Mass Spectra of 9H-Xanthene and 9H-Thioxanthene Derivatives

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The mass spectra (MS) of 9-(1H-benzimidazol-2-ylmethyl)-9H-xanthene (1), 9-(1H-benzimidazol-2-ylmethyl)-9H-thioxanthene derivatives (2), and the 10-oxide (3) and 10,10-dioxide (4) derivatives of 2 were measured by electron ionization.

The MS of 1 and 2 showed a peak corresponding to the loss of the substituent at the 9-position and a peak at m/z 152. The MS of 3 showed peaks corresponding to the loss of OH radical, the 1H-benzimidazol-2-ylmethyl group at the 9-position, and the oxygen atom. The MS of 4 showed peaks corresponding to the loss of OH radical, the 1H-benzimidazol-2-ylmethyl group at the 9-position, and SO₂.

Keywords 9-(1H-benzimidazol-2-ylmethyl)-9H-xanthene; 9-(1H-benzimidazol-2-ylmethyl)-9H-thioxanthene; 9-(1H-benzimidazol-2-ylmethyl)-9H-thioxanthene 10-oxide; 9-(1H-benzimidazol-2-ylmethyl)-9H-thioxanthene 10,10-dioxide; mass spectrometry; mass fragmentation; stereochemistry

The mass spectra (MS) of 9H-xanthene, 9H-thioxanthene and 9H-thioxanthene 10,10-dioxide were investigated previously.^{1,2)} However, no report has appeared on the MS of 9-substituted 9H-xanthene and 9H-thioxanthene derivatives. The sulfur-containing analogues exhibit valuable pharmacological activity; for example, chlorpromazine (a 10-substituted phenothiazine derivative) and thiothixene (an 9-alkylenethioxanthene derivative) are useful tranquilizers. As a part of a continuing study on the relationships between structure and biological activity, the present paper deals with the study of the MS fragmentations of 9-(1H-benzimidazol-2-ylmethyl)-9H-xanthene and 9-(1H-benzimidazol-2-ylmethyl)-9H-thioxanthene and their derivatives (1-4), and the relationships between the structure and MS.

Experimental

The compounds used in the present investigation are shown in Chart 1. They were synthesized according to the procedure described in our previous papers.³⁾ 9-(1H-Benzimidazol-2-ylmethyl)-9H-9-deuteriothioxanthene 10-oxide (5) was prepared from 9H-thioxanthene-9-ol by the use of sodium borodeuteride instead of sodium borohydride in the preparation of 9H-thioxanthene-9-ol,⁴⁾ in a manner similar to that described for the preparation of 3. The deuterium composition, determined by mass spectrometry, was 9% d_0 and 91% d_1 . 9-(1H-Benzimidazol-2-ylmethyl)-9H-thioxanthene 10,10-dioxide (6) was prepared from 9H-thioxanthene-9-ol and malonic- d_4 acid in a manner similar to that described for the preparation of 3. The deuterium composition, determined by mass spectrometry, was 51% d_0 , 38% d_1 and 11% d_2 .

Chart 1

MS were measured with a Hitachi RMU-7MG double-focusing mass spectrometer under the following conditions; ionization energy, 70 eV; ionization current, 80 μ A; accelerating voltage, 3 kV. The temperature of the ion source was approximately 180 °C. All the samples were introduced with a direct insertion probe.

Results and Discussion

MS of 9-(1H-Benzimidazol-2-ylmethyl)-9H-xanthene (1) and 9-(1H-Benzimidazol-2-ylmethyl)-9H-thioxanthene (2) MS of 1 and 2 are shown in Fig. 1. The elemental compositions of the fragment ions were established by high-resolution mass spectrometry (Table I). For compound 1,

Fig. 1. MS of Compounds 1 and 2

the following fragmentations were observed (Chart 2): expulsion of 1*H*-benzimidazole and 1*H*-benzimidazol-2-ylmethyl radical produced the ions at m/z 194 and 181, respectively. Similar fragmentations were observed in the spectrum of **2** (Chart 2).

