Synthesis of 2-substituted benzoxazoles and benzimidazoles based on mass spectral *ortho* interactions

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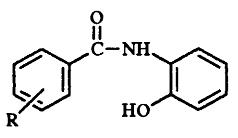
The *ortho* interactions of the hydroxy and amino groups with the amide function in *N*-(2-hydroxyphenyl)- and *N*-(2-aminophenyl)-benzamides on electron impact lead to the elimination of H_2O from the molecular ions resulting in the formation of 2-substituted benzoxazoles and benzimidazole radical cations, respectively. This mass spectrometric reaction has been successfully mimicked in the laboratory to synthesise these heterocyclic compounds in excellent yields by the thermolysis of the corresponding *N*-(2-hydroxyphenyl)- and *N*-(2-aminophenyl)-benzamides. The mechanisms and ion structures proposed in the mass spectral study are supported by high-resolution data, B/E and B^2/E linked-scan spectra, Collision-Activation-Decomposition (CAD)-B/E linked-scan spectra, chemical substitution and ^{2}H-labelling.

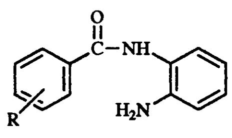
The modern mass spectrometer is visualised as a complete chemical laboratory[1] in the sense that the ion-source of the mass spectrometer can be utilised to perform unimolecular decomposition reactions of organic substrates in the gas phase. The structures of the product ions are identified by CAD-MIKES spectra. Thus, a few condensed phase reactions such as the Claisen rearrangement,[2] Beckmann rearrangement,[3] Smiles rearrangement,[4] *etc.*, have been observed in the gas phase under electron impact.

The electron impact and thermal behaviour of many carbonyl[5] and sulfonyl[6] compounds are shown to exhibit close parallelism. It has also been identified that the elimination of neutral species is favourable in *ortho* substituted anilides[7–9] under both electron impact and pyrolytic conditions. Pyrolysis of *ortho*-allylsalicylic amides is reported[10] to form isoindolones and phthalides in moderate yields. The observation[11] of $[M - RCO_2H]^{\bullet +}$ ions corresponding to 2-substituted benzimidazole radical cations in the mass spectral study of *N,N′*-diacylbenzene-1,2-diamines has been exploited for a useful synthetic transformation hitherto unknown.

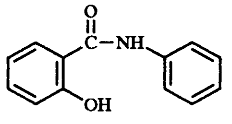
Even though the *ortho* interactions of an amide function with carboxyl[12] and keto[13] groups have been studied, its interaction with polar moieties like –OH and $-NH_2$ are not known. In order to study the *ortho* interaction of an amide function with –OH and $-NH_2$ groups and also to evaluate the correlation between electron impact and thermal behaviour, the mass spectral study of various *N*-(2-hydroxyphenyl)benzamides (**1–9**) and *N*-(2-aminophenyl)benzamides (**13–21**) under electron impact has been undertaken.



	R
1	H
2	*o*-CH_3
3	*p*-CH_3
4	*o*-Cl
5	*p*-Cl
6	*o*-NO_2
7	*p*-NO_2
8	*o*-OCH_3
9	*p*-OCH_3



	R
13	H
14	*o*-CH_3
15	*p*-CH_3
16	*o*-Cl
17	*p*-Cl
18	*o*-NO_2
19	*p*-NO_2
20	*o*-OCH_3
21	*p*-OCH_3



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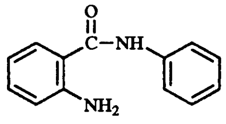

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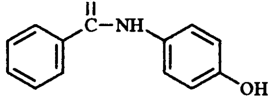

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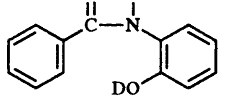

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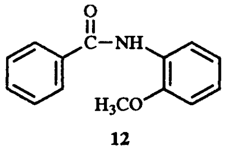

