Mass Spectral Fragmentation Patterns of Heterocycles. VII [1]. Reinvestigation of Fundamental Processes in Phenothiazines

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Electron impact induced fragmentation patterns of simple phenothiazines have been reinvestigated using metastable ion studies, exact mass measurements and deuterated derivatives. Secondary fragmentation processes involving ions m/e 198, 171, 167, 166, 154, 140 and 139 have been clarified. Mechanisms for the release of sulfur (SH· and CSH·) nitrogen (HCN and H_2CN·) containing fragments from phenothiazine molecular ion are proposed based on the deuterium content of the daughter ions obtained from 1,9-dideuteriophenothiazine. A revised mechanism for the expulsion of ketene from 10-acetylphenothiazine is suggested based on the fragmentation pattern of the 1,9-dideuterioderivative. The composition of m/e 140 was determined by high resolution measurement to be $C_{10}H_6N$ and not $C_{11}H_7$ as previously reported.

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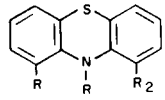
The mass spectra of phenothiazine and its derivatives have been the subject of numerous investigations [3-9]. Because of our interest in the electron impact induced fragmentation of tetracyclic phenothiazine derivatives [10,11], we decided to reinvestigate the behavior of the simpler tricyclic system in order to clarify some of the secondary fragmentation processes. We, therefore, investigated phenothiazine (**1**), two of its analogues, **3** and **4**, and the deuterated derivatives **2** and **5**.



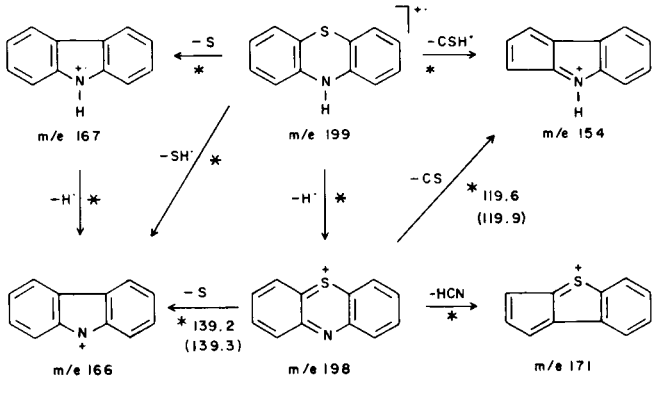
1 R = R_1 = R_2 = H
2 R = H, R_1 = R_2 = D
3 R = R_1 = H, R_2 = Cl
4 R = $COCH_3$, R_1 = R_2 = H
5 R = $COCH_3$, R_1 = R_2 = D

Primary fragmentation pathways for **1** had, for the most part been previously described by Audier, *et al.* [3] and later confirmed, with the aid of metastable ion studies and exact mass measurements, by Gilbert and Millard [7]. Thus, the spectrum of **1** is characterized by an intense molecular ion (base peak), a moderately intense M-1 ion (M/2, 9.5% relative intensity), and a doubly charged molecular ion (M/2, 9.5% relative intensity). Loss of neutral sulfur containing fragments (S, ·SH and C=S) from the molecular ion has been shown (metastable studies) to give rise to fragment ions at m/e 167, 166 and 154 [7]. The low intensity m/e 171 ion, on the other hand, is derived exclusively from m/e 198 [7]. Our investigation shows that the M-1 ion is also a source of m/e 166 (m* = 139.2) and m/e 154 (m* = 119.6) ions. Fragmentation pathways for the M and M-1 ions are summarized in Scheme 1.

A few secondary fragmentation pathways for **1** had also been previously established by metastable ion studies [7]. Thus, the m/e 167 ion is a source of m/e 140 and the m/e 139 ion is derived from m/e 166. However, an exact mass measurement (peak matching) clearly shows that the peak at m/e 140 is a singlet having the composition $C_{10}H_6N$ with no evidence for the existence of the isoelectronic $C_{11}H_8$ ion. This result is in agreement with studies on carbazole fragmentation [1,12]. Further, our metastable ion measurements indicate that m/e 166 is also a source of m/e 140 (m* = 118.1) and m/e 139 is also derived from m/e 167 (m* = 115.6).

