** both of which may be present (Scheme 7).



SCHEME 5



SCHEME 6

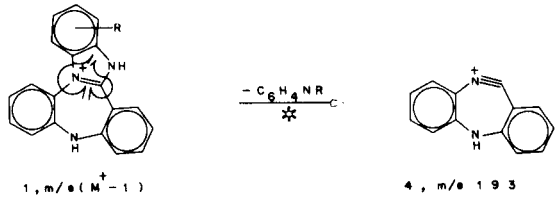


SCHEME 7

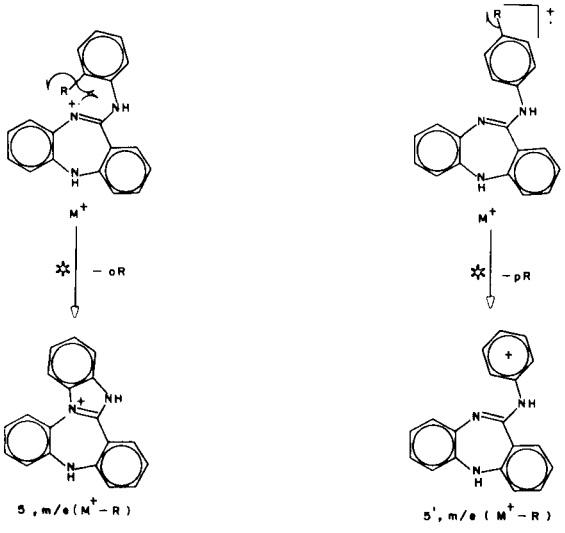
In the third pathway (Scheme 8) loss of a C_6H_4NR unit from **1** yields **4** of m/e 193; it is interesting to note that the relative abundance of **4** ion for *para* and *ortho* compounds IV is essentially analogous to that **1** ion presents and probably it is influenced by the -R substituent.

Pathway B.

Another interesting fragmentation pathway of IV is the elimination of the R-substituent from the molecular ion giving rise to a fragment at m/e ($M^+ - R$), **5** (Scheme 9) base peak for the majority of *ortho* compounds with the exception of *o*-amino and *o*-hydroxy compounds. An explanation of this difference can be found in the different structures of the ($M^+ - R$) ion. For *ortho* isomers it is stabilized by cyclization, which is quite impossible, however for *para* isomers. A similar *o*-R interaction has been reported for 1,4-dibenzodiazepin-1-ones [11] and 1,5-diazepines (I) [6,7].

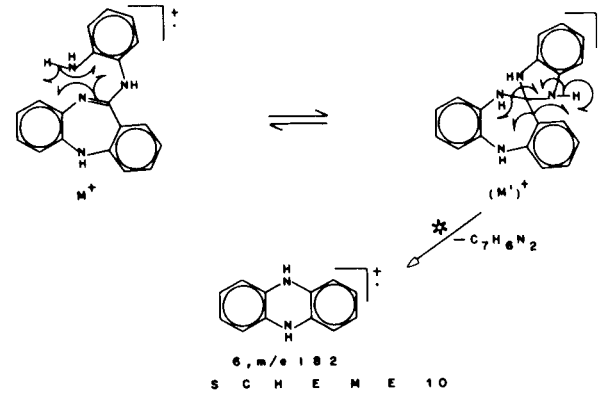


SCHEME 8

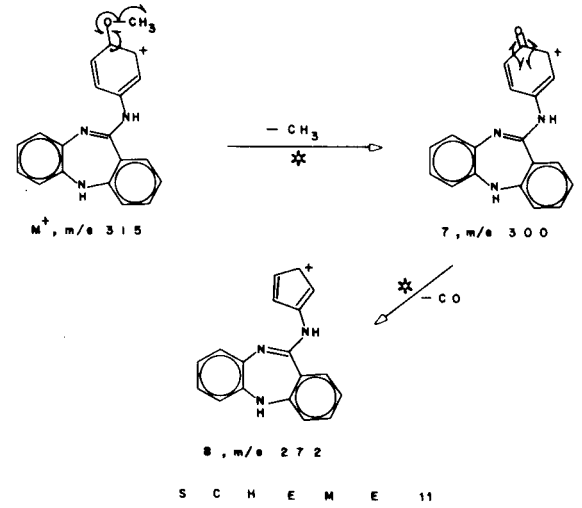


SCHEME 9

In addition to showing the characteristic fragments for *ortho* and *para*-substituted compounds the mass spectra of *o*-amino and *p*-methoxy compounds show other fragments which cannot be explained by the typical 1,4-dibenzodiazepines (IV) fragmentation pathways. These fragments originate directly from molecular ions, as confirmed by the presence of the appropriate metastable transitions. A fragment at m/e 182, **6**, is the base peak for the *o*-amine compound. This fragment is formed from the molecular ion, probably through *ortho* interaction of the NH_2 substituent with dibenzodiazepine's 10-nitrogen to yield the ion **6** (Scheme 10).



