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Mass Spectra of Stereoisomers of 1-Substituted Quinolizidin-1-ol Derivatives

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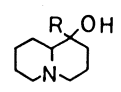
Stereospecific decomposition reactions of isomeric molecules of a series of 1-substituted quinolizidin-1-ols have been examined by using electron ionization mass spectra (EI-MS). Inspection of the MS indicates that the molecular ion and the other ions ($[M-17]^+$, *m/z* 154 and 168) for *cis*-isomers are much more abundant than those for *trans*-isomers. The configurations of epimers can be distinguished on the basis of the relative intensities of the molecular ion, the ions corresponding to $[M-1]^+$, $[M-17]^+$ and $[M-29]^+$, and the ions at *m/z* 154 and 168 in EI-MS, and the peaks due to elimination of a hydroxyl radical from the molecular ion in the ion kinetic energy spectra.

Keywords——electron ionization mass spectrum; ion kinetic energy spectrum; stereochemistry; mass fragmentation

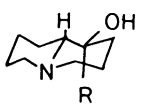
Introduction

Recently the study of stereoisomers by various mass spectrometric methods has become widespread.[1-5] Quantitative differences in mass spectra (MS) are sufficient to permit identification of both structural isomers and stereoisomers. The correlations between the MS and stereochemistry also seem to be applicable to the elucidation of stereochemical problems of other derivatives or related compounds. Furthermore, this stereochemical approach seems to be efficient for elucidating the mechanisms of various fragmentation processes occurring in a mass spectrometer.

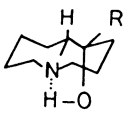
This paper deals with the results of our comparative investigation concerning the following series of stereoisomers of 1-substituted 1-hydroxyquinolizidines: series **1**—**6** consist of compounds possessing epimeric centers at the 1-position, *i.e.* each series forms two epimers. The compounds used in the present investigation are shown in Chart 1. Although a few papers[6] dealing with the MS fragmentation of 1-hydroxyquinolizidine have appeared, they have not covered the relationship with stereochemistry, or compounds containing a quater-



1: R = CH_3
2: R = C_2H_5
3: R = *n*-C_3H_7
4: R = *n*-C_4H_9
5: R = *n*-C_5H_{11}
6: R = C_6H_5



trans isomer



cis isomer

Chart 1

nary carbon atom at the 1-position which usually exhibits a significant directing effect on fragmentation. Therefore, the main goal of this work has been to compare the MS of isomeric pairs of 1-substituted 1-hydroxyquinolizidines, and to explain the observed effects in the light of the mechanism of the decomposition processes.

Experimental

The compounds **1**—**6** used were prepared according to the literature,[7-9] and were purified by fractionation under reduced pressure and alumina column chromatography. The low- and high-resolution MS were recorded with a Hitachi RMU-7MG double-focusing mass spectrometer, which was additionally equipped with an IKES apparatus. Metastable peaks were detected with the IKES attachment.

The elemental composition of the main fragment ions were determined in the high-resolution mode. The samples were introduced through a direct inlet system. The ion source was operated at 3.2 kV accelerating voltage, 70 eV electron energy and a pressure of approximately 5×10^{-7} Torr; its temperature was maintained at approximately 180 C.

Results and Discussion

MS of compounds **1**—**6** are given in Figs. 1 and 2, and the relative intensities of characteristic fragment peaks are summarized in Table I. The elemental compositions of the fragment ions were established by high-resolution mass spectrometry (Table II).

Molecular Ion Stability

Stereoisomers studied here showed significant differences in the intensity of their molecular ions: the molecular ion intensities for *cis*-isomers are greater than those for the corresponding *trans*-isomers. In other words, the molecular ions of *cis*-isomers are more stable than those of *trans*-isomers. The difference in stability between *cis*- and *trans*-isomers is based on the hydrogen bond between the nitrogen atom at the 5-position and the hydroxyl group at the 1-position in *cis*-isomers (Chart 1).[7-9] As the orientation of the substituents and the chain size of the alkyl group affect the stability of the molecular ion, careful examination of the spectrum enables the distinction between the two isomers to be made. Furthermore, the ratio of the molecular ion intensity between *cis*- and *trans*-isomers decreased with increasing chain size of the alkyl group. The results suggest that elimination of the substituents occurs more easily with increase in the chain size of the alkyl group.

