ELECTRON IMPACT MASS SPECTRA OF *para*-SUBSTITUTED *N*-HETEROARYL BENZYLAMINES°

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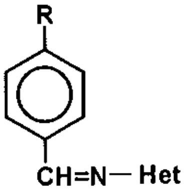
Abstract - The 70 eV electron impact mass spectra of some *para*-substituted *N*-heteroaryl benzylamines, synthesized through the corresponding Schiff bases, are reported. Typical fragmentation patterns are discussed with the aid of mass analyzed ion kinetic energy spectra and exact mass measurements. The compounds are relatively stable under electron impact, the molecular ion being the base peak or the second most intense ion in the spectra. The dominating breakdown process is the benzylic cleavage, that gives rise to the base peak in some of the investigated compounds and to the second intense peak in others.

Azoles are present in natural and synthetic antimicrobial agents of therapeutical value. [1] We have previously reported the synthesis of azole derivatives, a large number of which showed good antifungal activity. [2-7] As a part of a wider program on the synthesis of new antimicrobial agents and in connection with QSAR studies [8,9] of potential antibacterial compounds, we report here the synthesis and mass spectral behaviour of *para*-substituted *N*-heteroaryl benzylamines (**2**).

°Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.



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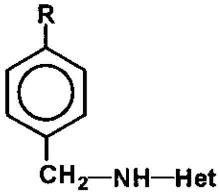


2

	R	Het
a	CH_3	2-Thiazolyl
b	Ph	2-Thiazolyl
c	NO_2	2-Pyrimidyl
d	H	2-Benzothiazolyl
e	NO_2	2-Benzothiazolyl
f	H	3-Quinolyl
g	CH_3	3-Quinolyl
h	Ph	3-Quinolyl

RESULTS AND DISCUSSION

The synthesis of amines (**2**) was carried out as previously described[2] by reduction of Schiff bases (**1**).

The physical, analytical and spectral data for Schiff bases (**1**) and amines (**2**) are reported in Tables 1 and 2. The 70 eV electron ionization mass spectra for **2** are collected in Tables 3 and 4. Common fragment ions are reported in Table 3 and depicted in Scheme 1. Fragmentations in Scheme 1 and in the following Scheme 2, were supported by collision induced dissociation-mass analyzed ion kinetic energy (CID-MIKE) spectra. When necessary, composition of the fragment ions was established by exact mass measurements. The CID-MIKE spectrum of the molecular ion of **2d** exhibiting the typical behaviour of all the examined compounds is reported in Figure 1.

All compounds were relatively stable under electron impact conditions. In fact the molecular ion is the base peak in compounds (**2c**), (**2d**), (**2e**), and (**2f**) and the second most intense peak in others. The main fragmentations in the spectra of amines (**2**) are originated by direct cleavage of the molecular ion, as shown in Scheme 1.

Table 1. Physical, analytical and spectral data for Schiff bases (**1**).

Compd. No	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd/Found C	H	N
1a[a]	125-126	47	$C_{11}H_{10}N_2S$	65.3	4.9	13.9
				65.1	4.9	13.9
1b	96-99	63	$C_{16}H_{12}N_2S$	72.7	4.5	10.6
				72.4	4.6	10.7
1c	83-86	40	$C_{11}H_8N_4O_2$	57.9	3.5	24.6
				57.8	3.6	24.6
1d	107-110	59	$C_{14}H_{10}N_2S$	70.6	4.2	11.8
				70.4	4.2	11.9
1e	244-247	52	$C_{14}H_9N_3O_2S$	59.4	3.2	14.8
				59.1	3.2	14.8
1f[b]	74-77	60	$C_{16}H_{12}N_2$	82.8	5.2	12.1
				82.6	5.3	12.2
1g	108-110	65	$C_{17}H_{14}N_2$	82.9	5.7	11.4
				82.6	5.8	11.4
1h	160-163	67	$C_{22}H_{16}N_2$	85.7	5.2	9.1
				85.5	5.3	9.2

[a] From ref. 10, mp 124 °C.

[b] From ref. 12, mp 74 °C.