An important process in the MS of **1** involves formation of the ion at m/z 181. This ion corresponds to the fragment ion at m/z 197 which was formed from **2**. In **2**, the oxygen at the 10-position is replaced by a sulfur. Therefore, the

Chart 2

TABLE I. High-Resolution MS Data for Xanthenes and Thioxanthenes

Compd.	Ion (m/z)	Elemental composition	Calcd (m/z)	Observed (m/z)	Error (mu)
1	312	C ₂₁ H ₁₆ N ₂ O	312.1261	312.1259	-0.2
	181	C ₁₃ H ₉ O	181.0653	181.0657	0.4
	152	C ₁₂ H ₈	152.0625	152.0612	-1.3
2	328	C ₂₁ H ₁₆ N ₂ S	328.1033	328.1049	1.6
	197	C ₁₃ H ₉ S	197.0423	197.0417	-0.6
	165	C ₁₃ H ₉	165.0704	165.0715	1.1
	152	C ₁₂ H ₈	152.0626	152.0632	0.6

difference of 16 mass units between these two ions indicates that this fragment ion is involved in the expulsion of the 1*H*-benzimidazol-2-ylmethyl radicals from **1** and **2**.

The ion at m/z 152, obtained from **1** and **2**, is formed from the ions at m/z 181 and m/z 197 by the loss of CHO and CHS radicals, respectively. These processes, represented in Chart 2, are also observed in the MS of 9*H*-xanthene and 9*H*-thioxanthene.¹⁾

Another ion at m/z 194, observed in the MS of **1**, may be formed from the molecular ion by the expulsion of the neutral fragment 1*H*-benzimidazole. But the counterpart of this ion was not observed in the MS of **2**. Furthermore, the ion at m/z 165, observed in the MS of **2**, was formed from the ion at m/z 197 by the loss of S. This process was also observed in the MS of 9*H*-thioxanthene. But no counterpart was observed in the MS of **1**. All these processes were confirmed by the method of metastable defocusing.

MS of 9-(1*H*-Benzimidazol-2-ylmethyl)-9*H*-thioxanthene 10-Oxide (3**) and 9-(1*H*-Benzimidazol-2-ylmethyl)-9*H*-thioxanthene 10,10-Dioxide (**4**)** MS of **3** and **4** are shown in

TABLE II. High-Resolution MS Data for Thioxanthene Oxide and Dioxide Derivatives

Compd.	Ion (m/z)	Elemental composition	Calcd (m/z)	Observed (m/z)	Error (mu)
3	344	C ₂₁ H ₁₆ N ₂ OS	344.0982	344.0998	1.6
	328	C ₂₁ H ₁₆ N ₂ S	328.1033	328.1019	-1.4
	327	C ₂₁ H ₁₅ N ₂ S	327.0954	327.0946	-0.8
	325	C ₂₁ H ₁₃ N ₂ S	325.0798	325.0772	-2.6
	197	C ₁₃ H ₉ S	197.0424	197.0445	2.1
	165	C ₁₃ H ₉	165.0703	165.0695	-0.8
	147	C ₈ H ₇ N ₂ O	147.0558	147.0571	1.3
	131	C ₈ H ₇ N ₂	131.0609	131.0627	1.8
	360	C ₂₁ H ₁₆ N ₂ O ₂ S	360.0930	360.0915	-1.5
	343	C ₂₁ H ₁₅ N ₂ OS	343.0904	343.0885	-1.9
4	296	C ₂₁ H ₁₆ N ₂	296.1312	296.1311	-0.1
	229	C ₁₃ H ₉ O ₂ S	229.0322	229.0328	0.6
	219	C ₁₅ H ₁₁ N ₂	219.0922	219.0924	0.2
	197	C ₁₃ H ₉ S	197.0424	197.0417	-0.7
	181	C ₁₃ H ₉ O	181.0653	181.0662	0.9
	178	C ₁₄ H ₁₀	178.0781	178.0773	-0.8
	165	C ₁₃ H ₉	165.0704	165.0707	0.3
	152	C ₁₂ H ₈	152.0625	152.0627	0.2
	131	C ₈ H ₇ N ₂	131.0608	131.0605	-0.3

Fig. 2. MS of Compounds **3** and **4**

TABLE III. Relative Intensities (%) of Some MS Peaks of **3** and Its Deuterium Analogues **5** and **6**

