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

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The mass spectra (MS) of 9-(1*H*-benzimidazol-2-ylmethyl)-9*H*-xanthene (1), 9-(1*H*-benzimidazol-2-ylmethyl)-9*H*-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 1*H*-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 1*H*-benzimidazol-2-ylmethyl group at the 9-position, and SO_2.

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

The mass spectra (MS) of 9*H*-xanthene, 9*H*-thioxanthene and 9*H*-thioxanthene 10,10-dioxide were investigated previously.[1,2] However, no report has appeared on the MS of 9-substituted 9*H*-xanthene and 9*H*-thioxanthene derivatives. The sulfur-containing analogues exhibit valuable pharmacological activity; for example, chlorpromazine (a 10-substituted phenothiazine derivative) and thiothixene (an 9-alkylidenethioxanthene 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-(1*H*-benzimidazol-2-ylmethyl)-9*H*-xanthene and 9-(1*H*-benzimidazol-2-ylmethyl)-9*H*-thioxanthene and their derivatives (**1**—**4**), and the relationships between the structure and MS.

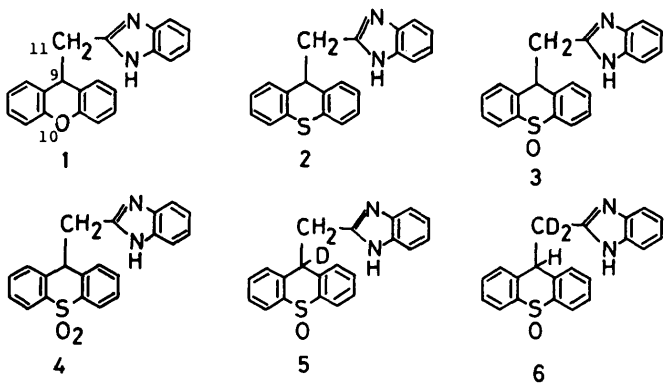

Chart 1

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-(1*H*-Benzimidazol-2-ylmethyl)-9*H*-9-deuteriothioxanthene 10-oxide (**5**) was prepared from 9*H*-thioxanthen-9-ol by the use of sodium borodeuteride instead of sodium borohydride in the preparation of 9*H*-thioxanthen-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-(1*H*-Benzimidazol-2-yldideuteriomethyl)-9*H*-thioxanthene 10-oxide (**6**) was prepared from 9*H*-thioxanthen-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.

MS were measured with a Hitachi RMU-7MG double-focusing mass spectrometer under the following conditions; ionization energy, 70 eV; ionization current, 80 μA; 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-(1*H*-Benzimidazol-2-ylmethyl)-9*H*-xanthene (1) and 9-(1*H*-Benzimidazol-2-ylmethyl)-9*H*-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**,

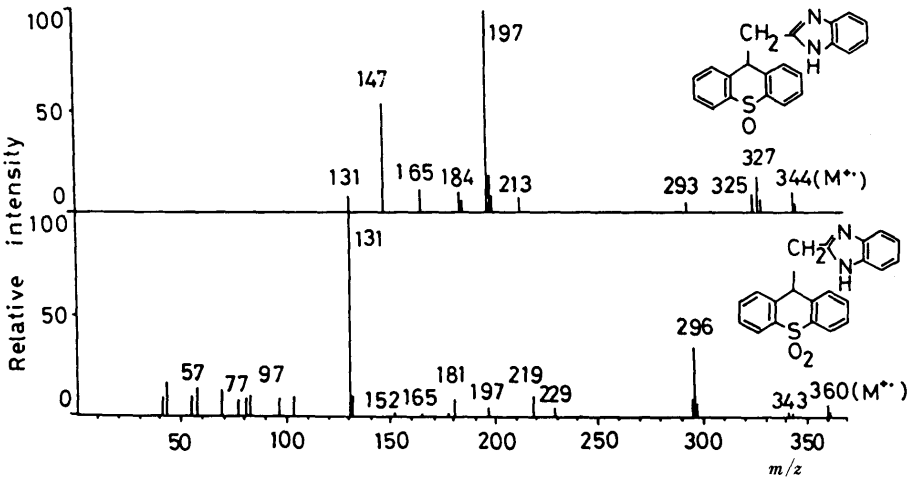

Fig. 1. MS of Compounds **1** and **2**

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 difference of 16 mass units between these two ions indicates that this fragment ion is involved in the explusion 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.

