N-Arylhexahydropyrimidines. Electron impact mass spectrometry

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Abstract
The behavior of a series of 1,3-di- and 1,2,3- trisubstituted *N*-arylhexahydropyrimidines under electron impact (20eV) is analyzed. The compounds under study were divided into four groups according to their substitution patterns, which in turn determine the dominant fragmentations. In general, $[M^{+\cdot}]$ ions are intense, as well as fragments originating from cleavage of the C-2 substituent, which give rise to highly stabilized amidinium ions ($[M\text{-}H]^+$ or $[M\text{-}R_2]^+$). Their dominant secondary fragmentation involves loss of imines or azetidines. Additional fragmentations are also proposed, resulting from initial homolytic fragmentation of C2–N bonds in $[M^{+\cdot}]$ ions.

Keywords: Hexahydropyrimidines, mass spectrometry, electron impact

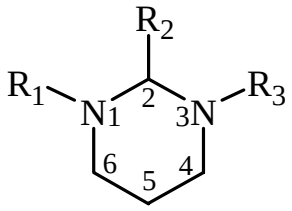
Introduction

Hexahydropyrimidines are of current interest owing to their pharmacological activity, as some members are prodrugs of biologically active di-,[1] and poly- amines.[1,2] Also, some suitably substituted derivatives form stable complexes with metal ions, acting as anti-amoebic agents.[3] The hexahydropyrimidine nucleus is present in some natural compounds such as tetraponerines,[4] verbamethine and verbametrine.[5]

In connection with previous research of our group on the characterization of nitrogen-containing heterocycles by mass spectrometry,[6–9] we have focused our attention on mass spectral analysis of six membered cyclic aminals (hexahydropyrimidines **1**, Table 1). In spite of their considerable practical interest, there are only scattered reports concerning the mass spectrometric analysis of hexahydropyrimidines. In 1967, Evans reported the mass spectra of unsubstituted hexahydropyrimidine and its 2-methyl and 2,2-dimethyl derivatives.[10] Braekman *et al.* discussed the fragmentation of some tricyclic hexahydropyrimidines (tetraponerines) isolated from natural sources.[4] To our knowledge, however, no systematic study on hexahydropyrimidines is available in the literature. In the present work, the fragmentation patterns of a series of *N*-

arylhexahydropyrimidines **1** (Table 1) are discussed. The behavior of these heterocycles under electron impact depends on the nature of both *N*- substituents and on the presence or absence of a 2- substituent. The results are correlated with data reported for the corresponding five membered homologues (imidazolidines).[9] New fragmentation pathways are proposed to account for some important peaks in the spectra of the compounds under study.

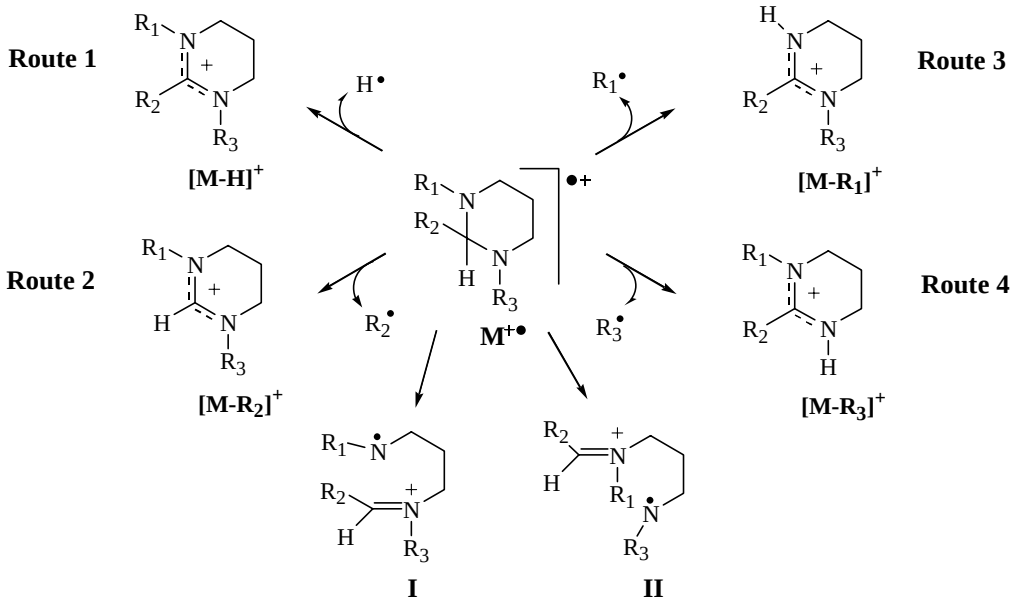
Table 1. *N*- Arylhexahydropyrimidines, **1a-j**



