ORGANIC MASS SPECTROMETRY, VOL. 23, 816–820 (1988)

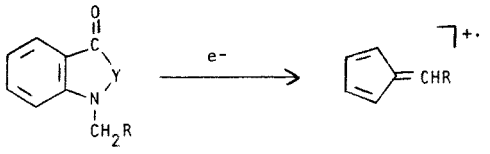
A Mass Spectral Rearrangement of 2-(Alkylamino)benzoic Acid Derivatives and Related Heterocyclic Systems

Robert J. Barbuch and Norton P. Peet
Merrell Dow Research Institute, Cincinnati, Ohio 45215, USA

The behavior of a series of 2-(alkylamino)benzoic acid derivatives and related heterocyclic systems has been investigated using electron impact mass spectrometry and fragmentation pathways have been formulated. Deuterium-labeled and ^{13}C-labeled compounds were used in this study. An interesting rearrangement of the alkylamino compounds, in which the alkyl substituent is incorporated into a fulvene ion, was observed. This rearrangement had previously been observed for 1-alkylisatins and 1-alkyl-3-arylimino-2-indolinones.

INTRODUCTION

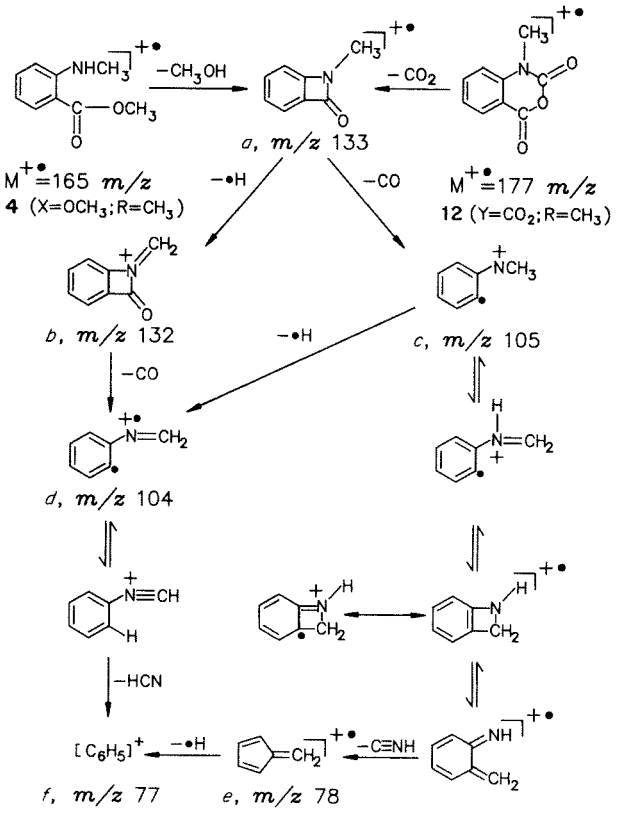
The mass spectral fragmentation of isatins[1] and isatin derivatives[2] has been studied by Ballantine and co-workers. In recent reports from our laboratory, we have described[3,4] additional mass spectral studies with isatins, and reported novel rearrangements of 1-methylisatin (Y = carbonyl, R = H) which produced fulvene ion (*m/z* 78). A study with a series of 3-alkylbenzotriazin-4-ones by Melville and Bowen[5] and work by Teeter[6] with 2-aminobenzoic acid derivatives bearing a 2-methylamino group show the *m/z* 78 ion to be a common fragment ion. Therefore, we extended our study to include other heterocyclic systems (Y = other connecting groups) and 2-(alkylamino)benzoic acid derivatives to determine whether rearrangement to incorporate the *N*-alkyl group and expulsion of the elements of CNH would occur in similar fashion to yield fulvene ions.



RESULTS AND DISCUSSION

Scheme 1 shows the proposed fragmentation pathway for 2-(methylamino)benzoic acid methyl ester (**4**) and *N*-methylisatoic anhydride (**12**). The exact structures of the ions shown in Scheme 1 are not known, but they are consistent with the flow of the proposed fragmentation pathway. Compounds **4** and **12** are representative of the 2-(alkylamino)benzoic acid derivatives in Table 1 and the related heterocyclic systems containing a 2-(alkylamino)benzoyl unit in Table 2, respectively. Ion *a* arises from loss of methanol from compound **4** and carbon dioxide from compound **12**. Ions *b*, *c* and *d* arise from respective losses of hydrogen radical, CO and hydrogen radical plus CO from ion *a*. The fulvene ion radical *e* results from the expulsion of the elements of CNH from ion *c*. 1-Methylisatin, whose mass spectral fragmentation pathway has been reported earlier, also forms the same cascade of fragment ions (*a–f*) shown in Scheme 1.[3,4]

The mass spectra of 2-(methylamino)benzoic acid methyl ester (**4**) and *N*-methylisatoic anhydride (**12**) are presented in Figs 1 and 2, respectively. The respective relative abundances of the *m/z* 78 ion *e* (fulvene) for these compounds are 22% and 45%.