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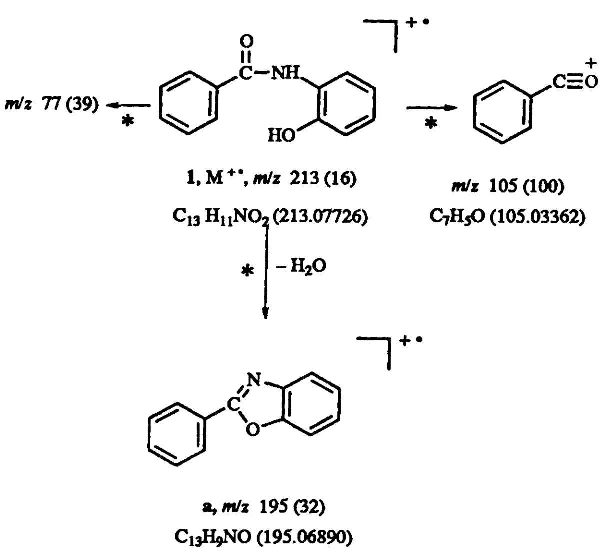
Results and discussion

The major fragmentation process observed in the molecular ion of *N*-(2-hydroxyphenyl)benzamide (**1**) is the expected simple α-cleavage with respect to the carbonyl group leading to the benzoyl cation at *m/z* 105 (Scheme 1). The most interesting fragment ion in its mass spectrum due to the *ortho* interaction is the ion **a** at *m/z* 195. The high-resolution study reveals its elemental composition to be $C_{13}H_9NO$ which corresponds to the elimination of H_2O from the molecular ion. The direct formation of the ion **a** from the $M^{\bullet +}$ ion of **1** is identified from the B/E linked-scan spectrum of the molecular ion (Table 1) and the B^2/E linked-scan spectrum of ion **a** (Table 2).

The 2-phenylbenzoxazole radical cation structure, assigned to ion **a** at *m/z* 195, is based on the comparison of the CAD-B/E linked-scan spectra of the $[M - H_2O]^{\bullet +}$ ion of **1** with that of the $M^{\bullet +}$ of 2-phenylbenzoxazole chosen as the reference compound (Fig. 1). The $[M - H_2O]^{\bullet +}$ ions corresponding to ion **a** are present in low abundances in all the substituted *N*-(2-hydroxyphenyl)benzamides studied (Table 3, **1–9**).

A similar cyclodehydration reaction is also noticed in the molecular ion of *N*-(2-aminophenyl)benzamide (**13**) yielding ion **b** at *m/z* 194 (Scheme 2). The elemental composition of ion **b**, as determined by high-resolution technique, is $C_{13}H_{10}N_2$. This agrees with the proposed expulsion of H_2O from the molecular ion of **13**.



Scheme 1

Table 1 B/E linked-scan spectral data of compounds **1** and **13**

Compd.	Parent ion, m/z	m/z Values of the daughter ions, relative abundance (%)
1	$M^{\cdot+}$, 213	195 (100), 105 (51), 77 (13)
	195	167 (100), 166 (42), 165 (18), 77 (10)
13	$M^{\cdot+}$, 212	195 (100), 194 (68), 105 (12), 77 (18)
	195	194 (100), 167 (12), 166 (4), 77 (10)
	194	193 (100), 167 (32), 166 (10), 77 (23)

Table 2 B^2/E linked-scan spectral data of compounds **1** and **13**

Compd.	Daughter ion, m/z	m/z Values of the parent ions, relative abundance (%)
1	195	213 (100)
	105	213 (100)
13	195	212 (100)
	194	212 (100), 195 (72)
	105	212 (100)

An interesting contrast in the formation of $[M - H_2O]^{\cdot+}$ ion in **13** when compared with that in **1** is the evidence of stepwise ejections of ˙OH and ˙H in the former in addition to its direct formation. The loss of ˙OH radical from the molecular ion of **13** leads to ion **c** at m/z 195 for which a protonated 2-phenylbenzimidazole structure has been proposed (Scheme 2). The elimination of hydrogen atom from ion **c** yields **b**. The fact that the CAD-B/E linked-scan spectra of the $[M - H_2O]^{\cdot+}$ ion from **13** and that of the molecular ion of 2-phenylbenzimidazole chosen as the reference compound are found to be identical, confirms the 2-phenylbenzimidazole radical cation structure envisaged for **b** (Fig. 1).

