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Mass Spectral Studies of Aza- and Diazabenzobicycloalkanes. I.[1] Some Aspects of Mass Spectrometry of 1,3-Bridged 1,2,3,4-Tetrahydroisoquinolines

SHUNSAKU SHIOTANI[2a] and KEMMOTSU MITSUHASHI[2b]

Toyama Technical College[2a] and Faculty of Pharmaceutical Sciences, University of Toyama[2b]

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The mass spectra of some 1,3-bridged 1,2,3,4-tetrahydroisoquinoline derivatives were investigated and it was revealed that these compounds decompose to form completely aromatic evenelectron isoquinolinium ions as the major fragmentation processes by electron impact.

In the previous papers[3] we reported the syntheses of aza- and diazabenzobicycloalkanes for our studies on structure-activity relationship of analgetics. Now, we attempted to present investigations on the fragmentation patterns of aza- and diazabenzobicyclic systems by mass spectrometry, which seem to be important and convenient for mass spectral analysis of the systems. In this paper, we report the mass spectra and fragmentation patterns of 1,3-bridged 1,2,3,4-tetrahydroisoquinoline derivatives shown in Chart 1.

The 70 eV spectra are shown in Fig. 1, 2 and 3. Assignments of individual peaks were made with the help of shifts observed in spectra of the derivatives and high resolution mass spectra (hrms) of compounds III and IV, while individual fragmentation processes were documented by metastable ion peaks (Table II) and shifts observed in spectra of 4,4-d_2 derivatives of compound I and IV (I' and IV').

All the spectra of the compounds examined showed a fragment peak ascribable to N-substituted or unsubstituted isoquinolinium ion (type c ion) as the most intense peak, and the main fragmentation processes of these compounds would be correlated with the formation and the decomposition of the ion.

Considering the fragmentation processes of compounds related to morphine[4] and tropane[5] alkaloids, one might expect cleavage at the three carbon-carbon bonds β to the nitro-

1) This forms Part XI of "Studies on Structure-Activity Relationship of Analgetics" by K. Mitsuhashi. Part X: K. Mitsuhashi and S. Shiotani, *Chem. Phem. Bull.* (Tokyo), **18**, 75 (1970).

2) Location: *a) Hongo, Toyama; b) Gofuku, Toyama.*

3) *a)* S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **12**, 647 (1964); *b) Idem, ibid.*, **14**, 324 (1966); *c) Idem, ibid.*, **14**, 608 (1966); *d) Idem, ibid.*, **15**, 761 (1967); *e)* S. Shiotani, T. Hori and K. Mitsuhashim, *ibid.*, **15**, 88 (1967); *f) Idem, ibid.*, **16**, 239 (1968); *g)* K. Mitsuhashi, S. Shiotani, R. Ohuchi and K. Shiraki, *ibid.*, **17**, 434 (1969); *h)* K. Mitsuhashi and S. Shiotani, *ibid.*, **18**, 75 (1970); *i)* S. Shiotani and K. Mitsuhashi, *Yakugaku Zasshi*, **84**, 656 (1964); *j) Idem, ibid.*, **84**, 1032 (1964); *k) Idem, ibid.*, **86**, 169 (1966).

4) *a)* D.M.S. Wheeler, T.H. Kinstle and K.L. Rinehart, Jr., *J. Am. Chem. Soc.*, **89**, 4494 (1967); *b)* H. Nakata, Y. Hirata, A. Tatematsu, H. Tada and Y.K. Sawa, *Tetrahedron Letters*, **1965**, 829; *c)* A. Mandelbaum and D. Ginsburg, *ibid.*, **1965**, 2479.

5) E.C. Blossey, H. Budzikeiwicz, M. Ohashi, G. Fodor and C. Djerassi, *Tetrahedron*, **20**, 585 (1964).