$[M-1]^+$ Ions

The ions are observed as low intensity peaks in the MS of all compounds studied. The ion at $[M-1]^+$ was formed by loss of a hydrogen radical at the 10-position. The quaternary carbon atom usually exhibits a significant directing effect on fragmentation. The low intensity of this ion is due to the ease of cleavage of the C_1–C_{10} bond as compared with the C_{10}–H bond beta to the nitrogen atom.

$[M-17]^+$ Ions and the *m/z* 154 Ion

The characteristic ions at $[M-17]^+$ or *m/z* 154 are formed from the molecular ion by loss of the OH radical or the alkyl radical at the 1-position, respectively.

According to the suggestion of Hussain and his co-workers,[6] the formation of these ions involves the rearrangement of one hydrogen atom from the 4-position to the 1-position in the molecular ion. A large difference in the ion intensity was observed between *cis*- and *trans*-isomers of each set of isomerides: the $[M-17]^+$ and *m/z* 154 ion intensities for *cis*-isomers are stronger than those of *trans*-isomers. These results seem to be connected with the difference in stability of the molecular ion. However, the ion at *m/z* 154 was not observed in compound **6**, since the phenyl radical can not be eliminated. The ion at *m/z* 154 further loses water to give the ion at *m/z* 136 and forms the ion at *m/z* 110 by retro-Diels–Alder cleavage.