Another important difference noticed is that the elimination of H_2O from the molecular ions of *N*-(2-aminophenyl)-benzamides appears to be relatively more facile than in their hydroxy analogues (Table 3, **13**–**21**).

The mass spectral study of 2-hydroxy-*N*-phenylbenzamide (**10**), 2-amino-*N*-phenylbenzamide (**22**) and *N*-(4-hydroxyphenyl)benzamide (**11**) revealed the absence of loss of H_2O from the molecular ions of these compounds indicating the required regiochemistry for the formation of $[M - H_2O]^{\cdot+}$ ion as present in compounds **1** and **13** (Table 1).

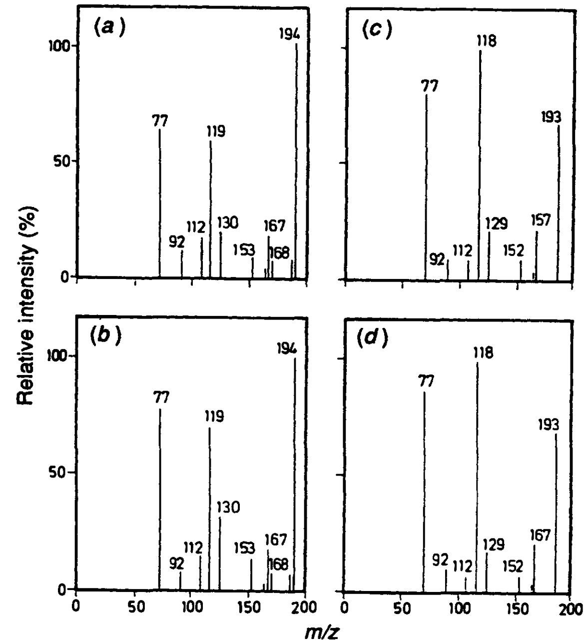


Fig. 1 CAD-B/E linked-scan spectra of ions at (*a*) m/z 195, from **1**; (*b*) m/z 195, $M^{\cdot+}$ of 2-phenylbenzoxazole; (*c*) m/z 194 from **13**; (*d*) m/z 194, $M^{\cdot+}$ of 2-phenylbenzimidazole

Furthermore, the absence of cyclodehydration in the molecular ion of *N*-(2-methoxyphenyl)benzamide (**12**) reveals the involvement of the hydrogen atom of the hydroxy and the amino groups in the H_2O loss from the molecular ions of compounds **1** and **13**.

Based on the these facts, it is proposed that the hydrogen atom from the XH group is transferred to the carbonyl oxygen in the *ortho* position leading to the cyclic ion **d**. Ejection of H_2O in **d** through 1,2-elimination affords the corresponding heterocyclic radical cation (Scheme 3). This mechanism is well supported by the observation of the exclusive formation of $[M - D_2O]^{\cdot+}$ ions in the mass spectrum of the deuterium labelled compound **23** (Fig. 2). An alternative mechanism for the cyclodehydration reaction in the molecular ion of **1** would be the involvement of the phenolic –OH and the amide hydrogen. This possibility is ruled out based on the fact that the molecular ion of *N*-(2-aminophenyl)benzamide (**13**) expels H_2O and not NH_3.