The fragmentation route originating most aboundant peaks is the benzylic cleavage. In this fragmentation, due to the formation of a stable tropylium ion, the charge remains preferentially localized on the aromatic moiety of the molecule (ion a Scheme 1). This ion represents the base peak for compounds (**2a**), (**2b**), (**2g**), and (**2h**) and is very intense for compounds (**2d**) and (**2f**). A noteworthy exception to this trend is observed for compounds (**2c**) and (**2e**), in which the formation of the tropylium ion is less favoured due the presence of a nitro group on the aromatic ring.

Cleavage of the NH-Het bond may originate two complementary fragments c and d. However, in the quinoline derivatives (**2f**), (**2g**), and (**2h**) the positive charge remains preferentially localized on the heterocyclic ring system and thus only ion d is detectable. On the contrary, in **2a** , **2c** , **2d** , and **2e** ion c is of sizeable intensity, whereas ion d is very low or even absent. In compound (**2b**), due to the most favourable occurence of the competitive CH_2-NH cleavage, both ions c and d are absent.

Table 2. Physical, analytical and spectral data for amines (**2**).

Compd. No	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd/Found C	H	N	^{1}H-Nmr ppm ($CDCl_3$)
2a[a]	151-152	52	$C_{11}H_{12}N_2S$	64.7	5.9	13.7	6.2-7.6 (m,7H), 4.5 (s,2H), 2.3 (s,3H)
				64.6	5.7	13.9	
2b	157-159	63	$C_{16}H_{14}N_2S$	72.2	5.3	10.5	7.1-7.6(m,11H),6.5 (d,J = 3Hz,1H), 4.53 (s,2H)
				71.9	5.3	10.6	
2c[b]	160-161	55	$C_{11}H_{10}N_4O_2$	57.4	4.3	24.3	7.3-8.4 (m,7H), 6.6 (t,J=3Hz,1H), 4.8 (d,J=3Hz,2H)
				57.3	4.7	24.5	
2d[c]	160-161	57	$C_{14}H_{12}N_2S$	70.0	5.0	11.7	6.8-7.6 (m,10H), 4.5 (s,2H)
				69.9	5.1	11.7	
2e	177-178	57	$C_{14}H_{11}N_3O_2S$	58.9	3.8	14.7	7-8.3 (m,9H), 4.7 (s,2H)
				58.9	3.8	14.7	
2f[d]	96-98	53	$C_{16}H_{14}N_2$	82.0	6.0	12.0	6.6-8.1(m,10H),8.6 (d,J=1.5Hz,1H), 5.9(s, broad,1H),4.4(d,J=6Hz, 2H)
				81.9	6.1	12.1	
2g	131-133	48	$C_{17}H_{16}N_2$	82.2	6.4	11.3	6.9-8.1(m, 9H), 8.5(d,J=3Hz,1H), 4.36 (s,3H), 2.33 (s,3H)
				82.0	6.6	11.4	
2h	193-194	49	$C_{22}H_{18}N_2$	85.2	5.8	9.0	7.1-8.1(m,14H),8.6 (d,J=1.5Hz,1H), 7.0 (d,J=1.5Hz,1H), 4.4 (s,2H)
				85.1	5.9	9.0	