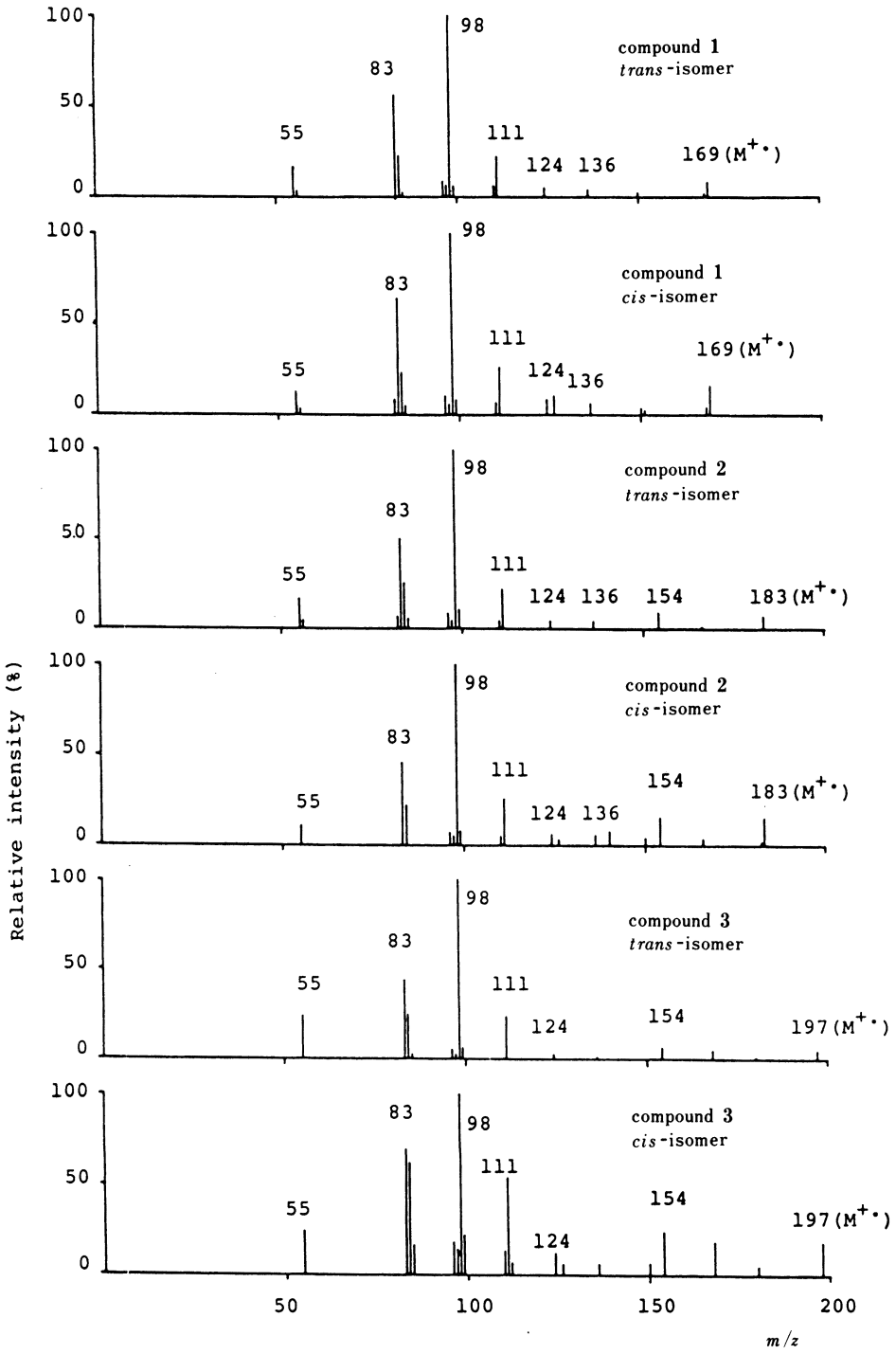


Fig. 1. Mass Spectra of Compounds **1**, **2** and **3**

The *m/z* 168 Ion

This characteristic ion was observed in the MS of **1**—**5** bearing the alkyl substituents. The ion is formed from the molecular ion by loss of a part of the substituent, the situation being