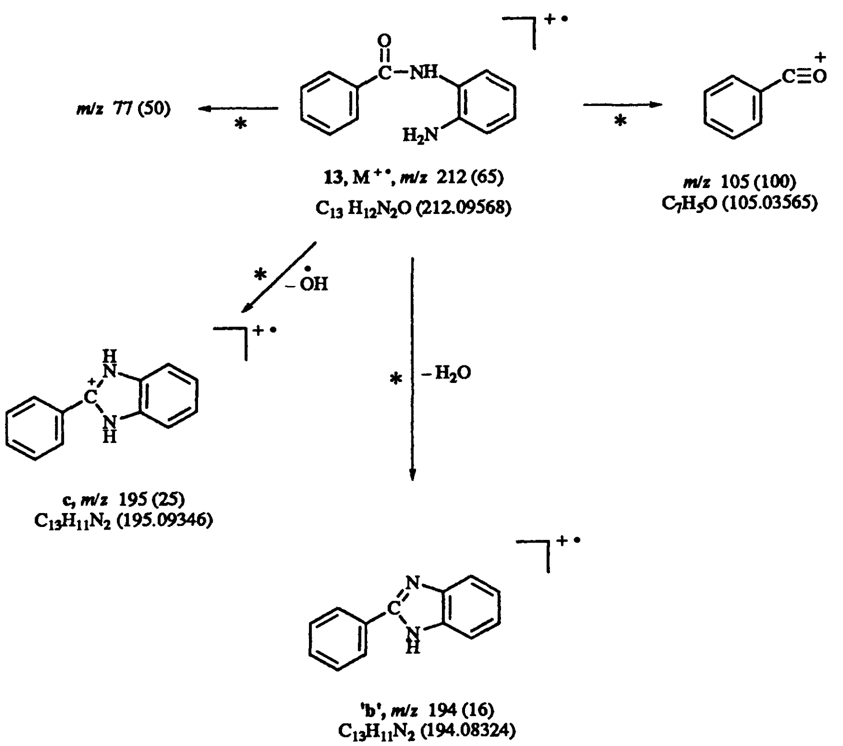
With the knowledge that *ortho* substituted anilides undergo thermal cyclisation reactions analogous to their electron impact behaviour, the pyrolytic study of *N*-(2-hydroxyphenyl)- and *N*-(2-aminophenyl)-benzamides were undertaken to investigate the possible formation of the heterocycles corresponding to the ions noticed during the mass spectral decomposition of these compounds. The thermolysis of these compounds have been systematically performed to isolate 2-phenylbenzoxazoles and benzimidazoles in good yields (Scheme 4). The versatility of this new pyrolytic method of synthesis of the two classes of heterocyclic compounds is quite evident from the short reaction times and easy work-up procedures adopted in obtaining them. The optimum reaction temperature and time conditions to obtain the maximum yield of each heterocycle are given in Table 4.

Conclusions

These studies reveal that a proper understanding of the mass spectrometric reaction in terms of the ion structure and

Table 3 Partial mass spectral data of compounds **2**–**22**

	m/z, relative abundance (%)				
Compd.	$M^{\cdot+}$	$[M - OH]^+$	$[M - H_2O]^{\cdot+}$	$Ar{-}C{\equiv}O^+$	Other ions
2	227 (32)	—	209 (2)	119 (100)	91 (38)
3	227 (20)	—	209 (4)	119 (100)	91 (75)
4	247 (42)	—	229 (2)	139 (100)	111 (7)
5	247 (39)	—	229 (4)	139 (100)	111 (11)
6	258 (100)	—	240 (6)	150 (37)	108 (90)
7	258 (86)	—	240 (17)	150 (100)	108 (72)
8	243 (100)	—	225 (4)	135 (78)	—
9	243 (18)	—	225 (3)	135 (100)	—
10	213 (52)	—	—	121 (78)	93 (100)
11	213 (22)	—	—	105 (100)	77 (40)
12	227 (23)	—	—	105 (100)	122 (41)
13	212 (65)	195 (25)	194 (16)	105 (100)	77 (50)
14	226 (100)	209 (5)	208 (4)	119 (26)	91 (72)
15	226 (100)	209 (10)	208 (6)	199 (42)	91 (58)
16	246 (85)	229 (18)	228 (14)	139 (100)	111 (45)
17	246 (76)	229 (24)	228 (14)	139 (100)	111 (54)
18	257 (100)	240 (22)	239 (74)	150 (44)	107 (90)
19	257 (100)	240 (30)	239 (79)	150 (76)	107 (84)
20	242 (82)	275 (6)	224 (12)	135 (100)	107 (11)
21	242 (86)	225 (5)	224 (4)	135 (100)	107 (11)
22	212 (37)	—	—	120 (100)	92 (46)



Scheme 2

mechanism can be exploited to synthesise organic compounds through thermal processes.