SCHEME 10



SCHEME 11

Table 2

Analytical and Physical Data for Compounds IV

Compound No.	R	Mp °C	Yield %	Molecular Formula	Analysis C	H	N
1	H	155	63	$C_{19}H_{15}N_3$	79.97 (79.95)	5.29 (5.25)	14.72 (14.68)
2	*o*-Cl	158-159	70	$C_{19}H_{14}ClN_3$	71.36 (71.30)	4.41 (4.39)	13.14 (13.10)
3	*o*-Br	108-110	60	$C_{19}H_{14}BrN_3$	62.65 (62.61)	3.87 (3.85)	11.53 (11.50)
4	*o*-Me	58-60	25	$C_{20}H_{17}N_3$	80.23 (80.21)	5.72 (5.72)	14.03 (14.00)
5	*o*-OMe	68-70	53	$C_{20}H_{17}N_3O$	76.16 (76.12)	5.43 (5.42)	13.32 (13.30)
6	*o*-NH_2	73-75	36	$C_{19}H_{16}N_4$	75.97 (75.95)	5.37 (5.34)	18.65 (18.61)
7	*o*-OH	72-75	43	$C_{19}H_{15}N_3O$	75.72 (75.70)	5.01 (5.00)	13.94 (13.91)
8	*p*-Cl	64-65	65	$C_{19}H_{14}ClN_3$	71.36 (71.33)	4.41 (4.39)	13.14 (13.10)
9	*p*-Br	62-63	57	$C_{19}H_{14}BrN_3$	62.65 (62.60)	3.87 (3.85)	11.53 (11.51)
10	*p*-OMe	70-72	45	$C_{20}H_{17}N_3O$	76.16 (76.11)	5.43 (5.40)	13.32 (13.29)
11	*p*-OH	117-119	75	$C_{19}H_{15}N_3O$	75.72 (75.71)	5.01 (4.91)	13.94 (13.90)

In the case of *p*-methoxy compound, we considered that the **7** ion of m/e 300 results from the molecular ion by the typical loss of a methyl radical [11]. Ion **7** then goes on to lose carbon monoxide giving the ion **8**, of m/e 272 (Scheme 11). The fact that the **7** and **8** ions do not appear in the spectrum of *o*-methoxy compounds is probably due to the easier loss of *o*-methoxy substituent to form the ion **5** of m/e ($M^+ - R$), base peak for this compound.

From mass spectral studies, some points can be underlined. First, the base peak of *ortho* isomers (except *o*-hydroxy, *o*-amine) is the ion at m/e ($M^+ - R$). Second, in the case of *para* isomers and *o*-hydroxy compound the base peak is the molecular ion. Likewise, as in the spectra of 1,5-benzodiazepines I, the relative abundance of ($M^+ - 1$) and ($M^+ - R$) ions are markedly influenced by the substituents on the aniline group.

An explanation of these differences can be attributed to the common *ortho* interactions observed in the mass spectra of 1,4-dibenzodiazepin-1-ones II and 1,5-benzodiazepines I [6,7].

In conclusion, the fragments **1**, **2**, **2a**, **2b**, **2c**, **3**, **3a**, **3b**, **3c**, **4** and **5** may be considered as characteristic peaks of pattern of fragmentation of [1,4]dibenzodiazepines (IV) (Scheme 12).

EXPERIMENTAL

The compounds were synthesized following reported procedures [8] with some modifications. The most distinguishable spectral property of these amidines was the ir spectrum. The ir spectra for all the compounds exhibited very strong bands at 3300-3400 (-NH); 1640-1625 (-C=N-), 1590, 1510, 750-730 (-C=C-) and 1370-1320, 1260-1210 (-C-N-C-) cm^{-1}. In addition, bands for the R-substituents are also shown. In Table 2 physical and analytical data for the new compounds are recorded.

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 283-B spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-7H double focusing mass spectrometer and a Hewlett Packard 5985 A quadropole mass spectrometer using the direct inlet system. The samples were recorded at an ionization chamber temperature of 190° and operating at 70 eV.

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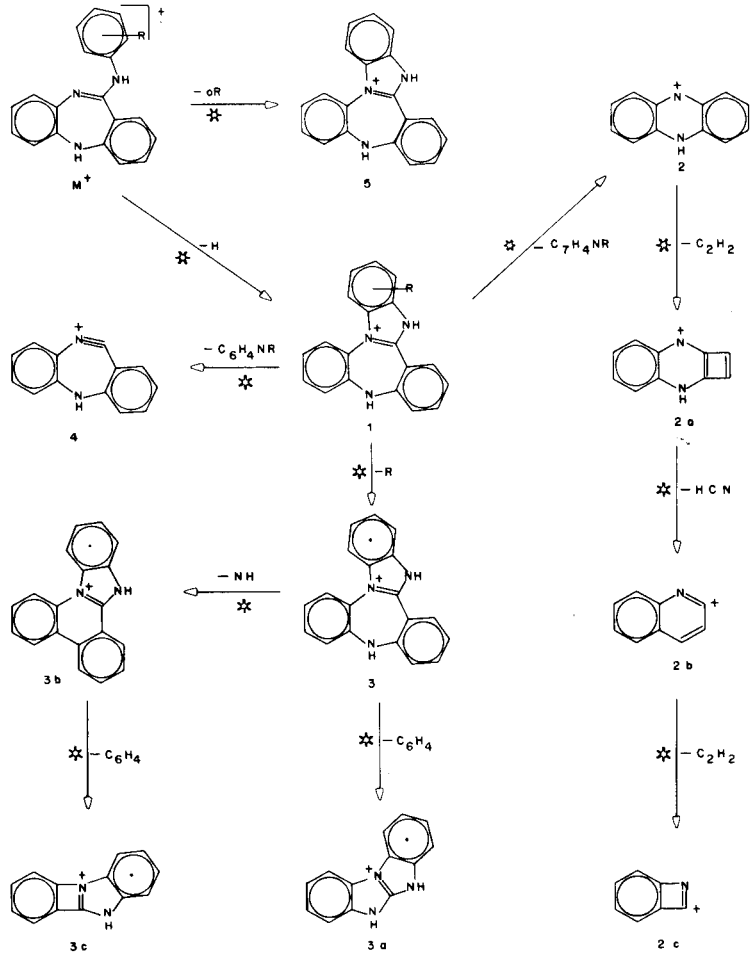

SCHEME 12

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[2] To whom correspondence should be addressed.

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