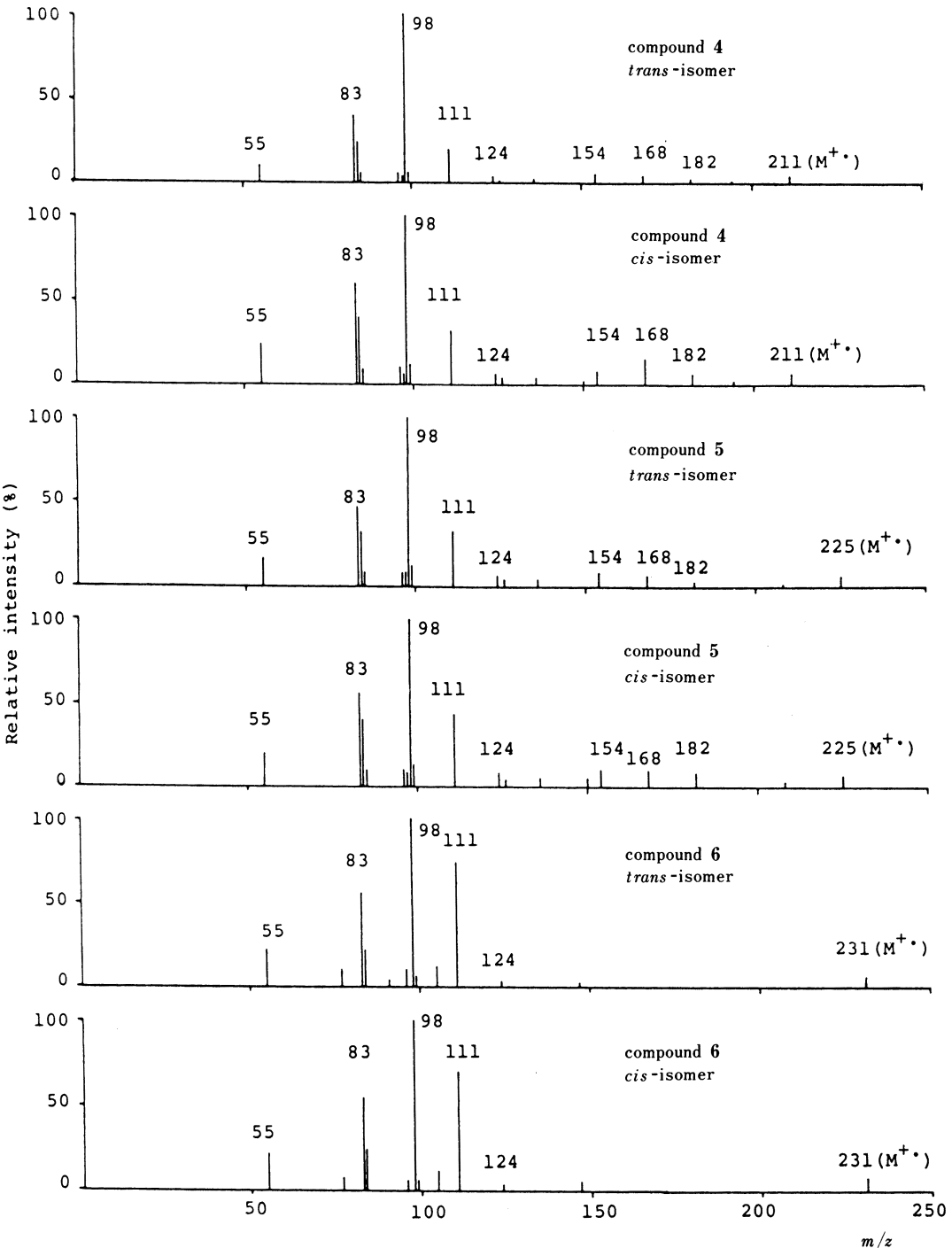


Fig. 2. Mass Spectra of Compounds **4**, **5** and **6**

evident from the high-resolution MS. The ion intensities for *cis*-isomers are much stronger than those for *trans*-isomers. As the ratio of the ion intensity at *m/z* 168 between *cis*- and *trans*-isomers is similar to that of the molecular ion intensity between the corresponding

TABLE I. MS Data (Relative Intensity, %) for Compounds **1**—**6**

Compounds		Produced ions				*m/z*									
		$M^{+\cdot}$	$[M-1]^+$	$[M-17]^+$	$[M-29]^+$	168	154	136	124	111	110	98	84	83	55
1	*trans*	8.7	2.2	2.0	0.7	2.2	2.6	4.1	5.3	22.2	6.3	100	21.7	56.5	16.6
	cis	14.8	3.0	3.0	2.2	3.3	2.6	4.7	7.1	25.8	6.5	100	22.2	64.2	12.2
2	*trans*	6.8	1.2	1.5	8.0	1.1	8.0	4.4	4.5	22.1	4.5	100	24.8	51.4	17.6
	cis	16.6	3.1	4.0	16.6	3.9	16.6	6.0	6.3	26.2	5.7	100	22.5	46.4	11.1
3	*trans*	5.2	0.9	0.9	4.8	4.7	5.2	1.5	2.8	22.7	6.0	100	24.5	42.7	15.2
	cis	18.4	4.1	4.1	18.4	18.4	25.4	6.8	12.1	52.6	12.6	100	62.1	70.5	33.6
4	*trans*	3.8	0.9	0.5	1.8	4.5	5.4	1.9	3.5	20.6	3.0	100	22.7	39.4	11.5
	cis	6.4	1.2	1.6	3.8	12.7	7.5	3.9	6.2	32.6	5.2	100	40.0	60.2	22.8
5	*trans*	5.5	1.6	0.9	0.8	5.8	7.9	4.0	5.9	29.2	4.7	100	33.5	47.4	15.6
	cis	7.1	1.8	2.0	1.3	10.3	10.3	4.3	7.8	42.8	5.8	100	40.7	55.9	19.9
6	*trans*	6.0	0.9	0.6	0.5	—	—	0.4	3.2	75.0	3.7	100	24.4	55.3	21.1
	cis	7.4	1.3	0.9	2.0	—	—	1.1	3.3	71.5	3.8	100	23.8	54.7	21.6

