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

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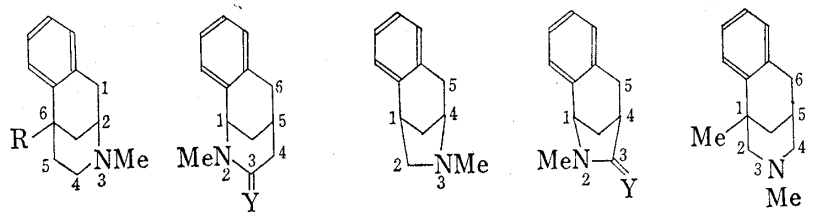
The mass spectra of 1,3-bridged 1,2,3,4-tetrahydronaphthalenes (I, I′, II, III and IV), 2,4-bridged 1,2,3,4-tetrahydroisoquinolines (VI, VII and VII′) and 1,3-bridged 1,2,3,4-tetrahydroquinolines (VIII and IX) were examined. Fragmentation pathways of these compounds are discussed. The compounds I—V undergo two major fragmentations; fission of the B-ring to give fragment ions of C-ring and A-ring, and formation of naphthalene and small nitrogen-containing fragment ions. While, the compounds VI—IX decompose to form quinoline- or isoquinoline-type fragment ions by loss of C-ring moiety. The position of nitrogen atom plays a dominant role in determining the predominance of the fragmentation.

In continuation of our previous paper concerning the mass spectrometry of 1,3-bridged 1,2,3,4-tetrahydroisoquinolines,[1] we now wish to report the mass spectra and the characteristic fragmentation processes of monoaza compounds of 1,3-bridged 1,2,3,4-tetrahydronaphthalene, 2,4-bridged 1,2,3,4-tetrahydroisoquinoline and 1,3-bridged 1,2,3,4-tetrahydroquinoline system shown in Chart 1. The 70 eV spectra are shown in Fig. 1 and 2. Assignments of



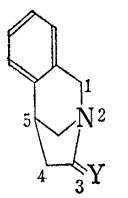
I : R=H
I′ : R=Me

II : Y=H_2
II-d_2 : Y=D_2

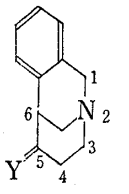
III

IV : Y=H_2
IV-d_2 : Y=D_2

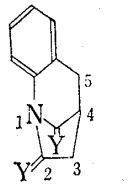
V



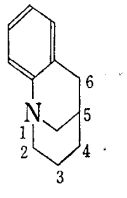
VI : Y=H_2
VI-d_2 : Y=D_2



VII : Y=H_2
VII′ : Y=O



VIII : Y=H_2
VIII-d_4 : Y=D_2



IX

Chart 1

1) Part I: S. Shiotani and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1 (1972). This paper forms Part XV of "Studies on Structure-Activity Relationship of Analgetics" by K. Mitsuhashi.
2) Location: *a*) *Hongo, Toyama*; *b*) *Gofuku, Toyama.*

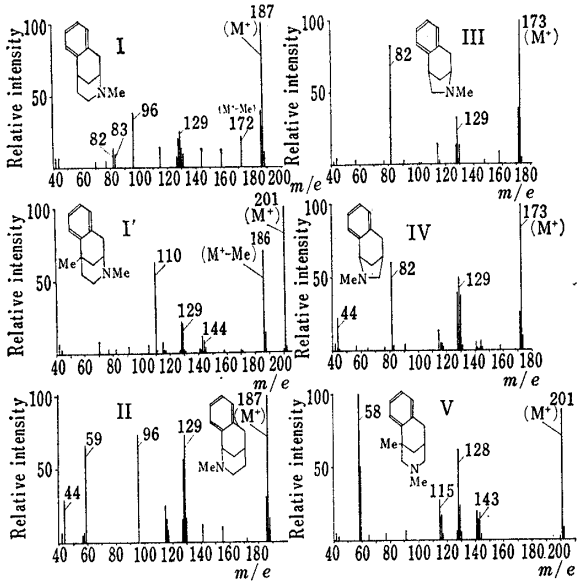


Fig. 1. Mass Spectra of I, I', II, III, IV and V

individual peaks were made with the help of high resolution mass spectra of compounds I, II, IV, VI, VII', and VIII, while some of the individual fragmentation processes were discussed with the help of the corresponding metastable ions and shifts observed in the spectra of the deuterium derivatives of compounds II, IV, VI, and VIII (II-d_2, IV-d_2, VI-d_2 and VIII-d_4).