The fate of the m/e 171 ion had not previously been investigated. Since this low intensity ion is derived exclusively from the M-1 ion of **1**, we sought an analogue that would provide a more intense source of the m/e 198 ion. In the spectrum of 1-chlorophenothiazine (**3**), the relative intensities of m/e 198 (M-35) and its daughter ion m/e 171 are 80% and 11.5%, respectively. The mass spectrum of **3** therefore, provided a means of studying the fragmentation of m/e 198 and 171 ions, independently (it is assumed that a facile C→N hydrogen atom shift in the M-35 ion occurs). Metastable ion studies indicate that daughter ions m/e 139 (m* = 112.9) and m/e 127 (m* = 94.1) are formed from m/e 171. Previous work had shown that m/e 154 is also a source of m/e 127 as well as m/e 128 [7]. Secondary fragmentation pathways for **1** are summarized in Scheme 2.

Scheme I



The observation that **3** is a source of m/e 198 also allows an estimate of the relative contributions made by the M and M-1 ions to the formation of daughter ions mutually derived from them (*i.e.*, m/e 167, 166, 154, 140 and 139) when phenothiazine (**1**) is subjected to electron impact. Since m/e 198 is the sole source of these ions in the mass spectrum of **3**, an adjustment for its relative intensity in the mass spectrum of **1** should provide the relative contribution from the M-1 ion. The results, summarized in Table 1, show that m/e 198 is an important contributor to the formation of the m/e 154 ion (33%) and contributes about 10% to the formation of m/e 166, 140 and 139 ions. The carbazole radical ion (m/e 167), on the other hand, is derived almost exclusively from the molecular ion.

The mass spectral fragmentation of 10-acetyl phenothiazine (**4**) had been reported previously by Heiss and Zeller [8]. The major fragmenation process for this compound involves the loss of ketene ($CH_2=C=O$) to form the molecular ion of phenothiazine (m/e 199). Hydrogen transfer from the methyl group to the 1(9)-positions of **4**, followed by expulsion of ketene, was invoked as a mechanism to explain this facile process [8]. However, fragmentaion of the corresponding 1,9-dideuterio derivative **5** gave nearly the same distribution of M-42 and M-42-1 ions (relative intensities 100% and 65%) and no loss of deuterium (M-42-2; m/e 198). If hydrogen atom transfer to the 1(9)-positions had occurred, then some loss of deuterium following the expulsion of ketene would surely have occurred. We, therefore, alternatively propose that hydrogen transfer to nitrogen initially must occur, followed by expulsion of ketene as shown in Scheme 3.

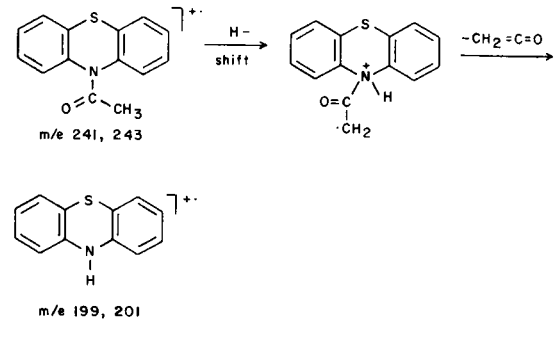
Table 1

Sources of Daughter Ions

Daughter ion (m/e)	Parent Ion (%) Contribution of M (m/e 199)	Contribution of M-1 (m/e 198)
167	99.5	0.5
166	90	10
154	67	33
140	90	10
139	91	9