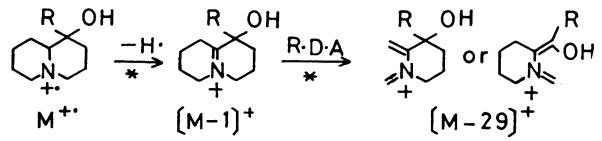


Chart 2

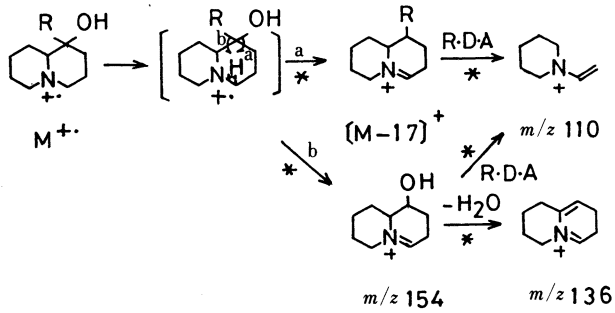


Chart 3

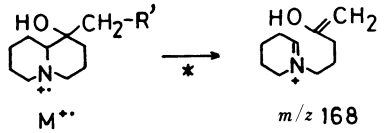


Chart 4

isomers, the high stereospecificity of formation of the *m/z* 168 ions is responsible for the stability of the molecular ion. This peak was not observed in the MS of **6**, where the phenyl group is the C_1-substituent, because removal of the phenyl radical is difficult.

Other Characteristic Ions (*m/z* 124, 111, 98, 84 and 83)

These ions showed strong peaks in all MS. In particular, the ion at *m/z* 98 is the base peak for all compounds. All the ions are formed from the molecular ion by cleavage of the C_1–C_{10} bond. The ion at *m/z* 111 shows the difference in peak intensity depending on the substituents. Compounds **1**—**5**, containing the alkyl group, show moderate peak intensity at *m/z* 111, but the MS of **6**, containing a phenyl group as the substituent, gave the ion at *m/z* 111 with intensity of more than 70%. The difference in peak intensity is based on the stability of the leaving moiety (α-hydroxystyrene or acetophenone) from compound **6**.

The ions at *m/z* 83 and 84 arise from the intermediate ion formed from the molecular ion by cleavage of C_1–C_{10}. The peak intensity at *m/z* 83 is stronger than that at *m/z* 84. This is probably because the ion at *m/z* 84 results from the molecular ion with simultaneous rearrangement of one hydrogen atom from the leaving group to the resultant ion. The ion at *m/z* 83 further gives the ion at *m/z* 55 by retro-Diels–Alder cleavage.