Scheme 1

0030–493X/88/120816–05 $05.00

Received 8 February 1988
Accepted 28 April 1988

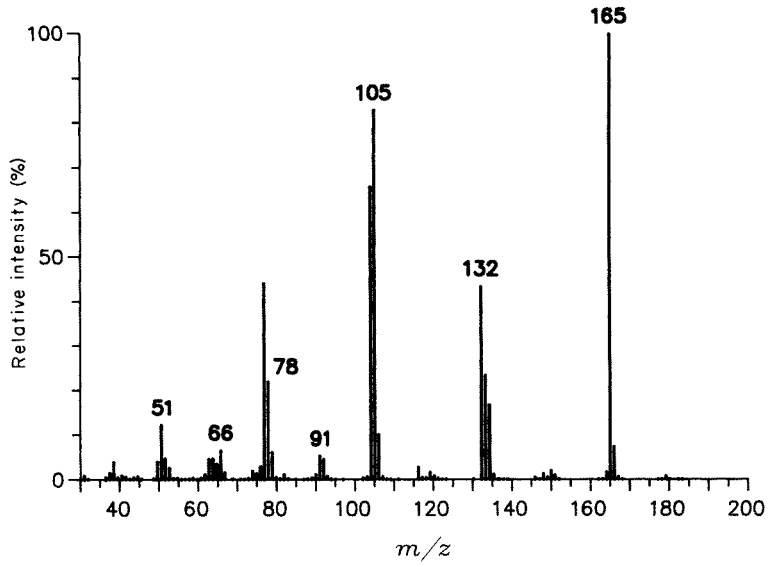


Figure 1. Mass spectrum of 2-(methylamino)benzoic acid methyl ester (**4**).

Tables 1 and 2 display the major fragment ions and ion abundances of the 2-(alkylamino)benzoic acid derivatives and related heterocyclic compounds, respectively. Initial examination of compound **4** (Table 1) showed an ion at *m/z* 78 which was probably due to fulvene ion *e*. The (^{13}C)methyl analog **5** substantiated the incorporation of the *N*-methyl carbon and loss of a phenyl ring carbon as CNH to form the fulvene ion (*m/z* 79). This

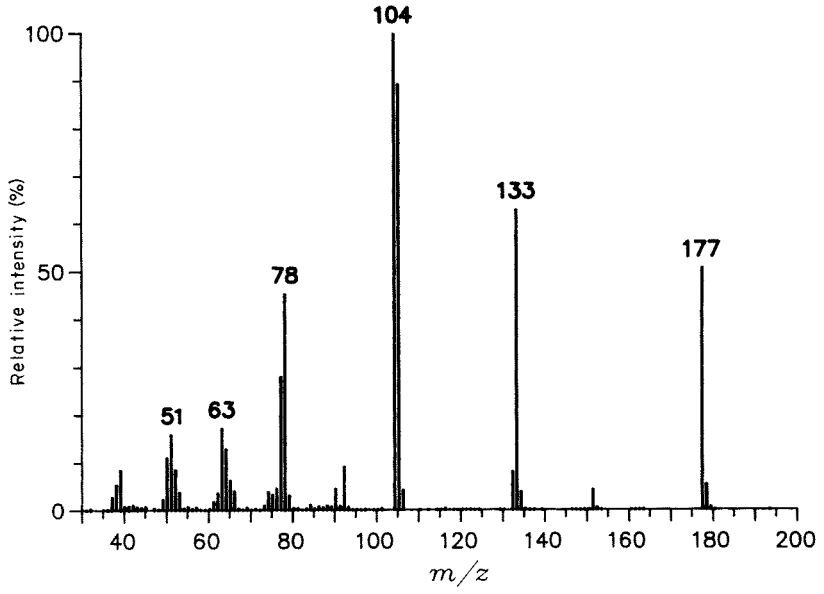
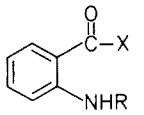


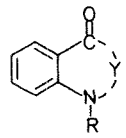
Figure 2. Mass spectrum of *N*-methylisatoic anhydride (**12**).

