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Chromone Studies. Part 12.[1] Fragmentation Patterns in the Electron-impact Mass Spectra of 2-(*N,N*-Dialkylamino)-4*H*-1-benzopyran-4-ones and -naphthopyran-4-ones

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ABSTRACT

The major electron-impact mass fragmentation patterns exhibited by 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones and -naphthopyran-4-ones have been explored using a combination of low-resolution, high-resolution and *B/E* linked-scan data.

KEYWORDS

2-Aminochromones, 2-amino-4*H*-1-benzopyran-4-ones, mass spectrometry, fragmentation patterns.

Chromone (4*H*-1-benzopyran-4-one) derivatives are widely distributed in nature and many exhibit interesting biological activity.[2] The synthetic bischromone derivative, sodium cromoglycate, is used in the treatment of bronchial asthma,[3] while various 2-aminochromones have been shown to exhibit anti-platelet acitivity.[4] As part of an ongoing study of chromone derivatives, we have examined the influence of substituents on, amongst others, C(2)–N rotational barriers in *N,N*-disubstituted 2-aminochromones[5] and the basicity of 2-(*N,N*-dimethylamino) analogues.[6] In this communication we discuss the results of a mass spectrometric study of a series of variously substituted *N,N*-disubstituted 2-aminochromone derivatives **1–12**.

We have reported the use of several established methods to access the title compounds **1–12** (Scheme 1).[5] Thus, the 2-(*N,N*-dimethylamino) derivatives **1–5**, **11** and **12** were conveniently obtained from the corresponding *o*-hydroxyacetophenones **13**, following the method reported by Morris *et al.*[7] Compounds **1** and **6–8** were prepared using the approach of Bantick and Suschitzky,[8] involving reaction of 2-ethylsufinyl-4*H*-1-benzopyran-4-one **15** (obtained, in turn, from the thiolactone **14**) with each of the secondary amines dimethylamine, diethylamine, piperidine and pyrrolidine. Treatment of methyl salicylate precursors **16** with the lithium enolate of *N,N*-dimethylacetamide, and cyclization of the resulting intermediates **17** mediated by trifluoromethanesulfonic anhydride,[7] afforded the 2-aminochromones **1** and **9**, while the parent system **1** and the methoxy analogues **5** and **10** were obtained from the (*N,N*-dimethylcarbamoyl)acetate ester **18** and the corresponding phenols **19**.[9]

The electron-impact (E.I.) mass fragmentation patterns exhibited by the *N,N*-disubstituted 2-aminochromone derivatives **1–12** were studied using a combination of low-resolution, high-resolution and *B/E* linked-scan data. The fragmentation pathways proposed for the 'parent' system, 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **1**, are outlined in Scheme 2, while Table 1 summarizes the *m/z* and relative abundance data for the corresponding fragments for compounds **1–12**.

The molecular ion **1a** (*m/z* 189; Scheme 2) is also the base peak – a pattern exhibited by most of the compounds examined, reflecting the stability of the highly delocalized systems **1–12**. No fewer than five distinct fragmentations of the molecular ion may be identified (*cf.* Paths I–V; Scheme 2). In path I [**1a** → **1b** (*m/z* 174)], loss of a methyl radical affords an even-electron species, formulated as an iminium cation. This fragmentation appears to be common to all of the 2-(*N,N*-dimethylamino) derivatives (**1–5** and **9–12**). In fragmentations supported by the linked-scan data, the diethylamino analogue **6** loses methyl and ethyl radicals from the molecular ion (Scheme 3), presumably to afford the corresponding iminium cations **6b** (*m/z* 202) and **6m** (*m/z* 188). Subsequent elimination of ethylene from the iminium cation **6b** would then account for the iminium cation **6n** (*m/z* 174).