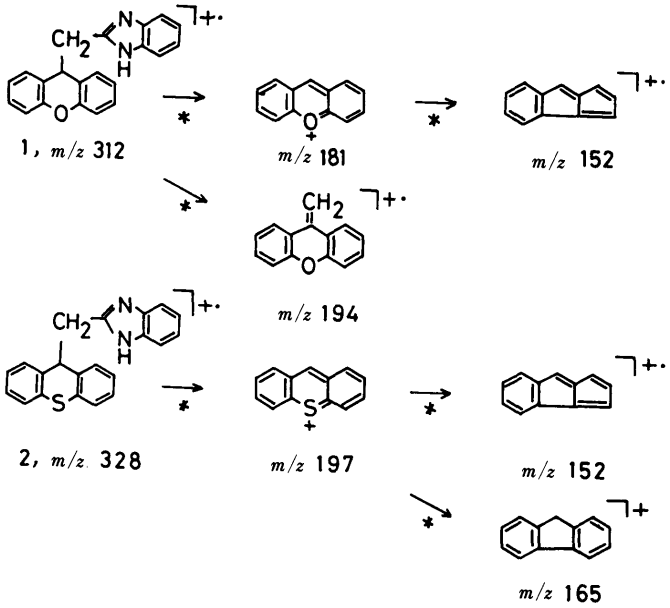

Chart 2

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 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	$C_{21}H_{16}N_2O$	312.1261	312.1259	−0.2
	181	$C_{13}H_9O$	181.0653	181.0657	0.4
	152	$C_{12}H_8$	152.0625	152.0612	−1.3
2	328	$C_{21}H_{16}N_2S$	328.1033	328.1049	1.6
	197	$C_{13}H_9S$	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

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	$C_{21}H_{16}N_2OS$	344.0982	344.0998	1.6
	328	$C_{21}H_{16}N_2S$	328.1033	328.1019	−1.4
	327	$C_{21}H_{15}N_2S$	327.0954	327.0946	−0.8
	325	$C_{21}H_{13}N_2S$	325.0798	325.0772	−2.6
	197	$C_{13}H_9S$	197.0424	197.0445	2.1
	165	$C_{13}H_9$	165.0703	165.0695	−0.8
	147	$C_8H_7N_2O$	147.0558	147.0571	1.3
	131	$C_8H_7N_2$	131.0609	131.0627	1.8
4	360	$C_{21}H_{16}N_2O_2S$	360.0930	360.0915	−1.5
	343	$C_{21}H_{15}N_2OS$	343.0904	343.0885	−1.9
	296	$C_{21}H_{16}N_2$	296.1312	296.1311	−0.1
	229	$C_{13}H_9O_2S$	229.0322	229.0328	0.6
	219	$C_{15}H_{11}N_2$	219.0922	219.0924	0.2
	197	$C_{13}H_9S$	197.0424	197.0417	−0.7
	181	$C_{13}H_9O$	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	$C_8H_7N_2$	131.0608	131.0605	−0.3