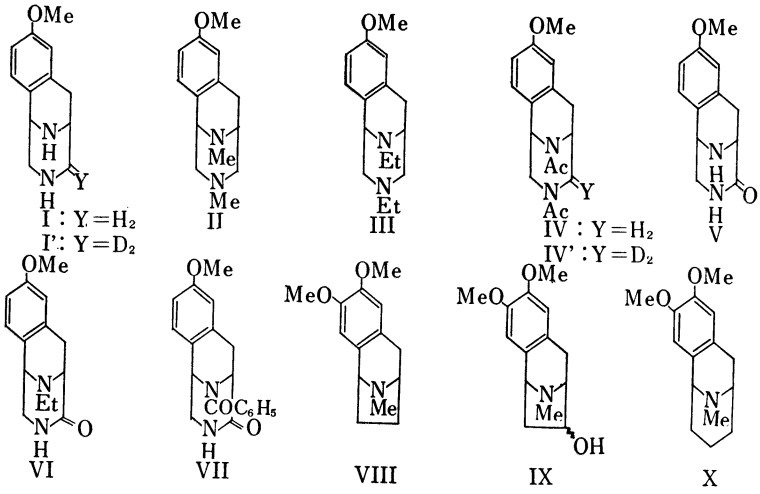


Chart 1

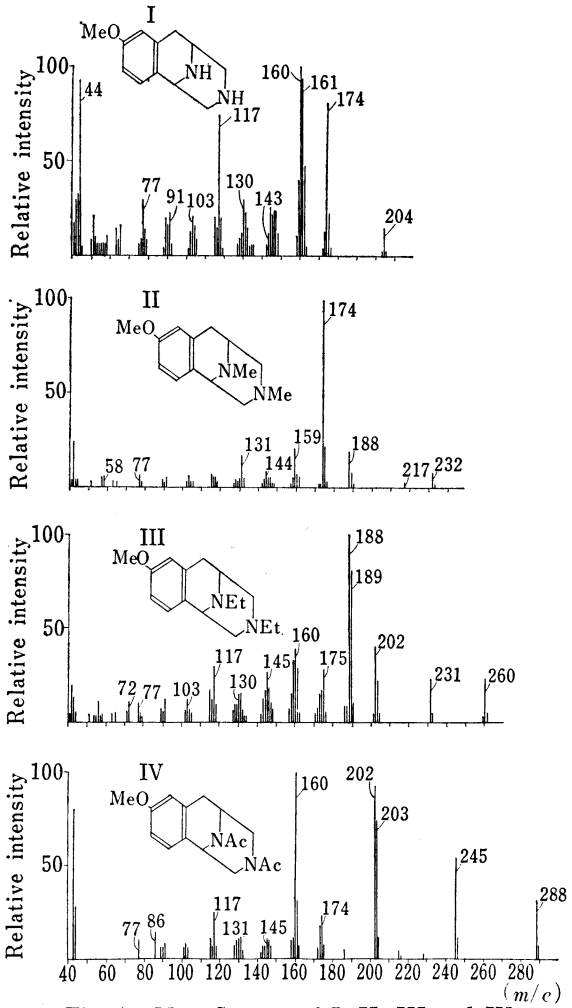


Fig. 1. Mass Spectra of I, II, III and IV

gen atoms affording ions a, a′ and a″ as an initial cleavage for this system. The possibility of the formation of ions a′ and a″, however, was considered to be neglisible because type p ions (detailed later) shifted higher 2 mass units in the spectra of 4,4-d_2 derivatives of I and IV and because the high-resolution data of III and IV revealed that the most of the nitrogen-containing fragment ions include only one nitrogen atom. Thus, the fragmentations to the most of the peaks in compounds I—X can be predominantly ascribed to type a ion. The major fragmentations of ion a are illustrated for the simplest representative, 8-methoxy-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (I), in Chart 2.

Homolytic cleavage of the 4—5 linkage in ion a-I would yield the radical ion b-I (*m/e* 161), which would lose a hydrogen atom to give the completely aromatic ion c-I (*m/e* 160). Alternatively, initial rupture of one of the C-6 hydrogens by the primary free radical site at C-2 in a-I would give secondary radical a‴-I, which would then undergo fission at 4—5 bond to produce ion c-I or ion d-I (*m/e* 44). Each of the processes was supported by the presence of an appropriate metastable ion (Table II), and by the fact that in the spectrum of I′ (4,4-d_2

TABLE I. Corresponding Peaks in Mass Spectra of 1,3-Bridged 1,2,3,4-Tetrahydroisoquinolines