Compound **1**	R_1	R_2	R_3
a	*p*-ClC_6H_4	H	*p*-ClC_6H_4
b	C_6H_5	H	C_6H_5
c	*p*-ClC_6H_4	H	CH_3CH_2
d	*p*-ClC_6H_4	H	$CH_3CH_2CH_2$
e	*p*-ClC_6H_4	H	$(CH_3)_2CH$
f	*p*-ClC_6H_4	H	$(CH_3)_3C$
g	*p*-ClC_6H_4	H	$(CH_3)_3CCH_2$
h	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4
i	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	CH_3
j	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$	CH_3CH_2

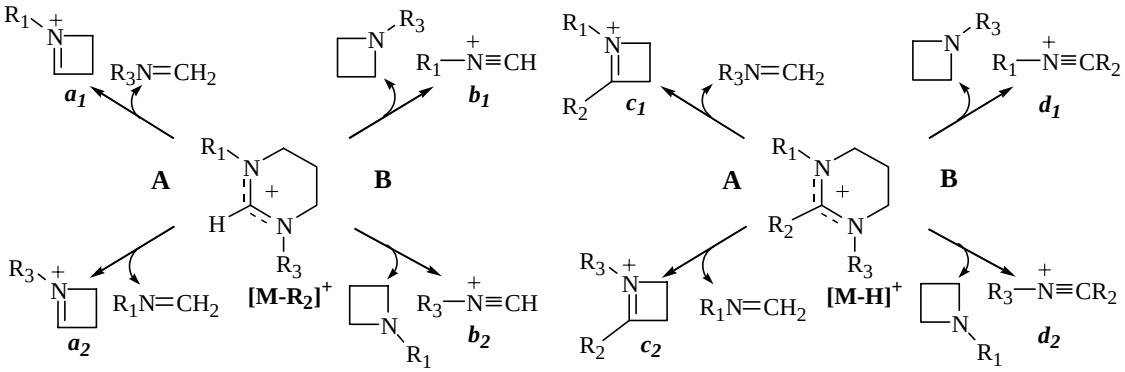
Results and Discussion

On the basis of previously reported work on the mass spectrometry of *N*-arylimidazolidines,[9] the primary fragmentation pathways expected for hexahydropyrimidines **1** are depicted in Scheme 1 and include: (a) loss of either H or R_2 by homolytic C2–R_2 or C2–H fission of the molecular ion, generating tetrahydropyrimidinium ions $[M\text{-}H]^+$ and $[M\text{-}R_2]^+$ (Routes 1 and 2, respectively); (b) loss of R_1 or R_3 by homolytic C-N fission of the molecular ion with hydrogen migration, leading to stabilized tetrahydropyrimidinium ions $[M\text{-}R_1]^+$ and $[M\text{-}R_3]^+$ (Routes 3 and 4 respectively); (c) initial ring cleavage of $M^{+\cdot}$ through homolytic C2–N1 or C2–N3 fission leading to ions **I** and **II**.