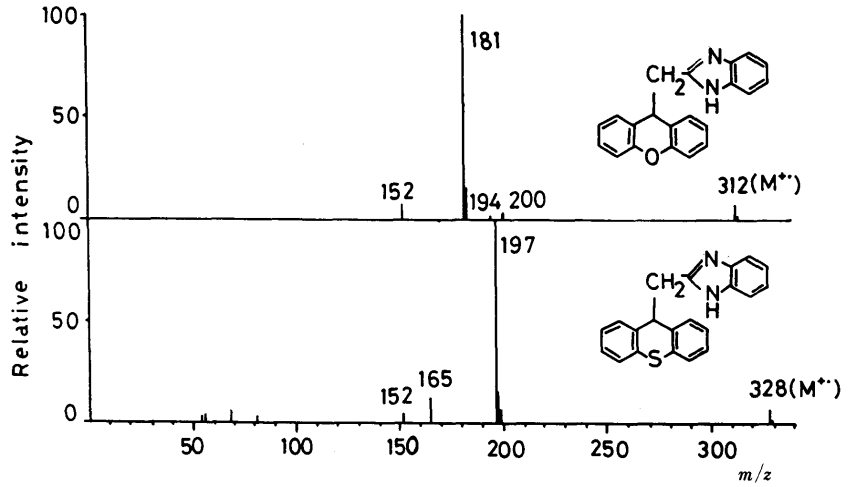

Fig. 2. MS of Compounds **3** and **4**

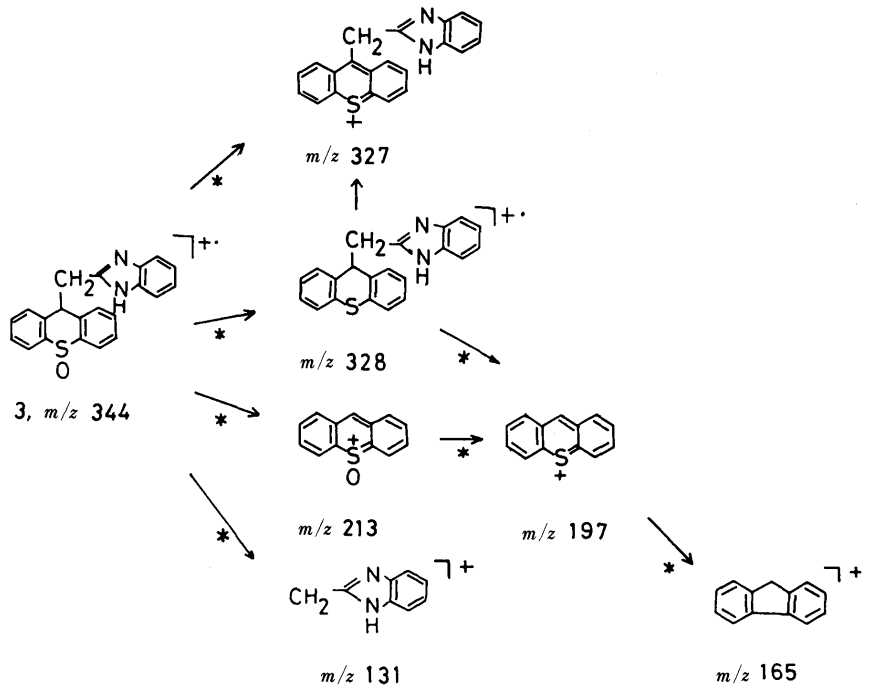

Chart 3

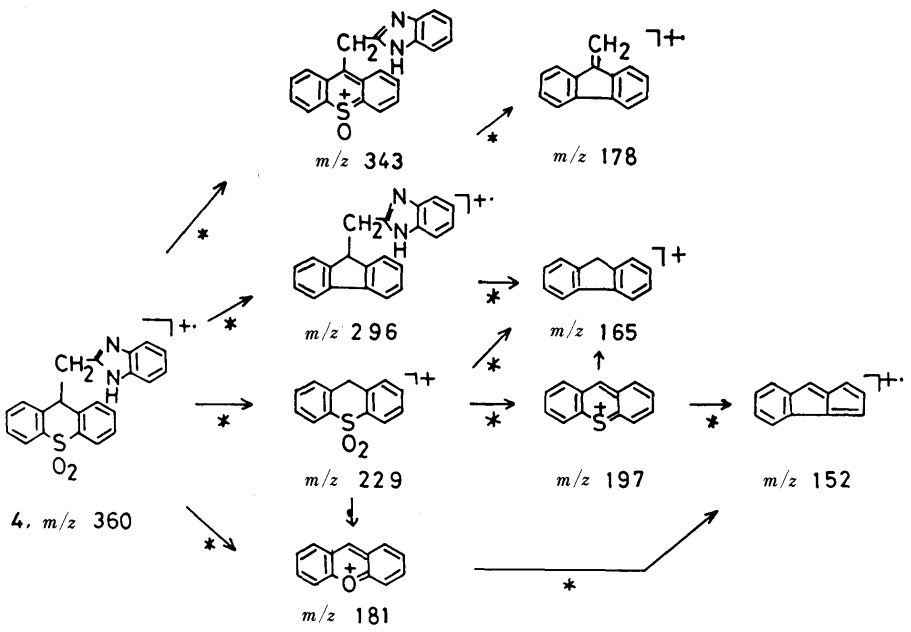

Chart 4

Fig. 2, and these fragmentations are shown in Charts 3 and 4. The elemental compositions of the fragment ions are established by high-resolution mass spectrometry (Table II). The relative intensities of molecular ions were generally weak.

In **3** the ion at *m/z* 327 is formed from the molecular ion by loss of OH radical accompanied with rearrangement of a hydrogen atom. The migrating hydrogen atom seems to be the hydrogen atom at the 9- or 11-position of the 9*H*-thioxanthene 10-oxide derivative. Conformational data on 9-substituted 9*H*-thioxanthene 10-oxide have recently been presented in the literature.[5] In particular, we are interested in 9-(1-methylpiperidin-3-ylmethyl)-9*H*-thioxanthene 10-oxide,[5a] which is similar to **3**. Four possible stereoisomers

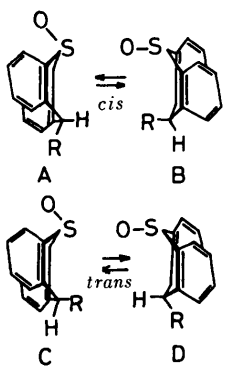

Chart 5

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

Compd.	m/z 346	345	344	329	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 O_2 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 SO_2. Further, in **4** the molecular ion gives the ion at *m/z* 296 by loss of SO_2. 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 $C_6H_5O_2S$. 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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