Ions	I	I'	II	III	(Compn.)[a]	IV	(Compn.)[a]	IV'	V	VI	VII	VIII	IX	X
M^+ (a)	204	206	232	260	$(C_{16}H_{24}ON_2)$	288	$(C_{16}H_{20}O_3N_2)$	290	218	246	322	233	249	247
	—	—	{217 M-Me	{231 M-Et	$(C_{13}H_{19}ON_2)$	{245 M-Ac	$(C_{14}H_{17}O_2N_2)$	{247 M-Ac	—	{217 M-Et	{217 M-C_6H_5CO	—	—	—
e	—	—	—	—		203	$(C_{12}H_{15}ON_2)$	205	—	—	—	—	—	—
e'	—	—	—	—		—		—	—	—	293	—	—	—
b-I	161	161	—	161	$(C_{10}H_{11}ON)$	161	$(C_{10}H_{11}ON)$	161	161	161	—	—	—	—
b-II	—	—	175	—		—		—	—	—	—	—	—	—
b-III	—	—	—	189	$(C_{12}H_{15}ON)$	—		—	—	189	—	—	—	—
b-IV	—	—	—	—		203	$(C_{12}H_{13}O_2N)$	203	—	—	—	—	—	—
b-VII	—	—	—	—		—		—	—	—	265	—	—	—
b-VIII	—	—	—	—		—		—	—	—	—	205	205	205
c-I	160	160	—	160	$(C_{10}H_{10}ON)$	160	$(C_{10}H_{10}ON)$	160	160	160	160	—	—	—
c-II	—	—	174	—		—		—	—	—	—	—	—	—
c-III	—	—	—	188	$(C_{12}H_{14}ON)$	—		—	—	188	—	—	—	—
c-IV	—	—	—	—		202	$(C_{12}H_{12}O_2N)$	202	—	—	—	—	—	—
c-VII	—	—	—	—		—		—	—	—	264	—	—	—
c-VIII	—	—	—	—		—		—	—	—	—	204	204	204
d-I	44	46	—	—		—		—	—	—	—	—	—	—
d-II	—	—	58	—		—		—	—	—	—	—	—	—
d-III	—	—	—	72	$(C_4H_{10}N)$	—		—	—	—	—	—	—	—
d-IV	—	—	—	—		86	(C_4H_8ON)	88	—	—	—	—	—	—
f-I	145	145	—	145		145	(C_9H_7ON)	145	145	145	145	—	—	—
f-II	—	—	159	—		—		—	—	—	—	—	—	—
f-III	—	—	—	173	$(C_{11}H_{11}ON)$	—		—	—	173	—	—	—	—
f-VIII	—	—	—	—		—		—	—	—	—	189	189	189
f'-VIII	—	—	—	—		—		—	—	—	—	188	188	188
g-I	117	117	—	117	(C_8H_7N)	117	(C_8H_7N)	117	117	117	117	—	—	—
g-II	—	—	131	—		—		—	—	—	—	—	—	—
g-III	—	—	—	145	$(C_{10}H_{11}N)$	—		—	—	145	—	—	—	—
g-VIII	—	—	—	—		—		—	—	—	—	161	161	161
g'-VIII	—	—	—	—		—		—	—	—	—	160	160	160
h	90	90	—	90	(C_7H_6)	90	(C_7H_6)	90	90	90	90	—	—	—
i-I	130	130	—	130	(C_9H_8N)	130		130	130	130	130	—	—	—
i-II	—	—	144	—		—		—	—	—	—	—	—	—
i-III	—	—	—	158	$(C_{11}H_{12}N)$	—		—	—	158	—	—	—	—
j	103	103	103	103		103	(C_8H_7)	103	103	103	103	—	—	—
k	77	77	77	77		77		77	77	77	77	—	—	—
l	159	159	—	159	$(C_{10}H_9ON)$	159	$(C_{10}H_9ON)$	159	159	159	159	—	—	—
m	129	129	—	129		129	(C_9H_7N)	129	129	129	129	—	—	—
n	102	102	—	102		102		102	102	102	102	—	—	—
o-I	175	177	—	175	$(C_{11}H_{13}ON)$	175	$(C_{11}H_{13}ON)$	177	—	—	—	—	—	—
o-II	—	—	189	—		—		—	—	—	—	—	—	—
o-III	—	—	—	203	$(C_{13}H_{17}ON)$	—		—	—	—	—	—	—	—
o-X	—	—	—	—		—		—	—	—	—	—	—	219
p-I	174	176	—	174	$(C_{11}H_{12}ON)$	174	$(C_{11}H_{12}ON)$	176	—	—	—	—	—	—
p-II	—	—	188	—		—		—	—	—	—	—	—	—
p-III	—	—	—	202	$C_{13}H_{16}ON)$	—		—	—	—	—	—	—	—
p-X	—	—	—	—		—		—	—	—	—	—	—	218
q-I	159	161	—	159	$(C_{10}H_9ON)$	159	$(C_{10}H_9ON)$	161	—	—	—	—	—	—
q-II	—	—	173	—		—		—	—	—	—	—	—	—
q-III	—	—	—	187		—		—	—	—	—	—	—	—
q-X	—	—	—	—		—		—	—	—	—	—	—	203
r-I	131	133	—	131	(C_9H_9N)	131		133	—	—	—	—	—	—
r-II	—	—	145	—		—		—	—	—	—	—	—	—
s	173	175	—	173	$(C_{11}H_{11}ON)$	173	$(C_{11}H_{11}ON)$	175	—	—	—	—	—	—
t	143	145	—	143	$(C_{10}H_9N)$	143	$(C_{10}H_9N)$	145	—	—	—	—	—	—
u	142	{144 143	—	142		142		{144 143	—	—	—	—	—	—
v	115	{117 116	—	115	(C_9H_7)	115	(C_9H_7)	{117 116	—	—	—	—	—	—

a) Composition of each fragment peak was determined by high resolution mass spectrometer (model JMS-OIS).