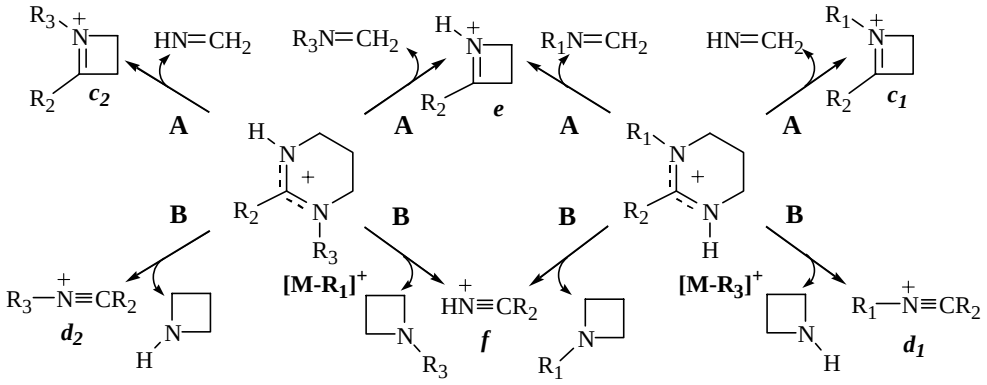


Scheme 1

Fragments arising from subsequent cleavage of ions $[M-R_2]^+$, $[M-H]^+$, $[M-R_1]^+$and $[M-R_3]^+$ through Routes A and B with loss of an imine or an azetidine moiety, respectively, (Schemes 2 and 3) may also be expected.



Scheme 2



Scheme 3

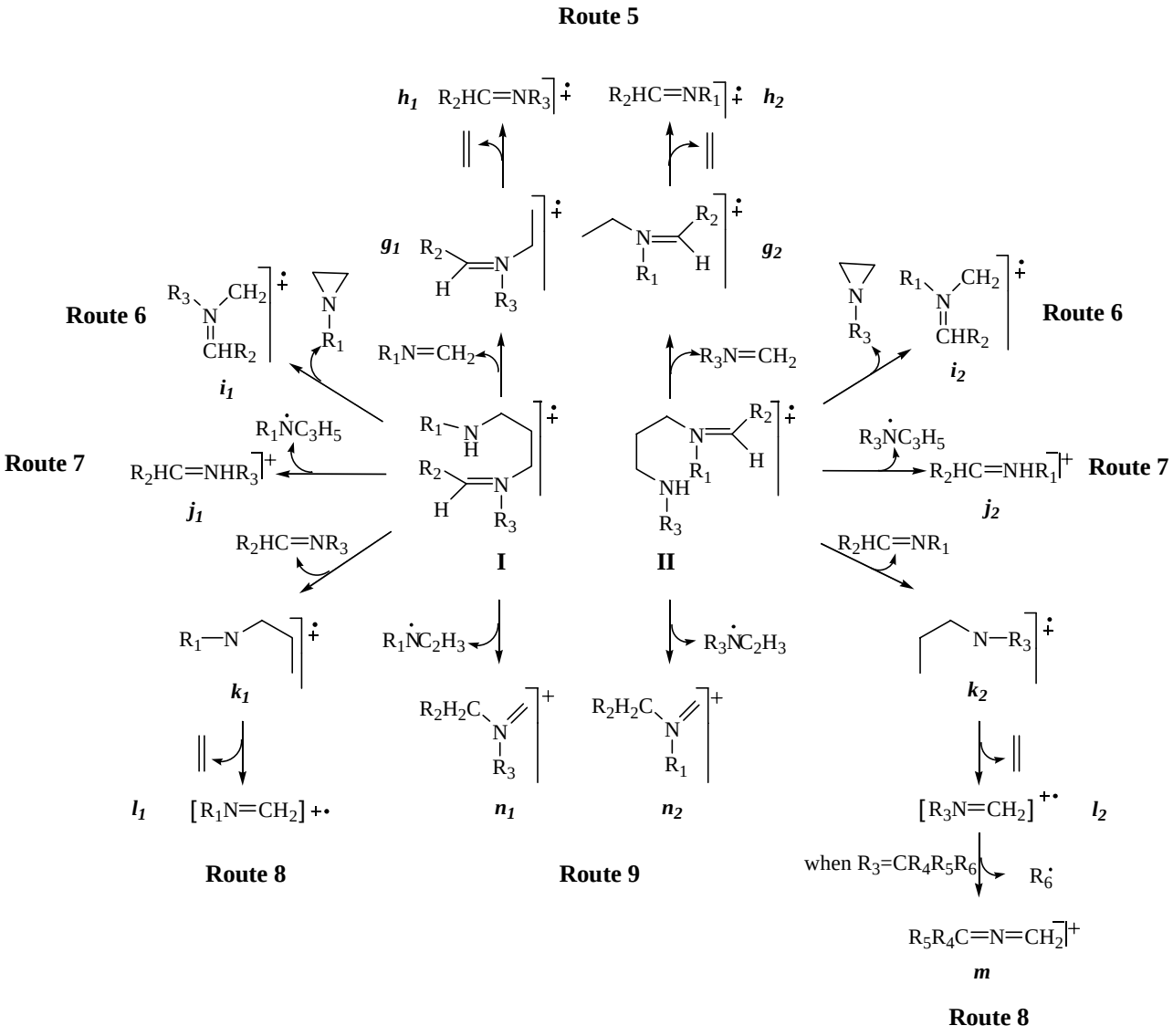
The fragmentations depicted in Schemes 1–3, however, do not account for some significant peaks observed in the spectra of hexahydropyrimidines **1**. For the compounds under study, we propose additional fragmentation pathways of ions **I** and **II (Scheme 1)**. Such mechanisms are depicted in Scheme 4 and involve: (a) homolytic α cleavage with loss of an imine, followed by elimination of ethylene, to produce ions *g,h* respectively (Route 5); (b) homolytic β- fission leading to ions *i* (Route 6); (c) heterolytic cleavage with hydrogen migration producing protonated imines *j* (Route 7); (d) heterolytic cleavage followed by loss of ethylene, leading to fragments *k* and *l*, respectively (Route 8). When R_3=alkyl, subsequent homolytic α-cleavage of ions l_2 may produce ions *m*; (e) heterolytic C4–C5 fission with hydrogen migration leading to ions *n* (Route 9). Additionally, R_1^+ and R_3^+ fragments which may arise from heterolytic C-N cleavage of different ions bearing positively charged nitrogen are also observed in some cases.