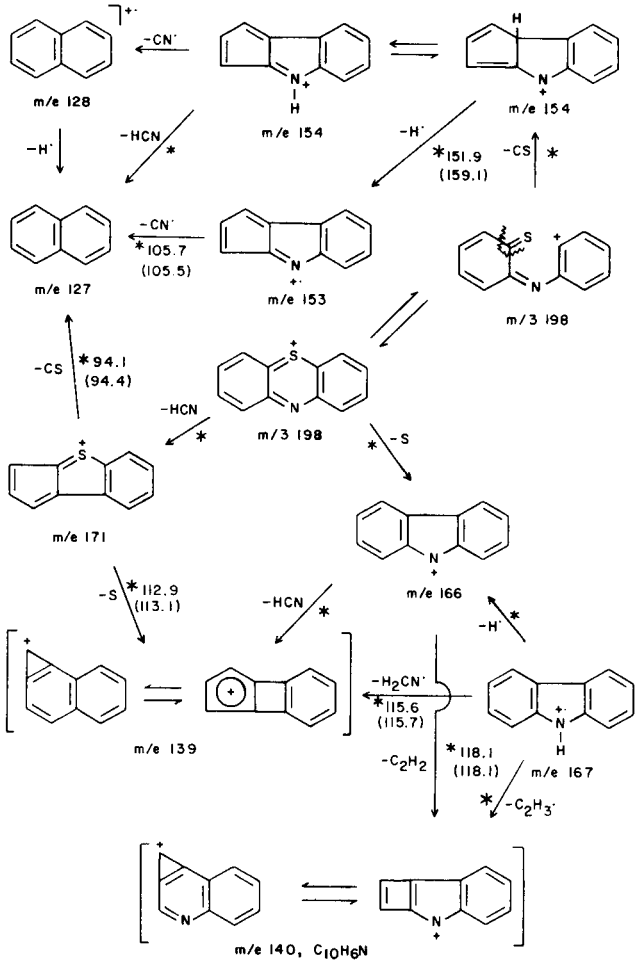
The spectrum of 1,9-dideuteriophenothiazine (**2**) shows evidence of deuterium scrambling in the expulsion of hydrogen cyanide (as HCN or $H_2CN\cdot$) from the m/e 198, 167 and 166 ions. Thus, ions corresponding to the loss of no deuterium (HCN or $H_2CN\cdot$) and one deuterium (DCN or DHCN·) from these ions are seen. On the other hand, little or no deuterium loss is apparent in the expulsion of sulfur containing radicals (SH· and CSH·) from the molecular ion. A mechanism consistent with deuterium scrambling in the release of HCN from the M-1 ion of **2** is shown in Scheme 4. Skeletal rearrangement of the M-1 ion to form the spiropentadienylbenzothiazine ion **1** is envisioned to occur initially, followed by a hydrogen (or deuterium) shift to give **a′**. Skeletal rearrangement of **a′** then forms ion **b**, which can then expell HCN (or DCN) to give the m/e 171 ion.

Scheme 3

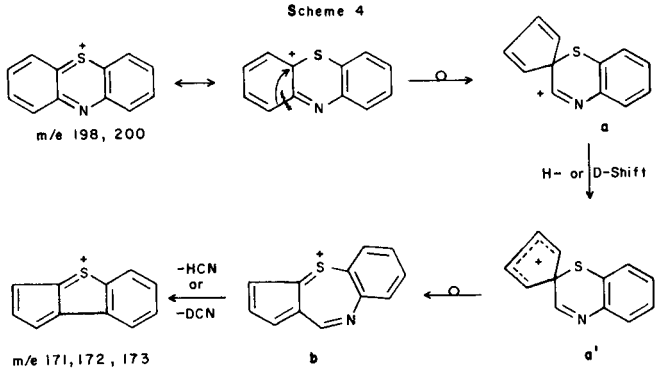


Mechanisms consistent with deuterium retention in the expulsion of SH· and CSH· from the molecular ion of **2** are given in Scheme 5. Both processes are believed to be initiated by a nitrogen-to-sulfur hydrogen atom shift to form ion **c**. Skeletal rearrangement of **c** to form **d** (path i) then occurs, followed by expulsion of SH· to form m/e 168. Alternatively, the intermediate ion radical **e**, formed from