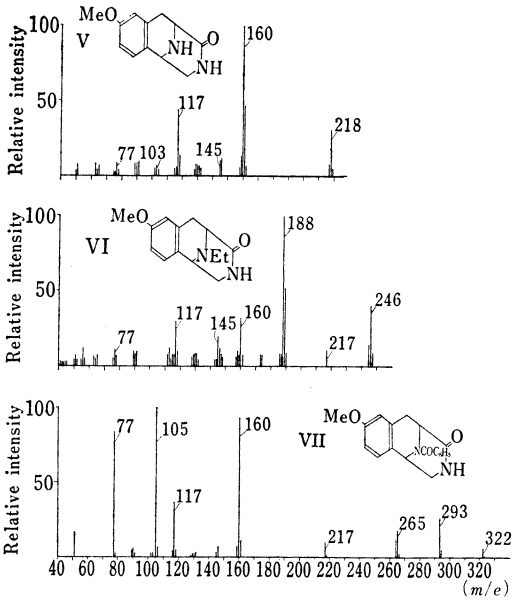


Fig. 2. Mass Spectra of V, VI and VII

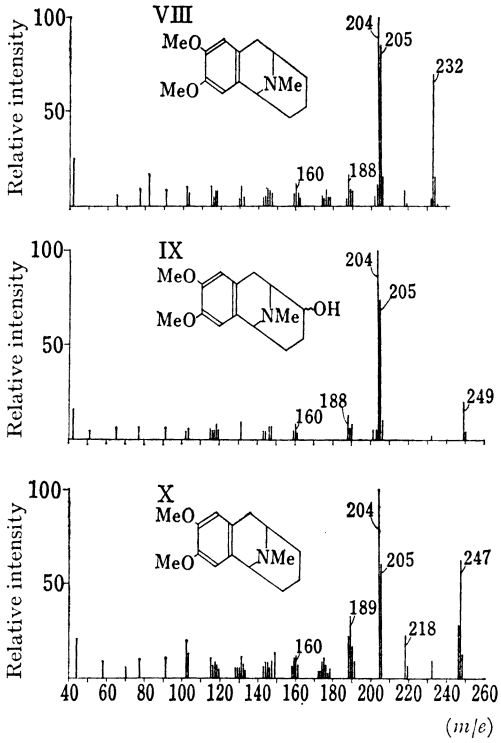


Fig. 3. Mass Spectra of VIII, IX and X.

TABLE II. Corresponding Metastable Ions in Mass Spectra of 1, 3-Bridged 1, 2, 3, 4-Tetrahydroisoquinolines

Fragmentation process	m* Found (Calcd.) I	I'	Fragmentation process	m* Found (Calcd.) II	Fragmentation	m* Found (Calcd.) III
a-I → b-I	127.1 (127.1)	126.0 (125.9)	a-II → c-II	130.5 (130.3)	a-III → c-III	136.0 (136.0)
b-I → c-I	159.0 (159.0)	159.0 (159.0)	b-II → c-II	173.0 (173.0)	b-III → c-III	187.0 (187.0)
a-I → c-I	125.5 (125.3)	124.3 (124.2)	c-II → f-II	145.5 (145.3)	c-III → c-I	136.3 (136.1)
c-I → f-I	131.5 (131.3)	131.5 (131.3)	f-II → g-II	108.2 (108.1)	b-I → c-I	159.1 (159.0)
f-I → g-I	94.5 (94.4)	94.5 (94.4)	o-II → p-II	187.0 (187.0)	M-Et → c-III	153.0 (153.0)
g-I → h	69.5 (69.3)	69.5 (69.3)			c-I → f-I	131.5 (131.3)
i-I → j	81.7 (81.7)	81.7 (81.7)			f-I → g-I	94.5 (94.4)
j → k	57.5 (57.5)	57.5 (57.5)			o-III → p-III	201.0 (201.0)
o-I → p-I	173.0 (173.0)	175.0 (175.0)			o-I → p-I	173.5 (173.0)
p-I → q-I	145.2 (145.2)	147.3 (147.2)			p-I → q-I	145.3 (145.2)
q-I → r-I	108.0 (107.9)					