TABLE II. High-Resolution MS Data for Compounds **3**, **4** and **6**

Ion	Elemental composition	Calculated mass	*trans*-Isomer		*cis*-Isomer	
			Observed mass	Error (mu)	Observed mass	Error (mu)
Compds. **3**						
197	$C_{21}H_{23}NO$	197.1779	197.1779	0.0	197.1773	−0.6
196	$C_{20}H_{23}NO$	196.1700	196.1666	−3.4	196.1689	−1.1
180	$C_{12}H_{22}N$	180.1750	180.1691	−5.9	180.1740	−1.0
168	$C_{10}H_{18}NO$	168.1387	168.1371	−1.6	168.1387	0.0
154	$C_9H_{16}NO$	154.1230	154.1217	−1.3	154.1243	1.3
136	$C_9H_{14}N$	136.1125	136.1116	−0.8	136.1107	−1.8
124	$C_8H_{14}N$	124.1126	124.1126	0.0	124.1098	−2.8
111	$C_7H_{13}N$	111.1046	111.1028	−1.8	111.1061	1.5
110	$C_7H_{12}N$	110.0968	110.0948	−2.0	110.0973	0.5
98	$C_6H_{12}N$	98.0968	98.0973	0.5	98.0988	2.0
84	$C_5H_{10}N$	84.0812	84.0785	−2.7	84.0800	−1.2
83	C_5H_9N	83.0734	83.0712	−2.2	83.0718	−1.6
55	C_3H_5N	55.0421	55.0437	1.6	55.0425	0.4
Compds. **4**						
211	$C_{13}H_{25}NO$	211.1934	211.1906	−2.8	211.1934	0.0
210	$C_{13}H_{24}NO$	210.1857	210.1858	0.1	210.1837	−2.0
194	$C_{13}H_{24}N$	194.1908	194.1933	2.5	194.1891	−1.7
182	$C_{11}H_{20}NO$	182.1543	182.1517	−2.6	182.1512	−3.1
168	$C_{10}H_{18}NO$	168.1387	168.1378	−0.9	168.1385	−0.2
154	$C_9H_{16}NO$	154.1230	154.1218	−1.2	154.1231	0.0
136	$C_9H_{14}N$	136.1125	136.1085	−4.0	136.1113	−1.2
124	$C_8H_{14}N$	124.1126	124.1135	0.9	124.1108	−1.8
111	$C_7H_{12}N$	111.1046	111.1046	0.0	111.1056	1.0
110	$C_7H_{11}N$	110.0968	110.0963	−0.5	110.0974	0.6
98	$C_6H_{12}N$	98.0968	98.0964	−0.4	98.0996	2.8
84	$C_5H_{10}N$	84.0812	84.0820	0.8	84.0801	−1.1
83	C_5H_9N	83.0734	83.0736	0.2	83.0714	−2.0
55	C_3H_5N	55.0421	55.0482	6.1	55.0482	6.1
Compds. **6**						
231	$C_{15}H_{21}NO$	231.1621	231.1614	−0.7	231.1612	−0.9
230	$C_{15}H_{20}NO$	230.1543	230.1558	1.5	230.1521	−2.2
214	$C_{15}H_{20}N$	214.1594	214.1580	−1.4	214.1559	−3.5
202	$C_{13}H_{16}NO$	202.1231	202.1236	0.5	202.1232	0.1
136	$C_9H_{14}N$	136.1125	136.1148	2.3	136.1111	−1.4
124	$C_8H_{14}N$	124.1126	124.1135	0.9	124.1125	−0.1
111	$C_7H_{13}N$	111.1046	111.1042	−0.4	111.1050	0.4
110	$C_7H_{12}N$	110.0968	110.0981	1.3	110.0980	1.2
98	$C_6H_{12}N$	98.0968	98.0973	0.5	98.0967	−0.1
84	$C_5H_{10}N$	84.0812	84.0805	−0.7	84.0808	−0.4
83	C_5H_9N	83.0734	83.0732	−0.2	83.0739	0.5
55	C_3H_5N	55.0421	55.0449	2.8	55.0463	4.2

Ion Kinetic Energy (IKE) Spectra

The IKE spectra of compounds **3** and **4** are shown in Figs. 3 and 4. The fragmentations corresponding to the IKE spectral peaks were determined with high-resolution MS data and metastable peaks observed in the normal spectra.

The spectra of **3** show a peak a at 0.91 E due to loss of a hydroxyl radical from the molecular ion (*m/z* 197 to 180). On the other hand, the spectra of **4** exhibited a peak c at 0.92 E