Table 1. Relative abundances of the major fragment ions of 2-(alkylamino)benzoic acid derivatives



Cpd	X	R	M$^{+\cdot}$	Mass fragment, *m/z* (relative abundance) *a*	*b*	*c*	*d*	*e*	*f*
1	NH_2	CH_3	150 (100)	133 (43)	132 (23)	105 (80)	104 (82)	78 (29)	77 (41)
2	NH_2	CD_3	153 (100)	136 (8)	134 (27)	108 (33)	106 (60)	80 (18)	78 (18)
3	NH_2	$^{13}CH_3$	151 (94)	134 (44)	133 (21)	106 (75)	105 (100)	79 (20)	78 (20)
4	OCH_3	CH_3	165 (100)	133 (23)	132 (43)	105 (83)	104 (66)	78 (22)	77 (44)
5	OCH_3	$^{13}CH_3$	166 (100)	134 (30)	133 (57)	106 (75)	105 (70)	79 (14)	78 (15)
6	OH	CH_3	151 (87)	133 (22)	132 (24)	105 (100)	104 (97)	78 (44)	77 (55)

Table 2. Relative abundances of the major fragment ions of heterocycles containing a 2-(alkylamino)benzoyl unit



Cpd	Y	R	Mass fragment, m/z (relative abundance) M+·	a	b	c	d	e	f
7	O ‖ NHC	CH_3	176 (100)	133 (13)	132 (10)	105 (83)	104 (80)	78 (30)	77 (30)
8	O ‖ NHC	CD_3	179 (100)	136 (10)	134 (7)	108 (57)	106 (62)	80 (22)	78 (14)
9	O ‖ NHC	$^{13}CH_3$	177 (100)	134 (10)	133 (7)	106 (52)	105 (58)	79 (12)	78 (10)
10	CH_3 | NC=O	CH_3	190 (92)	133 (35)	132 (11)	105 (100)	104 (12)	78 (36)	77 (38)
11	CH_3 | NC=O	CD_3	193 (100)	136 (28)	134 (7)	108 (84)	106 (60)	80 (22)	78 (16)
12	O ‖ OC	CH_3	177 (51)	133 (63)	132 (8)	105 (89)	104 (100)	78 (45)	77 (28)
13	O ‖ OC	$^{13}CH_3$	178 (52)	134 (59)	133 (10)	106 (100)	105 (67)	79 (28)	78 (20)
14	O ‖ OC	CD_3	180 (47)	136 (63)	134 (10)	108 (87)	106 (100)	80 (58)	78 (21)
15	CH_3 | NC=S	CH_3	206 (100)	133 (16)	132 (33)	105 (47)	104 (38)	78 (14)	77 (27)
16	CH_3 | NC=S	CD_3	209 (100)	136 (7)	134 (20)	108 (30)	106 (25)	80 (13)	78 (10)

rearrangement also occurred with 2-(methylamino)benzamide (**1**) where both the respective trideuteromethyl and (^{13}C)methyl analogs **2** and **3** were examined. The fulvene ions *e* were observed at *m/z* 80 and *m/z* 79, respectively.

For heterocyclic compounds **7–16** (Table 2), after the initial loss of a neutral Y from the parent ion the fragmentation was identical to that observed for the 2-(alkylamino)benzoic acid derivatives. Trideuteromethyl- and ^{13}C-labeled methyl analogs of these heterocyclic compounds were again used to confirm the incorporation of the *N*-methyl carbon and loss of a phenyl ring carbon as CNH to form fulvene ions.

In summary, this study shows that ion *e*, shown as a fulvene ion, which forms as a rearrangement ion in the fragmentation of 1-methylisatin, also forms during the fragmentation of 2-(alkylamino)benzoic acid derivatives and the related heterocyclic compounds which contain the 2-(alkylamino)benzoyl unit. The formation of the fulvene ion occurs with incorporation of the *N*-alkyl group, as was observed for 1-methylisatin.

EXPERIMENTAL

All mass spectra were recorded using a Finnigan MAT Model 4500 (70 eV, electron impact) mass spectrometer. Samples were introduced via the direct exposure probe at a heating rate of 20 mA s^{-1}. General procedures for the preparation of the compounds used in this study are illustrated with the specific preparations below. The physical constants for these compounds are recorded in Table 3. For the preparation of isotopically labeled compounds, iodomethane-d_3 was purchased from Aldrich Chemical Company and iodomethane-^{13}C was purchased from Stohler Isotope Chemicals. Isotopic purities of all labeled compounds were determined to be greater than 95%. Isotopic purity was established by finding the ratio of the parent ion ($M^{+\cdot}$) to the sum of $M^{+\cdot}$ and $[M-1]^{+\cdot}$ and multiplying by 100.