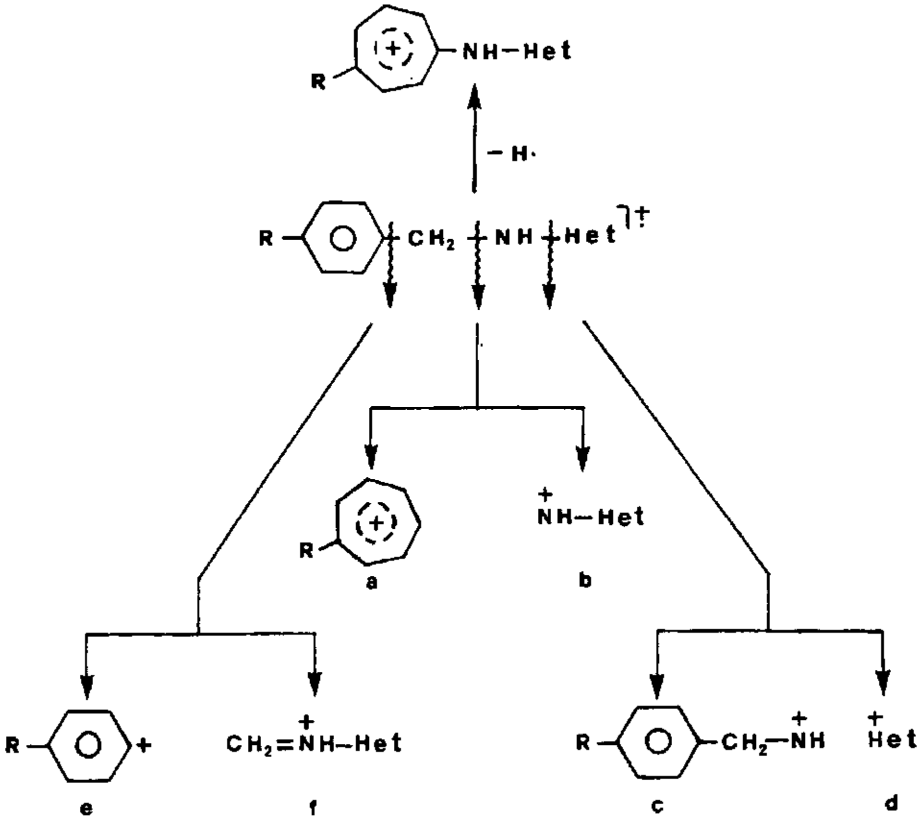
[a] From ref. 10, mp 120 °C.

[b] From ref. 11, mp 154 °C.

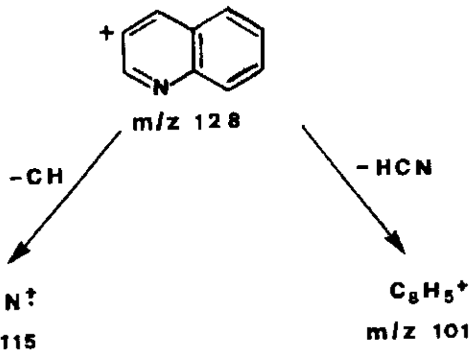
[c] From ref. 13. No mp available.

[d] From ref. 12, mp 98 °C.

A third possible fragmentation pathway of the molecular ion is the cleavage of the Ar-CH_2 bond. The two complementary fragments e and f which arise from this fission are of very low intensity in all cases. Elimination



Scheme 1



Scheme 2

of the benzylic hydrogen produces fragment ions detectable in all compounds with exception of (**2b**), and are particularly intense for (**2c**), (**2d**), (**2e**), and (**2f**) in which the competitive benzylic cleavage is not favoured. Other fragment ions present in the spectra are related to the specific substituent on the aromatic ring or to the heterocyclic ring system.

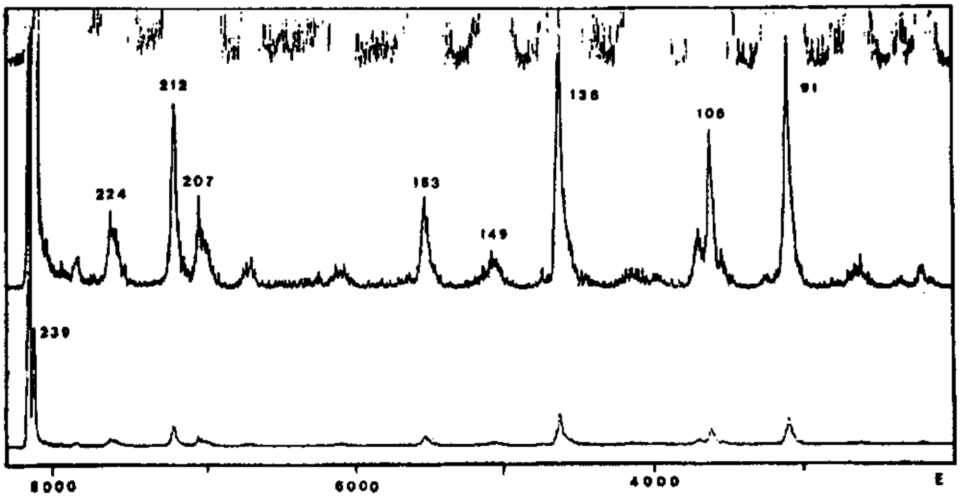


Figure 1. CID-MIKE spectrum of the molecular ion in compound (**2d**).