Fragmentation process	m* Found (Calcd.) IV	IV'	Fragmentation process	m* Found (Calcd.) V	Fragmentation	m* Found (Calcd.) VI
a-IV→ c-IV	142.0 (141.6)	140.5 (140.6)	a-V → c-I	117.5 (117.3)	a-VI→ c-Ⅲ	144.0 (143.7)
M-Ac→ e	168.5 (168.3)	170.0 (170.0)	b-I → c-I	159.1 (159.0)	b-Ⅲ → c-Ⅲ	187.1 (187.0)
e → c-I	126.0 (126.0)	125.0 (124.9)	c-I → f-I	131.5 (131.3)	b-I → c-I	159.0 (159.0)
c-IV→ c-I	127.0 (126.7)	127.0 (126.9)	f-I → g-I	94.5 (94.4)	c-Ⅲ → c-I	136.2 (136.1)
b-I → c-I	159.1 (159.0)	159.1 (159.0)			c-Ⅲ → f-Ⅲ	159.2 (159.2)
c-I → f-I	131.5 (131.3)	131.5 (131.3)			c-I → f-I	131.5 (131.3)
f-I → g-I	94.5 (94.4)	94.5 (94.4)			f-Ⅲ → g-Ⅲ	121.5 (121.6)
g-I → h	69.3 (69.3)	69.3 (69.3)			f-I → g-I	94.5 (94.4)
					g-I → h	69.3 (69.3)
					i-I → j	81.6 (81.6)
					M-Et→ l	117.0 (116.6)
					j → k	57.5 (57.6)

Fragmentation process	M* Found (Calcd.) VII	Fragmentation process	VIII	m* Found (Calcd.) IX	X
a-Ⅶ → e'	267.2 (267.2)	a-Ⅷ → b-Ⅷ	180.3 (180.3)	—	—
e' → b-Ⅶ	240.0 (239.9)	a-IX → b-Ⅷ	—	169.0 (168.9)	—
b-Ⅶ → c-Ⅶ	263.5 (263.2)	a-X → c-Ⅷ	—	—	168.5 (168.5)
c-I → f-I	131.5 (131.3)	b-Ⅷ → c-Ⅷ	203.0 (203.0)	203.0 (203.0)	203.0 (203.0)
f-I → g-I	94.8 (94.4)	c-Ⅷ → f-Ⅷ	175.0 (175.0)	175.0 (175.0)	175.0 (175.0)
M-C_6H_5CO → l	117.0 (116.6)	f-Ⅷ → f'-Ⅷ	187.0 (187.0)	187.0 (187.0)	187.0 (187.0)
C_6H_5CO → C_6H_5	56.5 (56.5)				

derivative of I) no significant peaks were found at *m/e* 161 or 162 and ion d-I shifted higher by 2 mass units. In the spectra of II—X, the corresponding type c ions were observed at *m/e* 174, 188, 202, 160, 188, 264, 204, 204 and 204, respectively, as the most intense peak in each spectrum. Type d ions were also observed in spectra of II, III and IV at *m/e* 58, 72 and 86, respectively. In the case of III, ion c-III may be produced through two other courses; that is, fission of ethyl radical at N-3-position in ion a-III to give an ion at *m/e* 231 (M-Et), followed by elimination of Me-N=CH_2 unit or a successive loss of CH_2=N-CH_2· radical and a hydrogen atom. The former process was documented by the presence of a metastable ion at *m/e* 153.0 for the fragmentation of M-Et (231)→c-III (calcd. 153.0). However, the presence of metastable ions at *m/e* 267.2 (a-VII→e'), 240.0 (e'→b-VII) and 263.5 (b-VII→c-VII) in the spectrum of VII and the absence of an appropriate metastable ion for the direct formation of c-VII from a-VII would favor the scheme illustrated in Chart 4.