2-(Methyl-d_3-amino)benzamide (2)

A mixture of 21.7 g (0.120 mol) of **14** and 200 cm^3 of ethanol was treated with 15 cm^3 of concentrated ammonium hydroxide and heated on a hotplate. Rapid evolution of carbon dioxide occurred and ammonium carbonate collected on the upper wall of the flask. The mixture was filtered and the filtrate was diluted with water (15 cm^3) and cooled. The resulting tan prisms were collected and oven-dried to give 8.38 g (46%) of **2**, m.p. 160–162 °C: infrared (IR) (potassium bromide) 3400, 3360 and 3180 (NH and NH_2), 1655 (C=O) cm^{-1}; nuclear magnetic resonance (NMR) (deuteriochloroform) δ 7.75 (br s, 1, NH), 7.38 (d, J = 7.8 Hz, 1, C6-H), 7.36 (dd, J = 8.3 Hz, J = 6.8 Hz,

Table 3. Physical constants for the 2-(alkylamino)benzoic acid derivatives and related heterocycles

Cpd	Yield (%)	m.p. (°C)[a]	Formula	Calc. (%) C	Calc. (%) H(D)	Calc. (%) N	Found (%) C	Found (%) H(D)	Found (%) N
1	54[b]	160–162	$C_8H_{10}N_2O$	63.98	6.71	18.65	—	—	—
2	46[b]	160–162	$C_8H_7D_3N_2O$	62.72	6.58	18.29	62.61	6.65	18.22
3	33[c]	161–162	$C_7{}^{13}CH_{10}N_2O$	64.22	6.67	18.53	63.56	6.68	18.60
4[d]	—	207–208 (b.p.)	$C_{10}H_{11}NO_2$	67.78	6.26	7.91	—	—	—
5[e]	—	—	$C_9{}^{13}CH_{11}NO_2$	67.96	6.22	7.86	—	—	—
6[f]	—	170–172	$C_8H_9NO_2$	63.56	6.00	9.27	—	—	—
7	28	265–267	$C_9H_8N_2O_2$	61.36	4.58	15.90	—	—	—
8	28[c]	268–269	$C_9H_5D_3N_2O_2$	60.32	4.50	15.64	60.14	4.60	15.39
9	15[c]	265–267	$C_8{}^{13}CH_8N_2O_2$	61.58	4.55	15.81	61.23	4.61	15.65
10	29[g]	164–165	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	—	—	—
11	27[g]	164–165	$C_{10}H_7D_3N_2O_2$	62.16	5.22	14.50	62.07	5.28	14.44
12[f]	—	165 (dec.)	$C_9H_7NO_3$	61.01	3.98	7.91	—	—	—
13	78[h]	176–177	$C_8{}^{13}CH_7NO_3$	61.23	3.96	7.86	60.94	3.96	7.97
14	100[h]	176–177	$C_9H_4D_3NO_3$	59.99	3.92	7.78	59.68	3.84	7.61
15	50[h]	179–181	$C_{10}H_{10}N_2OS$	58.23	4.88	13.58	—	—	—
16	41[h]	180–181	$C_{10}H_7D_3N_2OS$	57.38	4.82	13.39	56.53	4.89	13.86

[a] All melting points were consistent with reported literature values.
[b] Crystallized directly from reaction medium by addition of water.
[c] Crystallized directly from reaction medium by concentration.
[d] Purchased from Pfaltz and Bauer.
[e] Prepared *in situ* by addition of sodium methoxide to a solution of **13** in methanol.
[f] Purchased from Aldrich Chem. Co.
[g] Crystallized from ethanol–water.
[h] Crystallized from ethanol.

1, C4-H), 6.68 (d, J = 8.3 Hz, 1, C3-H), 6.58 (dd, J = 7.8 Hz, J = 6.8 Hz, 1, C5-H), 5.75 (br s, 1, NH_2).