Table 3. Fragment ions originated by common fragmentation reactions in the mass spectra of amines (**2**). Fragment ions of relative aboundance greater than 1% are reported; relative aboundances are in parentheses.

Compd. No	$M^{+\cdot}$	$[M-H]^+$	a	b	c	d	e	f
2a	204(60)	203(2)	105(100)	99(-)	120(4)	84(-)	91(2)	113(-)
2b	266(18)	265(-)	167(100)	99(-)	182(-)	84(-)	153(1)	113(-)
2c	230(100)	229(16)	136(-)	94(1)	151(49)	79(5)	122(-)	108(12)
2d	240(100)	239(26)	91(57)	149(3)	106(17)	134(1)	77(1)	163(5)
2e	285(100)	284(11)	136(10)	149(17)	151(23)	134(2)	122(3)	163(4)
2f	234(100)	233(8)	91(82)	143(2)	106(-)	128(5)	77(1)	157(5)
2g	248(66)	247(3)	105(100)	143(1)	120(-)	128(4)	91(1)	157(1)
2h	310(44)	309(6)	167(100)	143(-)	182(-)	128(5)	153(2)	157(-)

Table 4. Additional peaks in the mass spectra of amines (**2**). Fragment ions of relative aboundances greater than 1% are reported; relative aboundances are in parentheses.

2a	206 (3), 205 (7), 201 (2), 189 (3), 118 (2), 106 (10), 104 (3), 103 (5), 101 (3), 100 (3), 79 (5), 78 (2), 77 (7), 65 (1), 58 (2), 55 (1), 51 (1), 39 (1)
2b	268 (1), 267 (4), 168 (13), 166 (4), 165 (14), 152 (8), 151 (1), 139 (1), 133 (1), 128 (1), 115 (1)
2c	232 (1), 231 (13), 214 (3), 213 (4), 200 (1), 199 (1), 185 (1), 184 (12), 183 (26), 182 (7), 170 (2), 157 (2), 156 (2), 155 (2), 152 (4), 131 (1), 130 (1), 121 (1), 107 (1), 106 (3), 105 (6), 104 (2), 103 (1), 90 (3), 89 (7), 81 (3), 80 (17), 78 (3), 78 (4), 77 (2), 76 (1), 64 (1), 63 (4), 53 (5), 52 (2), 51 (2)
2d	242 (5), 241 (16), 224 (3), 223 (1), 213 (1), 212 (6), 211 (1), 210 (1), 207 (3), 197 (2), 137 (1), 136 (10), 135 (4), 122 (1), 120 (1), 119 (1), 109 (2), 108 (2), 107 (2), 105 (2), 103 (1), 92 (4), 90 (1), 89 (1), 78 (1), 69 (1), 65 (6), 63 (1), 57 (1), 45 (3), 39 (1)
2e	286 (18), 283 (2), 282 (2), 269 (2), 268 (1), 257 (3), 256 (2), 255 (8), 254 (1), 253 (3), 252 (2), 240 (2), 239 (5), 238 (5), 237 (3), 236 (1), 212 (1), 211 (1), 210 (1), 206 (4), 152 (3), 150 (5), 148 (1), 137 (2), 136 (10), 135 (13), 134 (1), 124 (1), 123 (2), 121 (1), 120 (1), 119 (5), 118 (1), 109 (2), 108 (5), 107 (3), 106 (32), 105 (7), 104 (1), 103 (1), 94 (1), 93 (1), 91 (2), 90 (6), 89 (5), 85 (2), 83 (3), 79 (2), 78 (5), 77 (3), 69 (2), 65 (2), 64 (2), 63 (5), 57 (1), 55 (1)
2f	236 (1), 235 (16), 232 (1), 231 (2), 142 (1), 129 (1), 117 (1), 116 (6), 115 (1), 102 (1), 101 (3), 92 (5), 90 (1), 89 (4), 77 (1), 65 (4), 63 (2), 51 (1)
2g	250 (1), 249 (13), 245 (1), 233 (1), 165 (1), 144 (3), 116 (3), 115 (1), 106 (8), 104 (2), 103 (3), 102 (2), 101 (2), 89 (2), 79 (4), 78 (1), 77 (4)
2h	312 (2), 311 (11), 308 (18), 307 (7), 168 (15), 166 (3), 165 (11), 155 (2), 154 (1), 153 (2), 152 (7), 129 (1), 128 (5), 116 (2), 115 (2), 101 (2), 89 (1), 77 (1)