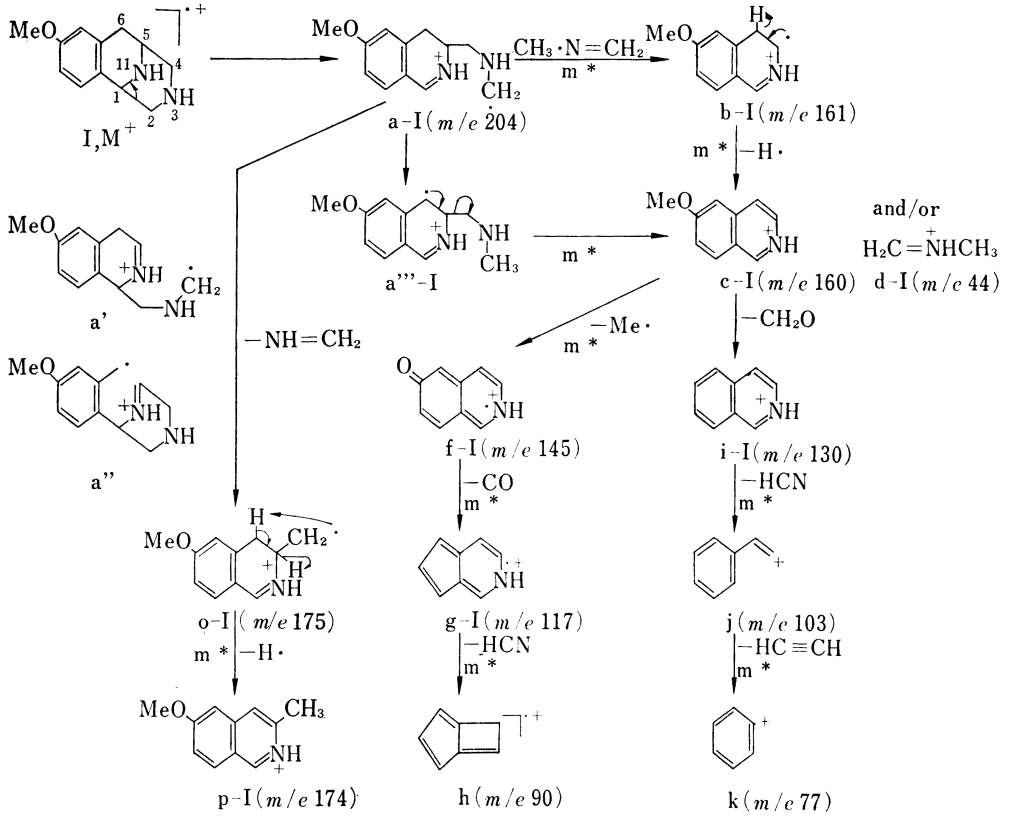


Chart 2

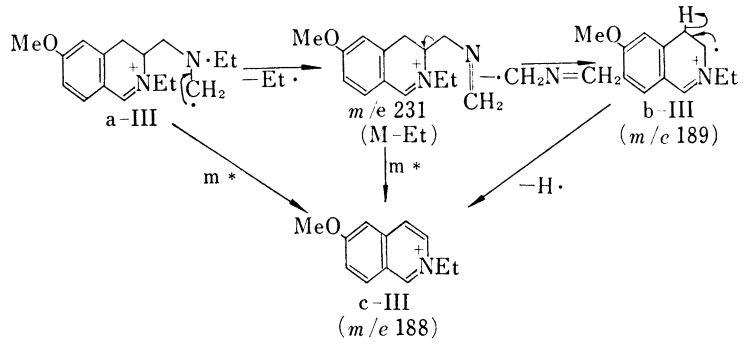


Chart 3

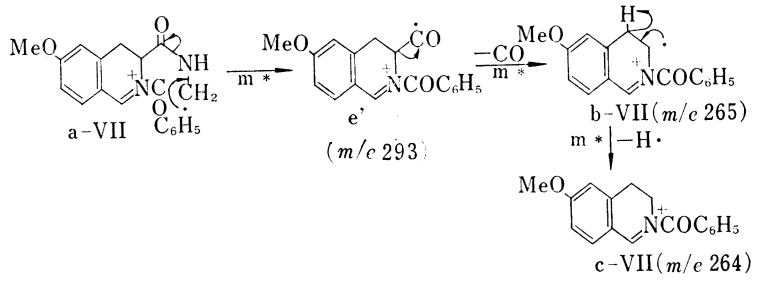


Chart 4

The N-substituted type b and c ions formed as above would lose the substituent, except the methyl, to give ion c-I. Loss of ethylene from c-III, ketene from c-IV and benzoyl radical from b-VII would produce the same ion c-I (Chart 5). In the case of IV, another process for the formation of ion c-I from a-IV could be postulated, which is supported by the presence of appropriate metastable ions. Ion a-IV would lose an acetyl radical to give the *m/e* 245 species (M-Ac), which would be followed by elimination of ketene yielding an intense ion e (*m/e* 203). Successive loss of CH_2=N-CH_2· radical and a hydrogen atom or loss of CH_2=NMe from ion e would give ion c-I. In the spectra of N-methyl derivatives (II, VIII, IX and X), ion c-I (or its methoxyl analogue) was almost neglisible as would be expected[6] (Chart 6).