The 2-piperidino- and 2-pyrrolidino derivatives (**7** and **8**, respectively) each lose an α-hydrogen atom to give the corresponding cyclic iminium cations **7o** and **8o** (Scheme 4). The 2-piperidino system **7** also loses a methyl radical to afford, it is suggested, a ring-contracted fragment **7b** identical to **8o**. A very weak peak at *m/z* 200 (<1% relative abundance) corresponding to loss of a methyl radical from the pyrrolidino molecular ion **8a** is also apparent. Loss of an α-hydrogen from such cyclic amines is common, while piperidine is known to undergo ring-opening followed by elimination of 15 and 29 mass unit fragments,[10] which would account for the loss of methyl and ethyl radicals and the formation of fragments **7b** and **7p**, respectively.

Extrusion of CO from the molecular ion (Path II; Scheme 2) produces the 2-aminobenzofuran fragment **1c** (*m/z* 161); loss of H• then provides access to the iminium cation **1d** (*m/z* 160), and elimination of $MeN{=}CH_2$ affords the benzofuran radical cation **1j** (*m/z* 118). In Path III, sequential loss of an aziridine species (C_2H_3N) and H• affords the benzopyranone fragments **1e** (*m/z* 148) and **1f** (*m/z* 147), respectively; in the case of the diethylamino analogue **6**, the linked-scan data support direct elimination of C_4H_8N•. Deamination (Path IV) of the molecular ion would account for the formation of the chromone radical cation **1g** (*m/z* 146). Extrusion of CO from the chromone radical cation **1g** forms another benzofuran fragment **1j** (*m/z* 118),[11] while formation of the phenylacylium cation **1k** (*m/z* 105) is attributed to loss of a ketene radical from the same precursor **1g**.

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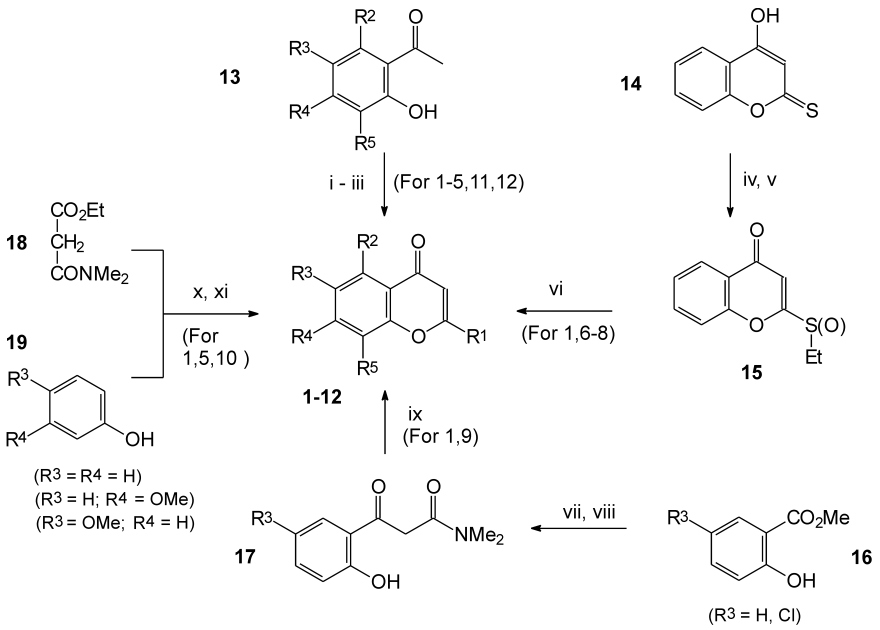
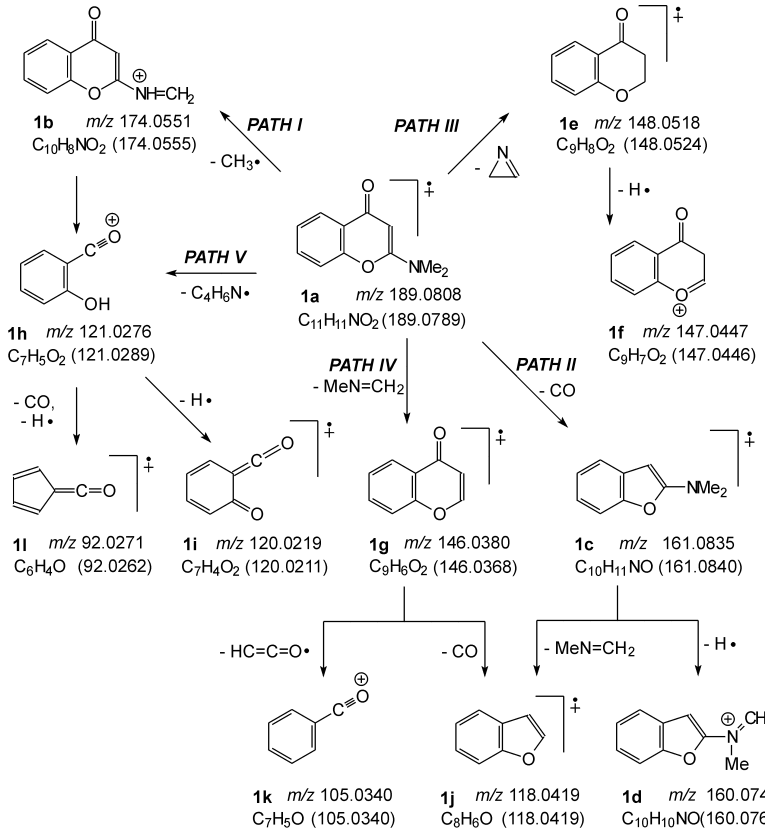