For a better understanding of their fragmentation, the compounds under study were divided into four groups according to their substitution patterns.

1,3-Diarylhexahydropyrimidines 1a,b (Table 2)

The molecular ions $M^{+\cdot}$ are intense, as are the $[M-1]^+$ fragments, the base peak for both compounds. Loss of $H^{\cdot}$ from $M^{+\cdot}$ could, in principle, take place from C2–H or from the trimethylene chain. However, the higher stabilization of the resulting tetrahydropyrimidinium ions resulting from C2–H homolytic fission and the absence of the $[M-H]^+$ fragment in 2,2-dimethylhexahydropyrimidine support the proposed fragmentation.[10]

For derivatives **1a,b**, ions *a=c* and *b=d*, which can alternatively originate from $[M-1]^+$, $[M-R_1]^+$ and/or $[M-R_3]^+$ (Schemes 2 and 3) are important for 1,3-diarylhexahydropyrimidines. However, ions $[M-R_1]^+$ and $[M-R_3]^+$ as well as peaks *e* and *f* resulting exclusively from their secondary fragmentation are not observed. This suggests that the most probable fragmentation pathway leading to fragments *a,b* involves $[M-1]^+$ ions.



Scheme 4

Fragmentation of ions **I** and **II** takes place mainly by heterolytic N–C cleavage followed by loss of ethylene (Scheme 4, Route 8) leading to ions *l*, and by heterolytic N–C and C4–C5 fission with hydrogen migration, producing ions *j* and *n* respectively (Scheme 4, Routes 7 and 9). Instead, peaks corresponding to homolytic α- or β- cleavage appear with low relative abundance in these derivatives.