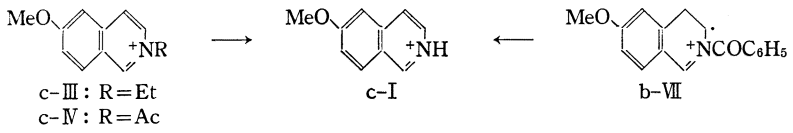


Chart 5

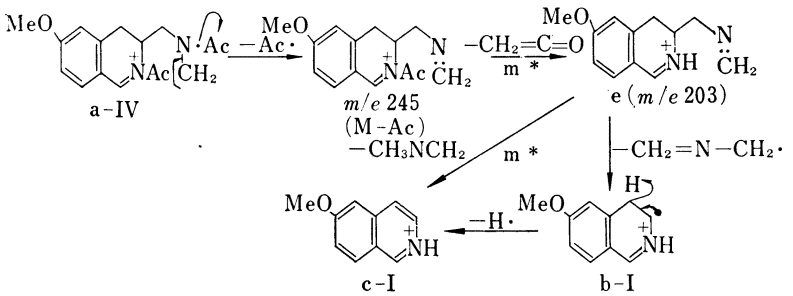
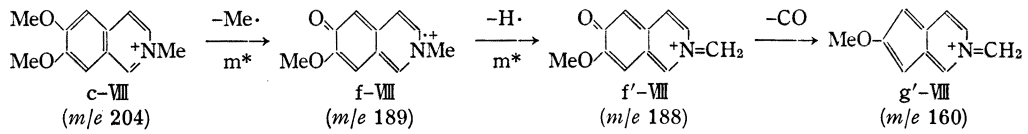


Chart 6

Type c ions could undergo further break-up involving the cleavage of the methoxyl group and the elimination of hydrogen cyanide which resemble to the decomposition of methoxyl derivatives of 1,2,3,4-tetrahydroisoquinolines[7] and pyridine and isoquinoline derivatives.[8] Homolytic cleavage of methyl radical at the methoxyl in ion c-I would give ion f-I (*m/e* 145), which would then yield ion g-I (*m/e* 117) by loss of carbonyl, the latter then lose a hydrogen cyanide to form ion h (*m/e* 90). Another mode of the further decomposition of ion c-I could involve loss of CH_2O unit and lead to ion i-I (*m/e* 130), loss of a hydrogen cyanide yielding ion j (*m/e* 103), the latter being the progenitor of ion k (*m/e* 77). The positions of ions f, g and i shifted higher 14 mass units for compound II and 28 for compound III, indicating that the modes of further decomposition of the skeleton of c-II and c-III are much similar to that of c-I. These fragmentation processes of type c are supported by the presence of corresponding metastable ions summarized in Table II (Chart 2).

Spectra of dimethoxyl derivatives, VIII, IX and X, showed a moderately intense peak at *m/e* 188, respectively, which would be ascribed to the cross-conjugated even-electron ion f'-VIII[8c] formed by loss of a hydrogen from ion f-VIII (*m/e* 189). Ion f'-VIII would afford ion g'-VIII (*m/e* 160) by repulsion of carbonyl.

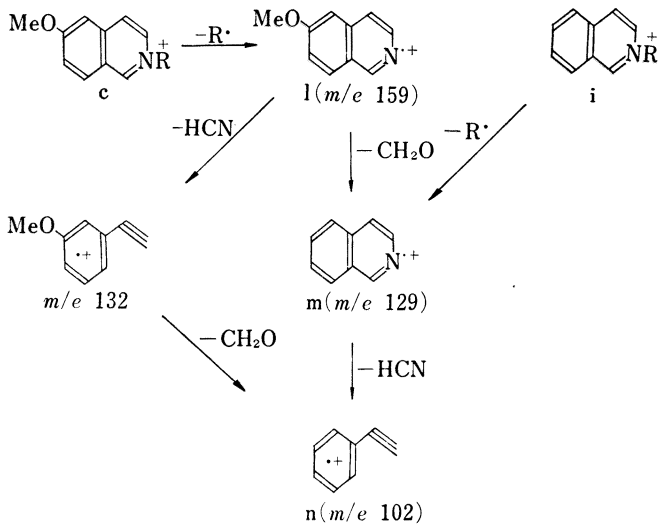
6) H. Budzikiewicz, C. Djerassi and D.H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, 1964, Chapter 5, pp. 92—110.
7) M. Tomita, H. Furukawa, T. Kikuchi, A. Kato and T. Ibuka, *Chem. Pharm. Bull.* (Tokyo), **14**, 232 (1966).
8) *a*) S.D. Sample, D.A. Lightner, O. Buchardt and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967); *b*) A. Kubo, S. Sakai, S. Yamada, I. Yokoe and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **16**, 1533 (1968); *c*) B.J.-S. Wang and E.R. Thornton, *J. Am. Chem. Soc.*, **90**, 1216 (1968).