	1	2	3	4	5	6	7	8	9	10	11	12
R^1	NMe_2	NMe_2	NMe_2	NMe_2	NMe_2	NEt_2	piperi-dino	pyrroli-dino	NMe_2	NMe_2	NMe_2	NMe_2
R^2	H	H	H	H	H	H	H	H	H	H	$-(CH)_4-$	H
R^3	H	H	H	H	OMe	H	H	H	Cl	H		H
R^4	H	Br	F	Cl	H	H	H	H	H	OMe	H	$-(CH)_4-$
R^5	H	H	H	H	H	H	H	H	H	H	H	

Scheme 1

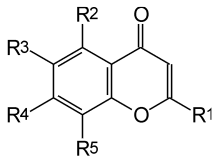
Reagents and conditions: **i**, BF_3OEt_2, Et_2O; **ii**, $[Cl_2C{=}NMe_2]^+ Cl^-$, $Cl(CH_2)_2Cl$; **iii**, MeOH, 50 °C; **iv**, K_2CO_3, EtI, $(CH_3)_2CO$; **v**, MCPBA, $Cl(CH_2)_2Cl$; **vi**, R_2NH (*i.e.* R^1H); **vii**, LDA, THF; **viii**, $MeCONMe_2$; **ix**, Tf_2O, CH_2Cl_2; **x**, $POCl_3$, C_6H_5Cl; **xi**, NaOAc, H_2O, 90–95 °C.



Scheme 2

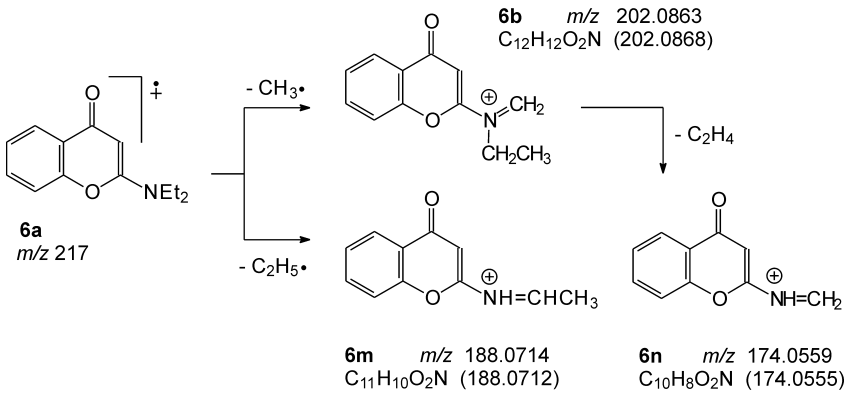
E.I. mass fragmentation pathways for 2-(*N*,*N*-dimethylamino)-4*H*-1-benzopyran **1**, all of which are supported by *B*/*E* linked-scan data. Accurate masses (*m*/*z*) are followed, in brackets, by calculated masses.