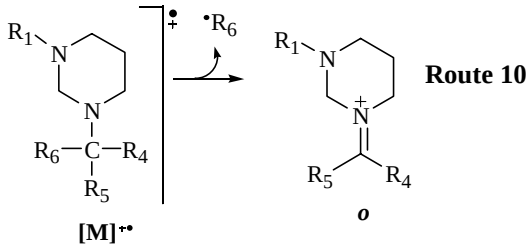
Table 2. Most abundant fragments in mass spectra of 1,3-diarylhexahydropyrimidines [*m/z* (% relative abundance)]

Compound	**1a**	**1b**
M+•	306 (45.9)	238 (48.9)
$[M-1]^+$	305 (100)	237 (100)
$[M-R_1]^+$ $[M-R_3]^+$	195 (2.0)	161 (2.4)
a_1=c_1 a_2=c_2	166 (20.3)	132 (23.9)
B_1=d_1 B_2=d_2	138 (12.1)	104 (23.8)
j_1 j_2	140 (12.3)	106 (15.5)
k_1 k_2	167 (4.9)	133 (5.3)
l_1 l_2	105 (31.7)	139 (20.4)
n_1 n_2	154 (28.9)	120 (25.1)

1-Aryl-3-alkylhexahydropyrimidines, 1c–g (Table 3)

The fragmentation patterns of hexahydropyrimidines **1c–g** show remarkable differences depending on the type of alkyl substituent R_3. As in 1,3-diaryl derivatives, the molecular ion is generally intense. The primary fragmentation of $M^{+\cdot}$ takes place mainly by loss of $H^{\cdot}$ leading to $[M-1]^+$ ions, the base peaks for derivatives **1c–f**. Peaks resulting from loss of substituents on either N-1 or N-3 (Scheme 1, Routes 3 and 4) are of low relative intensity in all cases, with the exception of compound **1f** where expulsion of a stable *tert*- butyl radical following Route 4 is favored. Although ions $[M-R_1]^+$ and $[M-R_3]^+$ are generally not relevant, peaks *e* corresponding to their secondary fragmentation are important in derivatives **1e–g**, bearing branched *N*-alkyl substituents. This suggests that the most probable fragmentation pathway leading to *e* fragments involves $[M-R_3]^+$ ions.

The peak of *m/z* 209 in compound **1g** cannot be explained by any of the primary fragmentation pathways already proposed. Such a fragment would arise from homolytic α-cleavage of the molecular ion, with expulsion of an alkyl radical $R^{\cdot}$ leading to ions *o* (Scheme 5, Route 10). Loss of methyl radical following Route 10 in compounds **1e,f** leads to the corresponding *o*=$[M-15]^+$ ions.



Scheme 5

For derivatives **1c–g**, ions *a*=*c* could, in principle, originate from $[M\text{-}H]^+$, $[M\text{-}R_1]^+$ and/or $[M\text{-}R_3]^+$ (Schemes 2 and 3). In this series, fragments a_2 appear with higher relative abundances than ions a_1, with the exception of compound **1g**, where a_1 is the base peak.

Fragmentation of ions I and II by elimination of an imine and ethylene (Scheme 4, Route 8) leads to ions *k* and *l*, of variable importance in this series. In compounds **1c, d, g,** homolytic α– cleavage of ions l_2 (when $R_3=CR_4R_5R_6$) with loss of an alkyl radical R_6 produces fragments *m* (*m/z* = 42, $R_4=R_5=H$), of increasing relative abundances in this series in which R_6 = methyl, ethyl, or *tert*- butyl. In compounds **1e, f**, α–cleavage of ions l_2 with loss of methyl radical yields the corresponding *m* ($R_4=R_5=CH_3$) fragments. As in 1,3-diarylhexahydropyrimidines, fragmentation following Route 9 is important. It can be observed that the fragments n_1 have higher relative abundance for the lower homologues **1c–e**, while n_2 ions follow the opposite trend. The R_3^+ ions are only important for the hexahydropyrimidine **1f** (R_3=*tert*-C_4H_9) as a consequence of the stability of the resulting positively charged fragment.