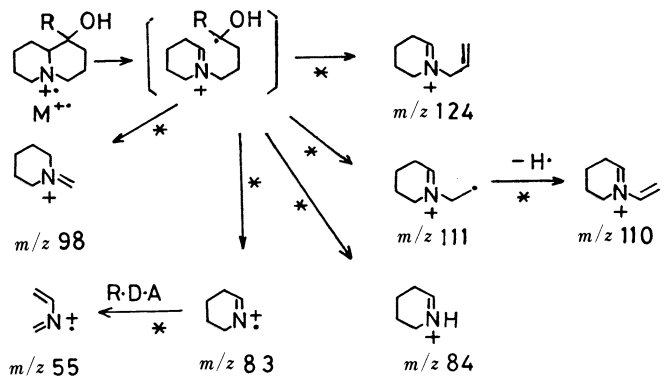


Chart 5

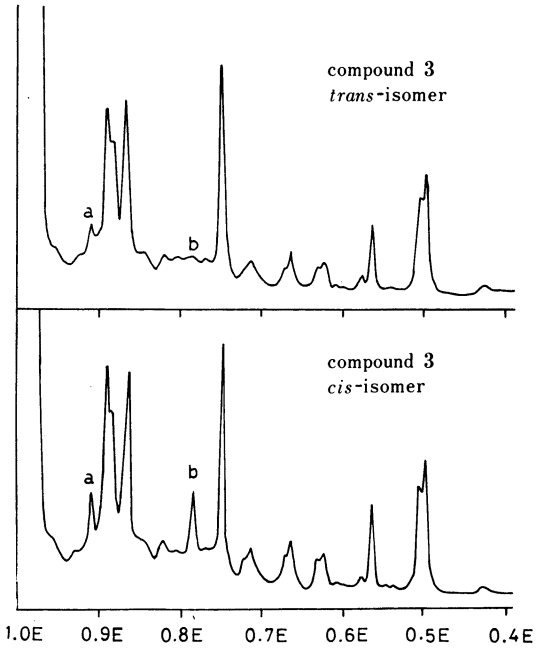


Fig. 3. IKE Spectra of Compound **3**

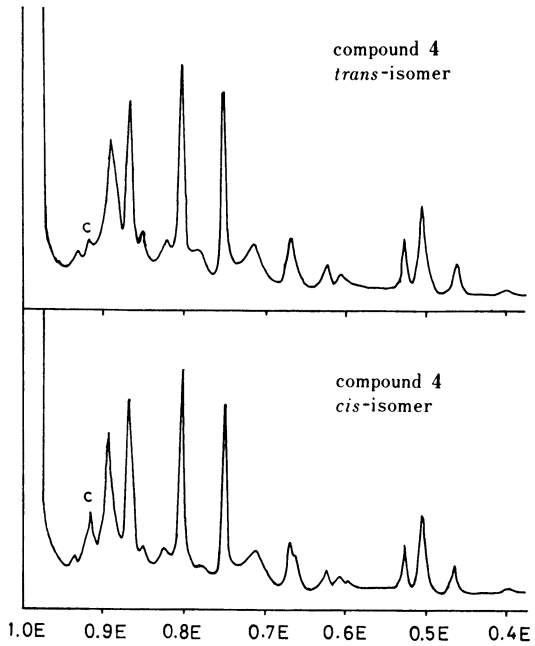


Fig. 4. IKE Spectra of Compound **4**

due to loss of a hydroxyl radical from the molecular ion (*m/z* 211 to 194). These peaks a and c of *cis*-isomers are stronger than those of *trans*-isomers. These facts show that the loss of a hydroxyl radical from the *cis*-isomers occurs much more easily than from the *trans*-isomers. These results are supported by the difference in relative intensity of these molecular ions.

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References and Notes

1) M. Barczai-Beke, G. Dornyei, J. Tamas and C. Szantay, *Chem. Ber.*, **105**, 3244 (1972).
2) V. G. Zaikin, A. A. Bakaev, N. S. Wulfson, A. A. Akhrem, L. I. Ukhova and N. F. Marchenko, *Org. Mass Spectrom.*, **12**, 173 (1977).
3) K. P. Madhusudanan, R. Pratap and S. P. Popli, *Indian J. Chem.*, **24**, 67 (1985).

4) K. P. Madhusudanan, M. Prasad, S. N. Rastogi and D. Fraisse, *Org. Mass Spectrom.*, **20**, 680 (1985).
5) J.-C. Tabet, Y. Tondeur, Y. Troin, D. Vallee-Goyet, J.-C. Gramain and D. Fraisse, *Org. Mass Spectrom.*, **20**, 770 (1985).
6) M. Hussain, J. S. Robertson and T. R. Watson, *Org. Mass Spectrom.*, **4**, 109 (1970).
7) J. D. England and J. Sam, *J. Heterocycl. Chem.*, **3**, 482 (1966).
8) D. L. Temple and J. Sam, *J. Heterocycl. Chem.*, **7**, 847 (1970).
9) S. Saeki, A. Yamashita, Y. Matsukura and M. Hamana, *Chem. Pharm. Bull.*, **27**, 2411 (1979).