c-Ⅷ (*m/e* 204) f-Ⅷ (*m/e* 189) f′-Ⅷ (*m/e* 188) g′-Ⅷ (*m/e* 160)

Chart 7

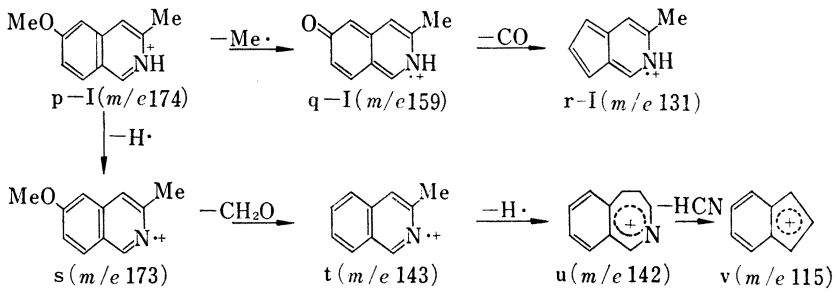
It may be plausible that type c ions could decompose to give a radical ion l (*m/e* 159) by loss of N-substituent, which would then lose a methoxyl and a hydrogen cyanide giving ions m (*m/e* 129) and n (*m/e* 102)[8b] (compositions of l and m were confirmed to be $C_{10}H_9ON$ and C_9H_7N, respectively, by hrms of III and IV). The radical ion l could lose a hydrogen cyanide to yield species of *m/e* 132, alternatively.



c l(*m/e* 159) i *m/e* 132 m(*m/e* 129) n(*m/e* 102)

Chart 8

A moderately intense peak at *m/e* 174 in the spectrum of I could be attributed to ion p-I, and the corresponding ions p-II (*m/e* 188), p-III (*m/e* 202), p-IV (*m/e* 216) and p-X (*m/e* 218) were also observed in the spectra of II, III, IV and X, respectively, with varying intensity. The structures of these type p ions were supported by the followings. The position of ion p-I shifted higher by 2 mass units in the spectra of I′ and IV′, and the compositions of p-I and p-II were confirmed to be $C_{11}H_{12}ON$ and $C_{13}H_{16}ON$, respectively, by hrms of IV and III. These type p ions would arise from type a ions by successive loss of CH_2=NR



p−I(*m/e*174) q−I(*m/e*159) r-I(*m/e* 131) s(*m/e* 173) t(*m/e* 143) u(*m/e* 142) v(*m/e* 115)

Chart 9

unit and a hydrogen atom via type o ions, and in the case of III, loss of ethylene from p-III or a successive loss of ethylene and a hydrogen atom from o-III would give ion p-I. The above mentioned fact would be an evidence showing that the bond at 1—2 in the molecular ion is preferentially cleaved to give initial type a intermediate. Further decomposition of type p ions would follow the similar pathway with that of type c ions as illustrated in Chart 9. The elimination pathway from p-I to r-I is supported by the presence of metastable ions at *m/e* 145.2 for p-I→q-I and 108.0 for q-I→r-I, while the fragmentation of type p ions to ion $v^{8a)}$ is supported by the shift of ions s and t by 1 or 2 mass units in the spectra of I′ and IV′ and by the composition of each fragment peak confirmed by hrms of III and IV.

Experimental

Compounds——The 4,4-d_2 derivative (I′) of compound I was prepared by reduction of V with $LiAlD_4$, which was derived to compound IV′ by acetylation with Ac_2O in AcOH. The other compounds used in the present work were prepared by the methods described in earlier papers.[3g,j,k]

Mass Spectral Measurements——The spectra were measured by the direct sample introduction technique on a Hitachi Mass Spectrometer Model RMU 6C and a JEOL Double-focussing Mass Spectrometer Model JMS-OIS. The sample heating temperature varied between 70° to 190°. The ionizing voltage was maintained at 70 eV for the single-focussing measurement, 75 eV for the double-focussing measurement.

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