Scheme 2

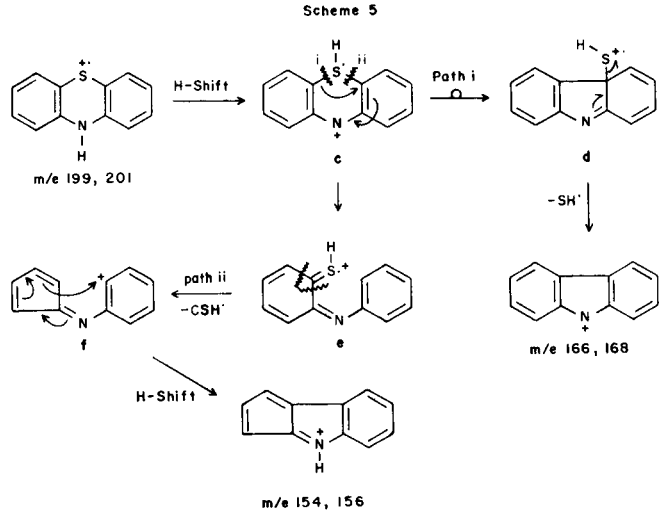


Scheme 4



rupture of the carbon-sulfur bond, can expell CSH· radical to form ion **f** (path ii). An additional ring closure, accompanied by a carbon to nitrogen shift of hydrogen gives m/e 156.

Scheme 5



EXPERIMENTAL

The mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer at 70 eV. The samples were introduced by a direct inlet probe and were heated at a rate of about 450° in 200 seconds. The metastable ion spectra were obtained by focusing on the parent ion and scanning the electrostatic sector and magnetic fields in the first field free region of the spectrum at a rate such that the ratio E/B remained constant at a constant accelerating voltage. The high resolution spectra were recorded at a resolution of 7000 and processed with a Varian SS-200 data system. The temperature was raised manually to obtain the optimum spectrum. Compound purity was checked by tlc and gc (Varian model 3700) with fid.

The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker WH-250 NMR Spectrometer at a frequency of 250.13 MHz (data point resolution 0.37 Hz) and 62.9 MHz (data point resolution 1.8 Hz) respectively. A 5 mm ^{1}H probe and a 10 mm broadband probe (32-105 MHz) were used. The samples were run as 0.5 *M* solutions and tetramethylsilane was used as internal standard.

Phenothiazine (**1**).

Phenothiazine (Aldrich Chemical Co.) was purified by sublimation, mp 183-186° (lit [13] mp 183-185°); ms m/e (%): 201 (M + 2, 5.7), 200 (M + 1, 15.9), 199 (M, 100%), 198 (18.8), 197 (3.7), 196 (1.9), 172 (1.5), 171 (4.6), 168 (8.6), 167 (65.4), 166 (22.4), 165 (1.4), 164 (1.6), 155 (3.4), 154 (12.8), 153 (1.9), 140 (6.3), 139 (6.6), 128 (3.6), 127 (5.4), 126 (1.4), 122 (1.2), 155 (1.5), 113 (1.0), 108 (1.5), 102 (1.2), 101 (1.4), 100 (1.6), 99.5 (8.3), 99 (1.4), 98.5 (2.8), 95 (1.7), 93 (1.2), 89 (1.6), 87 (1.0), 86.5 (2.5), 86 (1.2), 85.5 (1.1), 85 (1.0), 82 (2.0), 78 (1.5), 77.5 (1.7), 77 (5.6), 76 (2.2), 75 (2.6), 74 (2.6), 71 (1.0), 70 (2.2), 69 (8.8), 65 (2.5), 64 (2.1), 63 (6.4), 63 (2.3), 61 (1.3), 58 (1.2), 52 (2.3), 51 (5.2), 50 (5.5).

1,9-Dideuteriophenothiazine (**2**).