Table 1 Selected peaks (*m/z*), followed, in brackets, by percentage relative abundance from the E.I. mass spectra of the 2-(*N,N*-dialkylamino)-4*H*-1-benzopyran-4-ones and -naphthopyran-4-ones **1**–**12**, classified according to ion types **a–l** (Scheme 2).

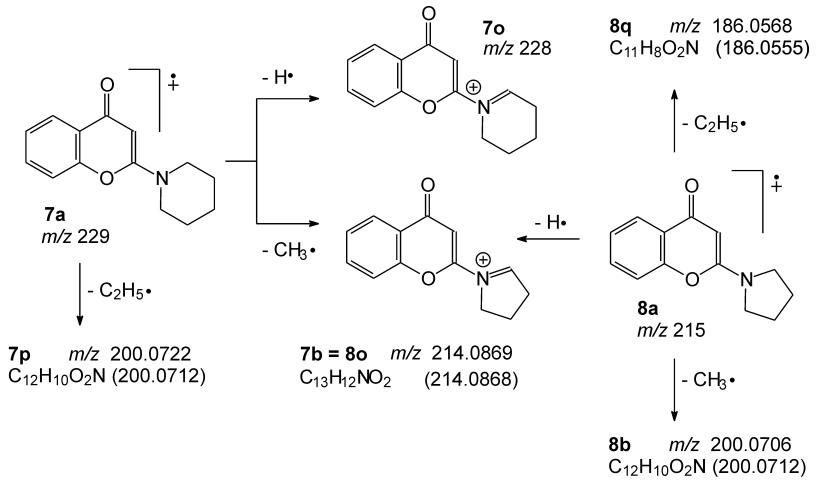


Compd	R^1	R^2	R^3	R^4	R^5	Ion types											
						a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**
1	NMe_2	H	H	H	H	189 [a] (100)	174 [a] (20)	161 [a] (9)	160 [a] (7)	148 [a] (8)	147 [a] (16)	146 [a] (62)	121 [a] (11)	120 [a] (4)	118 [a] (20)	105 [a] (7)	92 [a] (13)
2	NMe_2	H	H	Br	H	267 [a,b] (60)	254 [b] (10)	241 [b] (5)	240 [b] (3)	228 [b] (4)	227 [b] (10)	226 [b] (37)	201 [b] (4)	200 [b] (1)	198 [b] (11)	185 [b] (3)	172 [b] (5)
3	NMe_2	H	H	F	H	207 [a] (100)	192 (18)	179 (6)	178 (5)	166 (9)	165 (17)	164 (47)	139 (10)	138 (3)	136 (17)	123 (8)	110 (10)
4	NMe_2	H	H	Cl	H	223 [a,c] (100)	208 [c] (20)	195 [c] (11)	194 [c] (5)	182 [c] (30)	181 [c] (17)	180 [c] (52)	155 [c] (9)	154 [c] (7)	152 [c] (18)	139 [c] (7)	126 [c] (10)
5	NMe_2	H	OMe	H	H	219 [a] (100)	204 [a] (23)	191 (4)	190 (7)	178 (26)	177 (7)	176 (26)	151 (7)	150 (25)	148 (17)	135 [a] (21)	122 (22)
6	NEt_2	H	H	H	H	217 [a] (100)	202 [a,d] (58)	— [d]	— [d]	— [d]	147 [a] (3)	146 [a] (3)	121 [a] (48)	120 [a] (4)	118 [a] (1)	105 [a] (2)	92 [a] (8)
7	Piperidino	H	H	H	H	229 [a] (100)	214 [a] (20)	— [e]	— [e]	— [e]	147 [a] (6)	146 [a] (15)	121[a] (28)	120 [a] (9)	118 [a] (2)	105 [a] (3)	92 [a] (10)
8	Pyrrolidino	H	H	H	H	215 [a] (100)	200 [a] (<1)	— [e]	— [e]	— [e]	147 [a] (8)	146 [a] (53)	121[a] (9)	120 [a] (8)	118 [a] (3)	105 [a] (4)	92 [a] (8)
9	NMe_2	H	Cl	H	H	223 [a,c] (100)	208 [c] (23)	195 [c] (7)	194 [c] (5)	182 [c] (18)	181 [c] (10)	180 [c] (54)	155 [c] (6)	154 [c] (9)	152 [c] (12)	139 [c] (5)	126 [c] (9)
10	NMe_2	H	H	OMe	H	219 [a] (84)	204 (24)	191 (2)	190 (4)	178 (4)	177 (18)	176 (100)	151 (18)	150 (3)	148 (14)	135 (6)	122 (8)
11	NMe_2	–$(CH)_4$–		H	H	239[a] (100)	224 (20)	211 (23)	210 (6)	198 (10)	197 (14)	196 (52)	171 (6)	170 (12)	168 (11)	155 (5)	142 (11)
12	NMe_2	H	H	–$(CH)_4$–		239[a] (100)	224 (30)	211 (6)	210 (9)	198 (13)	197 (14)	196 (38)	171 (9)	170 (41)	168 (8)	155 (4)	142 (9)