1-(Methyl-d_3)-2,4-(1*H*,3*H*)-quinazolinedione (8)

To a mixture of 1.53 g (10.0 mmol) of **2** and 10 cm^3 of 2-methoxyethyl ether was added 1.19 g (11.0 mmol) of ethyl chloroformate (exothermic addition). After 1 h at reflux the solution was concentrated to half-volume and cooled. The resulting fine, off-white needles were collected, washed with ether and air-dried to give 0.510 g (28%) of **8**, m.p. 268–269 °C: IR (potassium bromide) 1700 (C=O), 1660 (C=O) cm^{-1}; NMR (dimethylsulfoxide-d_6) δ 7.99 (dd, J = 7.8 Hz, J = 1.5 Hz, 1, C5-H), 7.76 (ddd, J = 8.2 Hz, J = 7.8 Hz, J = 1.5 Hz, 1, C7-H), 7.41 (d, J = 8.2 Hz, 1, C8-H), 7.28 (dd, J = 7.8 Hz, J = 1.5 Hz, 1, C6-H), 3.38 (s, 3, CH_3).

1-(Methyl-d_3)-3-methyl-2,4-(1*H*,3*H*)-quinazolinedione (11)

A solution of 1.53 g (10.0 mmol) of **2** and 5 cm^3 of methyl isocyanate in 15 cm^3 of 2-methoxyethyl ether was heated at reflux for 22 h. The solution was cooled and diluted with 80 cm^3 of water. The cloudy solution deposited a white solid which was collected and recrystallized (ethanol–water) to give 0.520 g (27%) of **11** as off-white needles, m.p. 164–165 °C: IR (potassium bromide) 1705 (C=O), 1660 (br C=O) cm^{-1}; NMR (dimethylsulfoxide-d_6) δ 8.05 (dd, J = 7.8 Hz, J = 1.0 Hz, 1, C5-H), 7.78 (ddd, J = 8.8 Hz, J = 7.3 Hz, J = 1.0 Hz, 1, C7-H), 7.45 (d, J = 8.8 Hz, 1, C8-H), 7.30 (dd, J = 7.8 Hz, J = 7.3 Hz, 1, C6-H), 3.31 (s, 3, CH_3).

1-(Methyl-^{13}C)-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (13)

To a solution of 4.89 g (30.0 mmol) of isatoic anhydride in 30 cm^3 of dimethylformamide was added 0.826 g (34.4 mmol) of dry sodium hydride over a 5 min period, with water-bath cooling. The addition was exothermic, accompanied by vigorous gas evolution. After 10 min of stirring, a solution of 5.00 g (34.5 mmol) of iodomethane-d_3 in 20 cm^3 of dimethylformamide was added over a 10 min period. After 24 h the mixture was diluted with 250 cm^3 of water and the resulting beige solid was collected to give 4.17 g (78%) of **13**, m.p. 176–177 °C (ethanol): NMR (deuteriochloroform) δ 8.17 (dd, J = 7.8 Hz, J = 1.6 Hz, 1, C5-H), 7.79 (ddd, J = 8.3 Hz, J = 7.5 Hz, J = 1.6 Hz, 1, C7-H), 7.33 (ddd, J = 7.8 Hz, J = 7.5 Hz, J = 1.0 Hz, 1, C6-H), 7.20 (d, J = 8.3 Hz, 1, C8-H), 3.60 (d, J = 141.6 Hz, 3, $^{13}CH_3$).

1-(Methyl-d_3)-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (14)

To a solution of 24.5 g (0.150 mol) of isatoic anhydride in 200 cm^3 of *N*,*N*-dimethylacetamide was added 4.13 g (0.172 mol) of dry sodium hydride over a period of 10 min with water-bath cooling. After 10 min of stirring, gas evolution had diminished and 25.0 g (0.172 mol) of iodomethane-d_3 was added over 10 min. After 20 h the mixture was poured into 800 cm^3 of cold water. The resulting cream-colored solid was collected and oven-dried to give 27.0 g (100%) of **14**, m.p. 176–177 °C (tan prisms from ethanol): IR (potassium bromide) 1750 (C=O), 1715 (C=O) cm^{-1}.

REFERENCES

1. J. A. Ballantine, R. G. Fenwick and M. Alam, *Org. Mass Spectrom.* **1**, 467 (1968).
2. J. A. Ballantine, R. G. Fenwick and F. D. Popp, *Org. Mass Spectrom.* **5**, 1003 (1971).
3. N. P. Peet and R. J. Barbuch, *Org. Mass Spectrom.* **19**, 171 (1984).
4. R. J. Barbuch, N. P. Peet and J. E. Coutant, *Org. Mass Spectrom.* **21**, 521 (1986).
5. A. J. Melville and R. D. Bowen, *Org. Mass Spectrom.* **19**, 641 (1984).
6. R. M. Teeter, *Anal. Chem.* **38**, 1736 (1966).