Experimental

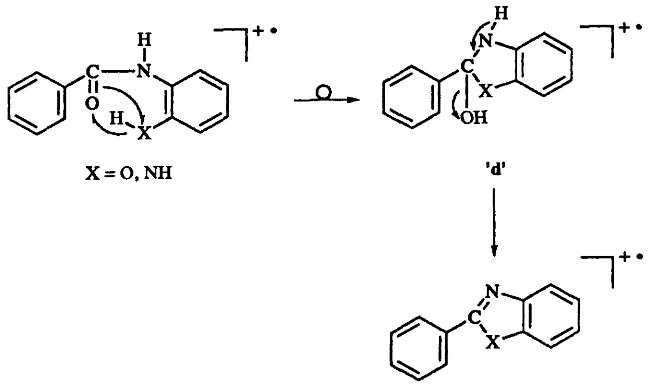
The various *N*-(2-hydroxyphenyl)benzamides and *N*-(2-aminophenyl)benzamides studied in this work were obtained according to the literature reported procedure.[14] Compounds **10**–**12** and **22** were also prepared through known procedures.[15,16] The ^{2}H-labelled compound **23** was obtained by refluxing benzamide **1** in the presence of D_2O (99.8% D, Aldrich) and anhydrous K_2CO_3 for 6 h in a nitrogen atmosphere. The compounds were purified by column chromatography with benzene–hexane as the eluent and recrystallisation. The structures were confirmed by IR and ^{1}H NMR data.

Mass spectra were recorded on a Finnigan MAT 8230 double focusing mass spectrometer. The mass spectra were run at 70 eV with an emission current of 100 μA and an accelerating voltage of 3 kV. All the compounds were introduced into the mass spectrometer through the direct insertion probe with probe temperatures ranging between 25 and 180 °C. Accurate mass measurements were carried out at a resolution of 8000 (10% valley) and perfluorokerosene was used as the reference. The

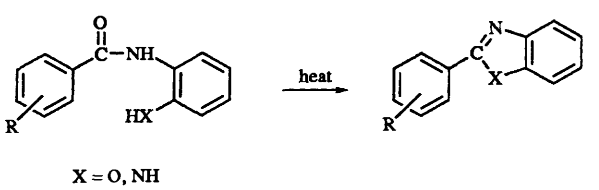
Table 4 Synthesis and characterisation data[a] of 2-substituted benzoxazoles and benzimidazoles