1,2,3-Triarylhexahydropyrimidine, 1h (Table 4)

For this compound the molecular ion is less important than in the corresponding 2- unsubstituted derivative **1a**. $[M\text{-}R_1]^+=[M\text{-}R_3]^+$ fragments have low relative intensities, while an $[M\text{-}H]^+$ ion is absent. Instead, as in other trisubstituted cyclic aminals,[9] the fragment corresponding to loss of R_2 (Scheme 1, Route 2) is the base peak. Peaks *b* and *d* corresponding to secondary fragmentation of such ion are also important.

Fragmentation of ions **I** = **II** takes place mainly by Route 5 (Scheme 4), absent in the corresponding 2- unsubstituted hexahydropyrimidine **1a.** It involves homolytic α–cleavage followed by elimination of ethylene, leading to fragments *h*. Fragments attributable to Routes 6–9 (Scheme 4) are not important. The routes already discussed, however, cannot account for fragment of *m/z* 140, for which we propose the structure $[R_1NH=CH_2]^+$. Such an ion is present in all trisubstituted derivatives in which R_1=4-chlorophenyl (**1h–j**). It is analogous to ion $\mathbf{j_2}$ (Scheme 4), and may arise from an intermediate which has previously lost R_2.

Table 3. Most abundant fragments in mass spectra of 1-aryl-3-alkylhexahydropyrimidines [*m/z* (% relative abundance)].

Compd.	1c	1d	1e	1f	1g
M+•	224 (46.3)	238 (33.9)	238 (60.0)	252 (56.0)	266 (11.7)
$[M-1]^+$	223 (100)	237 (100)	237 (100)	251 (100)	265 (7.2)
$[M-R_1]^+$	113 (4.2)	127 (4.4)	127 (5.9)	141 (8.8)	155 (2.4)
$[M-R_3]^+$	195 (-)	195 (-)	195 (9.1)	195 (35.1)	195 (3.9)
a_1=c_1	166 (4.6)	166 (17.9)	166 (8.0)	166 (9.9)	166 (100)
a_2=c_2	84 (39.2)	98 (27.7)	98 (35.3)	112 (10.8)	124 (2.7)
b_1=d_1	138 (5.3)	138 (13.2)	138 (4.8)	138 (16.8)	138 (9.5)
b_2=d_2	56 (5.6)	70 (20.2)	70 (7.2)	84 (19.2)	98 (4.4)
e	56 (5.6)	56 (6.4)	56 (20.7)	56 (19.8)	56 (12.1)
I_1	71 (22.8)	85 (10.7)	85 (19.8)	99 (3.6)	113 (3.2)
J_1	58 (8.3)	72 (7.2)	72 (7.3)	86 (13.7)	100 (0.8)
J_2	140 (6.4)	140 (9.9)	140 (7.6)	140 (31.7)	140 (7.5)
K_1	167 (2.5)	167 (4.4)	167 (4.2)	167 (5.9)	167 (11.6)
K_2	85 (7.2)	99 (4.4)	99 (4.6)	113 (7.1)	127 (1.5)
L_1	139 (7.9)	139 (11.3)	139 (8.3)	139 (19.2)	139 (5.1)
L_2	57 (19.8)	71 (5.5)	71 (11.3)	85 (4.8)	99 (0.8)
M	42 (7.3) [a]	42 (19.5) [a]	56 (20.7) [b]	70 (29.7) [c]	42 (84.2) [a]
	56 (5.6) [b]		70 (7.2) [c]		
N_1	72 (23.1)	86 (12.5)	86 (18.7)	100 (5.6)	114 (0.7)
N_2	154 (3.0)	154 (-)	154 (10.9)	154 (35.6)	154 (23.1)
O	209 (5.6) d]	209 (5.1) [d]	223 (3.6) [e]	237 (12.1) [f]	209 (23.9) [d]
Other ions		R_3^+: 43 (10.9)		R_3^+: 57 (48.5)	R_3^+: 71 (5.9)
				R_1^+: 111 (25.9)	R_1^+: 111 (8.6)

[a] R_4=R_5=H; [b] R_4=CH_3, R_5=H; [c] R_4=R_5=CH_3; [d] R_4=R_5=H; [e] R_4=CH_3, R_5=H; [f] R_4=R_5=CH_3

1,2-Diaryl-3-alkylhexahydropyrimidines, 1i, j (Table 5)

As in the previous series, $[M-R_2]^+$ ions appear with high relative abundances, being the base peak for the 3-ethyl derivative **1j**, while $[M-H]^+$, $[M-R_1]^+$ and $[M-R_3]^+$ fragments (Scheme 1) are not important. Secondary fragmentation of $[M-R_2]^+$ ions occurs mainly following Route B (Scheme 2), leading to fragments b_2. Ions *e*, *f*, arising probably from $[M-R_1]^+$, are also important for these derivatives.