Thus, para-methyl derivatives (**2a**) and (**2g**) show elimination of CH_3 from the molecular ion. The usual elimination of $CH\equiv CH$ from the fragment ions a and e originates fragments at m/z 79 and 65, respectively.

In benzylamines (**2d**) and (**2f**) the same fragmentation of the ions a and e gives rise to the fragment ions at m/z 65 and 51. The fragment ion a in compounds (**2a**) and (**2g**) gives also loss of 2H and $CH_2{=}CH_2$. Nitro compounds (**2c**) and (**2e**) exhibit the typical losses of O, NO, and NO_2 from the molecular ion and from the fragment ion $[M-H]^+$. Losses of NO and NO_2 are also observed from fragments a and c in the *para*-phenyl derivatives.

In **2h** loss of 2H from the biphenyl group occurs in the molecular ion and in the fragments $[M-H]^+$ and a, while in **2b** the above fragmentation is detectable only from fragment a, whereas it is not observed from ions $M^{+\cdot}$ and $[M-H]^+$ due to the low intensity of the precursor ions. Fragment a in compounds (**2b**) and (**2h**) gives elimination of H, 2H, and CH_3.

In compound (**2c**), in addition to the simple fission of the NH-Het bond with formation of the ion at m/z 79, an analogous cleavage with hydrogen transfer originates the m/z 80 ion, corresponding to pyrimidine, as indicated by exact mass measurements ($C_4H_4N_2$ calcd. 80.0374, meas. 80.0372).

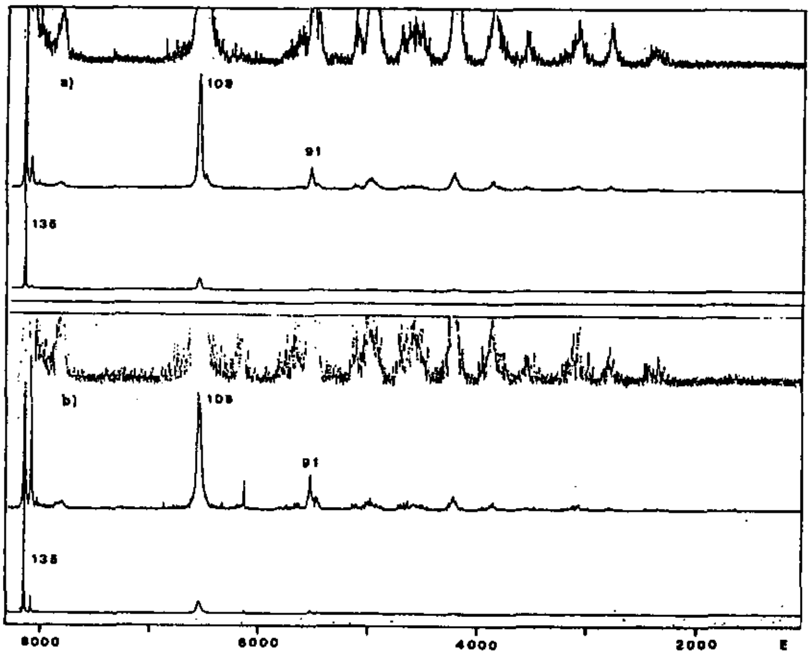


Figure 2. Comparison of CID-MIKE spectra of : a) molecular ion of benzothiazole; b) fragment ion at m/z 135 in compound (**2d**).