R	X	T/°C	t/min	Yield (%)	Mp (lit)[b]/°C	ν(KBr)(C=N)/cm^{-1}	Partial mass spectral data m/z (relative intensity)
H	0	200	30	76	102 (101)	1608 (s)	$M^{\bullet+}$, 195 (100), 167 (12), 77 (6)
o-CH_3	0	200	30	85	69–70 (72)	1610 (s)	$M^{\bullet+}$, 209 (100), 208 (13), 167 (11), 91 (24)
p-CH_3	0	175	60	92	115 (115)	1608 (s)	$M^{\bullet+}$, 209 (100), 208 (14), 167 (13), 91 (30)
o-Cl	0	200	30	82	72 (72)	1608 (s)	$M^{\bullet+}$, 229 (100), 201 (12), 167 (6), 111 (22)
p-Cl	0	200	30	76	135 (135)	1610 (s)	$M^{\bullet+}$, 229 (100), 201 (18), 111 (34)
o-NO_2	0	200	45	68	104 (103)	1605 (s)	$M^{\bullet+}$, 240 (39), 170 (17), 104 (100), 78 (60)
p-NO_2	0	225	60	70	258 (260)	1608 (s)	$M^{\bullet+}$, 240 (100), 195 (32), 139 (17)
o-OCH_3	0	225	60	74	58 (59)	1606 (s)	$M^{\bullet+}$, 225 (100), 196 (60), 195 (36), 120 (50)
p-OCH_3	0	200	30	74	100–102 (102)	1608 (s)	$M^{\bullet+}$, 225 (100), 182 (53), 77 (12)
H	NH	175	30	88	296 (296)	1606 (s)	$M^{\bullet+}$, 194 (100), 193 (48), 167 (12)
o-CH_3	NH	175	30	82	218 (220)	1606 (s)	$M^{\bullet+}$, 208 (100), 207 (17), 91 (25), 77 (18)
p-CH_3	NH	200	30	85	265 (266)	1604 (s)	$M^{\bullet+}$, 208 (100), 207 (29), 193 (11), 91 (21)
o-Cl	NH	200	60	76	230–231 (232)	1600 (s)	$M^{\bullet+}$, 228 (100), 193 (22), 168 (12), 111 (14)
p-Cl	NH	200	60	72	290–292 (292–293)	1600 (s)	$M^{\bullet+}$, 228 (100), 227 (15), 193 (18), 111 (14)
o-NO_2	NH	200	60	62	264–265 (263–265)	1602 (s)	$M^{\bullet+}$, 239 (100), 222 (70), 134 (22), 91 (54)
p-NO_2	NH	225	60	60	326–327 (326–327)	1680 (s)	$M^{\bullet+}$, 239 (100), 209 (25), 193 (70), 90 (28)
o-OCH_3	NH	200	60	77	177–178 (178)	1605 (s)	$M^{\bullet+}$, 224 (100), 223 (60), 194 (72), 119 (61)
p-OCH_3	NH	200	60	80	234–235 (235–236)	1604 (s)	$M^{\bullet+}$, 224 (100), 209 (41), 187 (34), 90 (10)

[a] All the 2-substituted benzoxazoles and benzimidazoles were also characterised through ^1H NMR spectra. [b] See refs. 17–21.



Scheme 3



Scheme 4

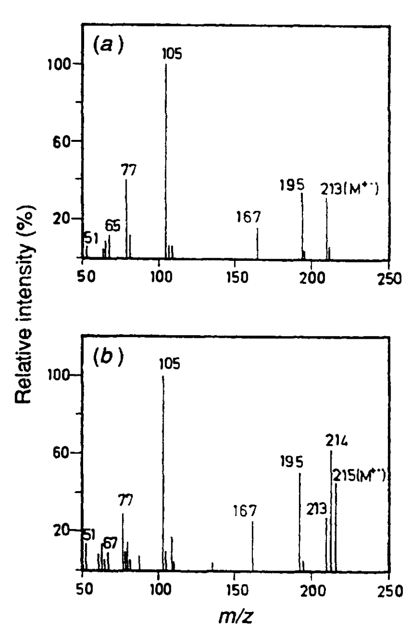


Fig. 2 Electron impact mass spectra at 70 eV of: (*a*) *N*-(2-hydroxyphenyl)benzamide; (*b*) [$^2H_2$]-*N*-(2-hydroxyphenyl)benzamide

CAD-B/E linked-scan spectra in the first field-free region were investigated using helium as the collision gas, at an ionisation energy of 70 eV and accelerating voltage of 3 kV, helium gas was introduced until the main beam was attenuated to 30% intensity.

General procedure adopted for the pyrolysis of *N*-(2-hydroxyphenyl)- and *N*-(2-aminophenyl)-benzamides

In a typical experiment the *N*-(2-hydroxyphenyl)- or *N*-(2-aminophenyl)-benzamide (1 mmol) was placed in a 50 cm^3 round-bottomed flask fitted with an air condenser and was heated on a sand bath according to the conditions specified in Table 4. The resulting residue was extracted with dichloromethane (3 × 40 cm^3). The extract was washed thoroughly with saturated sodium hydrogen carbonate solution (100 cm^3). The solvent was evaporated using a rotary evaporator and the crude product was obtained. Purification was effected by recrystallisation in suitable solvents. All the 2-substituted benzoxazoles and benzimidazoles obtained by the pyrolysis of *N*-(2-hydroxyphenyl)- and *N*-(2-aminophenyl)-benzamides, respectively, were characterised thoroughly by their melting points and spectral data (Table 4).

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