This compound was reported by us previously [14] and had mp 187-189° (phenothiazine, lit 183-186°). No traces of either undeuterated or monodueterated compound could be detected in either the ^{1}H-nmr or ^{13}C-nmr spectra [14]; ms m/e (%): 203 (M + 2, 5.3), 202 (M + 1, 23.1), 201 (M +, 100), 200 (18.5), 199 (8.1), 198 (4.2), 197 (1.5), 174 (2.1), 173 (5.6), 172 (2.5), 171 (2.4), 170 (15.8), 169 (76.6), 168 (21.7), 167 (6.4), 166 (2.4), 165 (1.2), 157 (4.3), 156 (16.1), 155 (4.5), 154 (2.5), 147 (1.2), 146 (1.0), 143 (1.3), 142 (7.0), 141 (12.4), 140 (4.8), 139 (1.7), 130 (4.2), 129 (10.6), 128 (4.8), 127 (2.0), 123 (1.7), 117 (2.5), 116 (2.1), 115 (2.4), 114 (2.0), 110 (1.2), 109 (2.5), 104 (1.5), 103 (1.9), 102 (2.3), 101 (3.8), 100.5 (11.6), 100 (2.2), 99.5 (3.2), 99 (1.4), 97 (1.6), 96 (2.4), 95 (1.6), 94 (1.3), 93 (1.6), 91 (2.4), 90 (2.7), 989 (1.9), 88 (2.3), 87.5 (3.1), 87 (4.3), 86.5 (1.6), 86 (2.4), 85.5 (1.1), 85 (1.1), 84.5 (2.6), 84 (1.0), 83.5 (1.0), 83 (2.5), 82 (2.0), 79 (4.6), 78.5 (3.4), 78 (8.4), 77.5 (2.0), 77 (5.6), 76 (4.3), 75 (4.5), 74 (3.1), 73 (1.2), 72 (1.9), 71.5 (1.4), 71 (1.8), 71 (3.9), 70.5 (2.2), 70 (6.4), 69 (10.7), 67 (1.6), 66 (4.5), 65 (4.3), 64 (9.1), 63 (6.5), 62 (2.5), 61 (1.4), 59 (1.0), 58 (1.7), 57 (1.6), 55 (1.7), 54 (1.2), 53 (3.3), 52 (8.7), 51 (8.8), 50 (4.7).

Anal. High resolution ms: m/e Calcd. for $C_{12}H_7D_2NS$: 201.0581; Found 201.0567.

1-Chlorophenothiazine (**3**).

We have developed an improved synthesis of this compound [16], which had been previously prepared by a different method. It has mp 92-93° (lit [15] mp 92-93°); ms m/e (%): 235 (M + 2, 38.6), 234 (M + 1, 18.0), 233 (M, 100%), 232 (8.4), 204 (1.0), 203 (7.8), 202 (4.8), 201 (25.1), 200 (9.6), 199 (12.2), 198 (80.1), 197 (14.9), 196 (13.3), 190 (1.1), 188 (3.3), 173 (1.6), 172 (2.2), 171 (11.5), 170 (2.9), 169 (2.8), 167 (1.4), 166 (8.73), 165 (4.1), 164 (6.2), 155 (2.1), 154 (17.2), 153 (5.4), 152 (4.5), 146 (1.0), 145 (1.0), 140 (2.3), 139 (2.3), 138 (2.2), 128 (2.4), 127 (4.6), 126 (3.3), 125 (2.2), 120 (1.3), 117.5 (3.4), 117 (1.7), 116 (9.1), 114 (1.1), 113 (1.1), 108 (1.8), 107 (1.0), 102 (1.5), 101 (1.5), 100 (1.2), 99 (4.6), 98.5 (11.8), 98 (1.8), 97.5 (1.0), 95 (2.0), 94 (1.5), 93 (2.5), 89 (1.1), 88 (1.4), 87 (1.4), 86 (1.6), 85.5 (3.7), 85 (4.9), 84.5 (1.8), 84 (1.7), 82 (1.7), 77 (4.2), 76.5 (1.2), 76 (3.4), 75 (5.5), 74 (4.3), 73 (1.8), 72 (1.2), 70 (2.2), 69 (10.1), 65 (1.5), 64 (2.0), 63 (9.9), 62 (4.0), 61 (2.2), 58 (1.4), 55 (1.1), 52 (2.5), 51 (4.9), 50 (6.4).

10-Acetylphenothiazine (**4**).