Table 4. Most abundant fragments in mass spectra of 1,2,3-triarylhexahydropyrimidines [*m/z* (% relative abundance)]

Compound	**1h**
M+•	**427 (23.1)**
$[M-1]^+$	**426 (-)**
$[M-R_1]^+ = [M-R_3]^+$	**316 (7.2)**
$[M-R_2]^+$	**305 (100)**
A	**166 (2.9)**
B	**138 (15.2)**
C	**287 (5.4)**
D	**259 (11.3)**
G	**288 (5.6)**
H	**260 (22.5)**
I	**274 (3.5)**
J	**261 (5.7)**
K	**167 (4.4)**
L	**139 (9.8)**
N	**275 (6.8)**
Other ions	**$[R_1NHCH_2]^+$: 140 (19.7)**

Fragmentation of ions **I**, **II** takes place mainly by homolytic β–fission leading to ions i_1 and by heterolytic C4–C5 fission with hydrogen migration leading to ions n_1 (Scheme 4, Routes 6 and 9, respectively). Ions R_1^+, $[R_1NHCH_2]^+$ and $[R_3NHCH_2]^+$ are also important for these derivatives.

Compounds **1a–j** were described in the literature.[11,12] They were synthesized by condensation of *N,N'*- disubstituted 1,3-propanediamines with aldehydes and were characterized by ^{1}H- NMR and by their elemental analysis. Mass spectra were recorded in a MS Shimadzu QP-1000 spectrometer operating at 20 eV with direct sample introduction. The ion source temperature was 280ºC. The mass range studied was *m/z* 40–700.

Table 5. Most abundant fragments in mass spectra of 1,2-diaryl-3-alkylhexahydropyrimidines [*m/z* (% relative abundance)]

Compound	1i	1j
M+•	331 (10.7)	345 (19.1)
$[M-1]^+$	330 (4.9)	244 (3.5)
$[M-R_1]^+$	220 (4.5)	234 (3.1)
$[M-R_2]^+$	209 (61.8)	223 (100)
$[M-R_3]^+$	316 (-)	316 (0.6)
A_1	166 (3.7)	166 (5.4)
A_2	70 (19.3)	84 (7.3)
B_1	138 (11.3)	138 (23.4)
B_2	42 (100)	56 (95.8)
C_2	191 (13.0)	205 (16.1)
D_1	259 (3.1)	259 (1.7)
D_2	163 (33.2)	177 (14.1)
E	177 (22.2)	177 (14.1)
F	149 (48.7)	149 (13.5)
G_1	192 (5.9)	206 (6.6)
H_1	164 (8.1)	178 (4.7)
H_2	260 (6.9)	260 (2.7)
I_1	178 (14.0)	192 (16.5)
K_1	167 (11.6)	167 (4.6)
K_2	71 (37.3)	85 (4.5)
L_1	139 (6.8)	139 (12.3)
L_2	43 (64.6)	57 (8.8)
M	42 (100) [a] [c]	42 (25.7) [a]
		56 (95.8) [b] [c]
N_1	179 (10.0)	193 (10.9)
Other ions	$[R_1NHCH_2]^+$: 140 (16.1)	$[R_1NHCH_2]^+$: 140 (32.1)
	$[R_3NHCH_2]^+$: 44 (55.6)	$[R_3NHCH_2]^+$: 58 (38.0)
	R_1^+: 111 (17.2)	R_1^+: 111 (26.0)

[a] R_4=R_5=H; [b] R_4=CH_3, R_5=H; [c] isobaric with b_2

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