CID-MIKE spectra indicate that in both *N*-benzothiazole derivatives (**2d**) and (**2e**), the molecular ion undergoes loss of 16, 28, and 33 daltons as shown in Figure 1 for **2d** . Exact mass measurements show that the neutral fragments lost are NH_2 [(**2d**): $C_{14}H_{10}NS$ calcd. 224.0534, meas. 224.0547; (**2e**): $C_{14}H_9N_2O_2S$ calcd. 269.0415, meas. 269.0398], CH_2N [(**2d**): $C_{13}H_{10}NS$ calcd. 212.0534, meas. 212.0537; (**2e**): $C_{13}H_9N_2O_2S$ calcd. 257.0385, meas. 257.0393], and SH [(**2d**): $C_{14}H_{11}N_2$ calcd. 207.0922, meas. 207.0929; (**2e**): $C_{14}H_{10}N_3O_2$ calcd. 252.0773, meas. 252.0780], respectively. Furthermore the simple cleavage of NH-Het bond is accompanied by an analogous cleavage with transfer of one or two hydrogen atoms to give fragment ions at m/z 135 and 136, with elemental compositons C_7H_5NS [(**2d**): calcd. 135.0143, meas. 135.0150; (**2e**): calcd. 135.0143, meas. 135.0153] and C_7H_6NS [(**2d**) calcd. 136.0221, meas. 136.0221; (**2e**) calcd. 136.0221, meas. 136.0225], respectively.

Comparison of the CID-MIKE spectra of the molecular ion of benzothiazole with that of the m/z 135 ion in **2d** shows that the structure of these ions is identical (Figure 2). Analogous result is obtained for **2e** .

The m/z 136 ion further decomposes with elimination of SH and HCN.

In the quinoline substituted compounds (**2f**), (**2g**), and (**2h**), ion d fragments with loss of CH and HCN (Scheme 2), while ion b shows subsequent losses of two HCN molecules with formation of ions at m/z 116 and 89.

EXPERIMENTAL

Melting points are uncorrected. ir spectra (nujol mulls) were recorded on a Perkin-Helmer 297 spectrophotometer. ^{1}H-Nmr spectra were recorded at 90 MHz on a Varian EM-390 spectrometer (TMS as an internal standard) using $CDCl_3$ as solvent for all compounds except for (**2f**) (CD_3COCD_3). Chromatographic purification was carried out using Merck aluminum oxide as stationary phase and chloroform as eluent.

The low resolution mass spectra and metastable data were recorded by direct insertion into a VG-ZAB 2SE double focusing mass spectrometer operated under the following conditions: ionization energy 70 eV; source temperature 200 °C; trap current 100 μA; acceleration voltage 8 KV; sample temperature 30 °C; resolution 1500. For the high-resolution measurements the instrument was operated at 20000 resolving power, using perfluorokerosene (PFK) as the reference compound. The CID-MIKE analyses were performed introducing elium as the collision gas in the second-field-free collision cell at such a pressure that the intensity of the mass-selected beam was reduced by ≈ 75% of its original value.

General procedure for the synthesis of Schiff bases (**1**): 50 ml of dry benzene and two drops of glacial acetic acid were added to a solution of 0.007 mol of the appropriate benzaldehyde and 0.0066 mol of heteroarylamine in

100 ml of dry ethanol. The mixture was refluxed for 24 h. Water formed during the reaction was eliminated by a Dean-Stark apparatus. Evaporation of the solvent yielded a residue which was crystallized from dry ethanol.

General procedure for the synthesis of amines (**2**): A solution of $NaBH_4$ (0.34 g, 0.009 mol) in 20 ml of dry ethanol was added dropwise at 25 °C to a stirred solution of 0.003 mol of the appropriate Schiff base (**1**) in 20 ml of dry ethanol. The mixture was refluxed for 2 h and evaporated under reduced pressure. The residue was treated with water and chloroform; the organic layer separated, washed with water, dried on anhydrous sodium sulfate and evaporated. The residue was dissolved in chloroform and passed on a alumin oxide column. Evaporation of the eluates afforded a solid which was crystallized from ethanol. Elemental analysis, melting points and yields are reported in Table 2.

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