[a] Atomic composition confirmed by HRMS.
[b] *M/z* value corresponds to ^{81}Br.
[c] *m/z* value corresponds to ^{35}Cl.
[d] See Scheme 3.
[e] See Scheme 4.



Scheme 3
Fragmentations exhibited by compound **6**, all of which are supported by *B/E* linked-scan data.



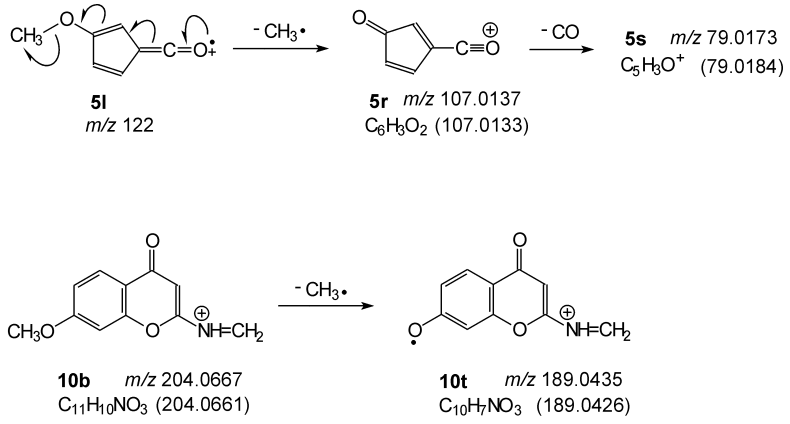
Scheme 4
Fragmentations exhibited by compounds **7** and **8**, all of which are supported by *B/E* linked-scan data.

Retro-Diels-Alder (RDA) fragmentations are common in chromone systems[11] and are exemplified by the $[RDA + H]^+$ fragmentation **1a** → **1h** (*m/z* 121; Path V); subsequent loss of H• and CO, with concomitant ring-contraction, then leads to the cyclopentylidene ketene species **1l** (*m/z* 92). The ketene fragments **1i** and **1l** could also be formed directly from the chromone radical cation **1g** *via* known RDA and [RDA – CO] fragmentations,[11] respectively.

The fragmentation patterns illustrated for the 'parent' system **1** in Scheme 2 are all supported by the *B/E* linked-scan data and appear to be representative, with a few exceptions, of the entire series of compounds examined (Table 1). Not surprisingly, the methoxy derivatives **5** and **10** exhibit additional fragmentations associated with characteristic[12] fission of the *O*-methyl ether link (Scheme 5).

Experimental

The preparation and characterization of the 2-(*N*,*N*-dialkylamino)chromones **1**–**12** have been reported previously.[5] Low-resolution mass spectra were obtained on a Hewlett-



Scheme 5
Additional fragmentations exhibited by the methoxy analogues **5** and **10**, all of which are supported by *B/E* linked-scan data.

Packard 5988A mass spectrometer, while high-resolution and *B/E* linked-scan data were obtained on Kratos MS80RF or VG70-SEQ Micromass double-focusing instruments (Cape Technikon Mass Spectrometry Unit).

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