This compound is reported in the literature [17]. It has mp 198-202°; ms m/e (%): low resolution; 243 (M + 2, 1.7), 242 (M + 1, 3.6), 241 (M, 19.5), 202 (1.1), 201 (7.6), 200 (17.7), 199 (100.0), 198 (64.8), 197 (8.9), 196 (5.9), 173 (1.0), 172 (3.1), 171 (8.6), 170 (2.2), 169 (2.4), 168 (4.6), 167 (31.9), 166 (14.0), 165 (1.4), 164 (2.6), 159 (1.1), 155 (3.9), 154 (23.1), 153 (5.3), 152 (2.4), 146 (1.8), 145 (1.5), 141 (1.4), 140 (8.5), 139 (7.0), 138 (1.8), 129 (1.5), 128 (8.8), 127 (15.0), 126 (4.0), 125 (1.6), 122 (1.1), 116 (1.1), 115 (2.7), 114 (1.6), 113 (2.3), 109 (1.2), 108 (3.2), 102 (2.0), 101 (3.5), 100 (1.1), 99.5 (2.0), 99 (2.5), 98.5 (2.5), 96 (1.6), 95 (3.5), 94 (1.3), 93 (1.9), 92 (2.6), 91 (5.1), 89 (3.0), 88 (1.5), 87 (1.6), 82 (4.3), 78 (2.2), 77 (7.9), 76 (4.2), 75 (5.1), 74 (3.2), 71 (3.7), 70 (4.0), 69 (16.1), 65 (3.8), 64 (2.7), 63 (11.3), 62 (2.8), 61 (1.2), 58 (2.80), 57 (1.4), 55 (1.3), 52 (2.4), 51 (8.7), 50 (8.2).

10-Acetyl-1,9-dideuteriophenothiazine (**5**).

One half g (0.0025 mole) of 1,9-dideuteriophenothiazine (**2**) was added to a mixture of 0.75 g (0.007 mole) of acetic anhydride and 0.34 g (0.0025 mole) of zinc chloride in 100 ml of toluene and the mixture was stirred and heated to reflux. After 18 hours the mixture was cooled and the clear solution was decanted from the pasty film formed in the bottom of the flask, and washed with water three times (50 ml portion), then dried over magnesium sulfate. Evaporation of the solvent *in vacuo* (aspirator) gave a

pale yellow solid, mp 199-202°, ms: m/e (%): 244 (M + 1, 2.9), 243 (M, 16.0), 203 (5.70), 202 (21.6), 201 (100.0), 200 (62.7), 199 (11.8), 198 (7.4), 197 (2.0), 187 (1.7), 185 (1.0), 175 (1.0), 174 (3.0), 173 (8.1), 172 (5.5), 171 (2.5), 170 (9.5), 169 (30.2), 168 (16.5), 167 (5.6), 166 (2.5), 165 (1.2), 157 (5.0), 156 (22.2), 155 (6.7), 154 (3.5), 153 (1.5), 147 (1.4), 146 (1.4), 143 (1.2), 142 (7.9), 141 (9.6), 140 (4.2), 139 (3.1), 135 (1.2), 131 (1.0), 130 (7.3), 129 (143.9), 128 (7.0), 127 (3.1), 126 (1.1), 123 (1.2), 121 (1.1), 117 (2.9), 116 (2.5), 115 (2.4), 114 (2.2), 111 (1.0), 110 (1.3), 109 (3.8), 104 (1.9), 103 (2.5), 102 (3.0), 101 (1.5), 100.5 (2.7), 100 (3.4), 99.5 (2.7), 99 (1.3), 97 (1.7), 96 (2.4), 95 (1.7), 94 (2.3), 93 (1.8), 92 (4.3), 91 (9.5), 90 (3.2), 89 (3.0), 88 (2.3), 87 (3.5), 86.5 (1.5), 86 (2.5), 85 (1.4), 84.5 (1.9), 83 (3.2), 82 (2.8), 81 (1.0), 79 (4.2), 78.5 (1.4), 78 (9.2), 77 (5.4), 76 (6.8), 75 (6.9), 74 (4.2), 73 (1.7), 72 (2.0), 71.5 (1.0), 71 (4.3), 70 (6.6), 69 (12.0), 67 (1.6), 66 (3.3), 65 (5.9), 64 (9.0), 63 (6.0), 62 (4.3), 61 (2.2), 60 (1.1), 59 (1.3), 58 (2.3), 57 (3.4), 55 (2.7), 53 (3.6), 52 (6.6), 51 (8.4), 50 (4.6), 47 (1.2).

Anal. High resolution ms: m/e Calcd. for $C_{14}H_9D_2NS$: 243.0687; Found: C, 243.0682.

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