Compd.	346	m/z 345	344	329	m/z 328	327
3	8.9	25.7	100	12.7	54.4	100
5	27.3	100	10.6	57.6	100	37.9
6	49.2	100	99.2	22.2	58.0	100

(A—D) of 9-substituted 9*H*-thioxanthene 10-oxide may exist from configurational and conformational standpoints, as shown in Chart 5. In this compound the bulk of the substituent at the 9-position is presumed to control the conformational distribution. Consequently, this compound exists in conformer B or C. Thus, since the 1*H*-benzimidazol-2-ylmethyl group prefers the (less-hindered) pseudoaxial orientation, compound **3** is expected to favor conformer B or C. Then, in order to determine the origin of the hydrogen atom of the OH radical, the 9-deuterium analogue (**5**) was synthesized. Examination of the MS of **5** reveals that the peak at m/z 327 is shifted to one mass unit higher to the extent of about 77% (Table III). This indicates that about 23% of the hydrogen for the OH radical is derived from the hydrogen atom at the 9-position, and the greater part results from the other hydrogen atom. Moreover, the 11-deuterium analogue (**6**) was synthesized and its MS was measured. The result indicates that the peak at m/z 327 is shifted the one mass higher to the extent of about 60.8%. The origin of the hydrogen for the OH radical is the hydrogen atom at the 11-position to the extent of 78.4%. The possible conformers which undergo loss of OH radical of **3** are conformers B and D. In this case it seems that the conformer C is inverted to conformer D by ionization energy in the mass spectrometer. From the results, the hydrogen atom of the OH radical is mainly the hydrogen atom from the 11-position and partly that from the 9-position, and **3** exists mainly in conformer B and partly in conformer C.

In **4** as well as **3** the ion at m/z 343 is formed from the molecular ion by loss of the OH radical. Furthermore, the ion at m/z 327 in **3** loses a hydrogen molecule to give the ion at m/z 325, which forms the ion at m/z 293 by loss of S. Similarly, in **4** the ion at m/z 343 loses a hydrogen molecule to give the ion at m/z 341, but the ion at m/z 309 corresponding to the ion at m/z 293 in **3** (formed by loss of

S) is not observed.

The molecular ions of **3** and **4** decompose into the ions at m/z 213 and 229 by elimination of a 1*H*-benzimidazol-2-ylmethyl radical, respectively. These intermediate ions at m/z 213 and 229 show the stable conjugated structure of the 10-thioxanthene cation. These ions decompose into an ion at m/z 197 by loss of O and O₂ molecule, respectively. In the MS of **3**, the ion at m/z 197 is the base peak, but in **4** this ion is a weak peak. The ion at m/z 197 further loses S to give the ion at m/z 165 and loses the CHS radical to give the ion at m/z 152. In **3** the ion at m/z 165 has a high intensity, but in **4** the ion at m/z 165 shows a weak intensity. In **4** the peak at m/z 152 is a weak one, as in **2**.

In **4** the ion at m/z 229 gives rise to the rearrangement and the loss of SO to give the ion at m/z 181, which loses CHO to give the ion at m/z 152. In another pathway the ion at m/z 229 in **4** gives the ion at m/z 165 by loss of SO₂. Further, in **4** the molecular ion gives the ion at m/z 296 by loss of SO₂. This ion at m/z 296 forms the ion at m/z 178 by elimination of 1*H*-benzimidazole. On the other hand, the ion at m/z 296 gives the ion at m/z 165 by loss of the 1*H*-benzimidazol-2-ylmethyl radical. The molecular ion of **4** gives the ion at m/z 219 by loss of C₆H₅O₂S. Formation of this ion involves rupture of the C–S bond and rearrangement.

In **3** the molecular ion gives the ion at m/z 328 by loss of O. This ion at m/z 328 further gives the ion at m/z 197 by loss of 1*H*-benzimidazol-2-ylmethyl radical. The molecular ion of **3** also gives the ion at m/z 147 by rearrangement of the 1*H*-benzimidazol-2-ylmethyl group to the oxygen of S–O, rupture of the S–O bond and loss of the 9*H*-thioxanthene radical.

All these processes were confirmed by the method of metastable defocusing.

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