A) Fragmentations of 1,3-Bridged 1,2,3,4-Tetrahydronaphthalenes

The spectra of compounds I, I', II, III and IV, in each of which the nitrogen atom of C-ring is attached directly to the B-ring, are similar to those of morphinan and benzomorphan derivatives,[3] that is, the spectra indicated that upon electron impact these compounds undergo two major fragmentation processes initiated by cleavage of a carboncarbon bond β to the nitrogen atom or a benzylic bond: disruption of the molecular ion to A-ring and C-ring moieties through the fission of B-ring and formation of naphthalene and small nitrogen-containing fragment ions with the cleavage of C-ring.

Table I. Corresponding Peaks in Mass Spectra of 1,3-Bridged 1,2,3,4-Tetrahydronaphthalenes

Ions	I	(compn.)[a]	I'	II	(compn.)[a]	II-d_2	III	IV	(compn.)[a]	IV-d_2	V
M+	187	($C_{13}H_{17}N$)	201	187	($C_{13}H_{17}N$)	189	173	173	($C_{12}H_{15}N$)	175	201
b	96	($C_6H_{10}N$)	110	96	($C_6H_{10}N$)	98	82	82	(C_5H_8N)	84	—
c	130	($C_{10}H_{10}$)	—	130	($C_{10}H_{10}$)	130	130	130	($C_{10}H_{10}$)	130	
c'	129	($C_{10}H_9$)	129	129	($C_{10}H_9$)	129	129	129	($C_{10}H_9$)	129	
c''	128	($C_{10}H_8$)	128	128	($C_{10}H_8$)	128	128	128	($C_{10}H_8$)	128	
c-I'	—		144	—		—	—	—		—	—
c'-I'	—		143	—		—	—	—		—	—
d	83	(C_5H_9N)	—	—		—	—	—		—	—
d'	82	(C_5H_8N)	—	—		—	—	—		—	—
e-II	—		—	59	(C_3H_9N)	61	—	—		—	—
e-IV	—		—	44	(C_2H_6N)	46	—	44	(C_2H_6N)	46	—
g	—		—	—		—	—	—		—	59
g'	—		—	—		—	—	—		—	58
h	—		—	—		—	—	—		—	143
h'	—		—	—		—	—	—		—	142
h''	—		—	—		—	—	—		—	141
i	—		—	—		—	—	—		—	128
j	—		—	—		—	—	—		—	115

a) Composition of each fragment was determined by high resolutions mass spectrometer (JEOL Model JMS-01SG).

The most characteristic feature of the spectra of these compounds is the appearance of $(M-91)^+$ peaks ascribable to type **b** ions (dihydropyridinium type for I, I', and II, pseudo-

3) *a*) H. Nakata, Y. Hirata, A. Tatematsu, H. Tada, and Y.K. Sawa, *Tetrahedron Letters*, **1965**, 829; *b*) A. Mandelbaum and D. Ginsburg, *ibid.*, **1965**, 2479; *c*) H. Audier, M. Fetixon, D. Ginsburg, A. Mandelbaum and Th. Rüll, *ibid.*, **1965**, 13; *d*) D.M.S. Wheeler, T.H. Kinstle and K.L. Rinehart Jr., *J. Am. Chem. Soc.*, **89**, 4494 (1967).

pyrrole-type for III and IV). Formation of this type ion could be associated by loss of an aromatic moiety from the molecular ion through the type **a** intermediate ion which would be induced by cleavage of the B-ring linkage at the position β to the nitrogen atom.[3] The process is supported by the presence of metastable ions at *m/e* 49.2 for I, 60.2 for I′, and 39.0 for IV, and by the fact that type **b** ions shifted higher by 2 mass units in the spectra of II-d_2 and IV-d_2.

The common peaks at *m/e* 130 (ion **c**), 129 (ion **c′**) and 128 (ion **c″**) were found to be nitrogen-free ($C_{10}H_{10}$ for **c**, $C_{10}H_9$ for **c′** and $C_{10}H_8$ for **c″**). In the spectra of II-d_2 and IV-d_2 no significant peaks were observed at *m/e* 131 and 132. Therefore, it may be concluded that these ions are ascribable to naphthalene-type and arise from each of the molecular ions (type **a′**) by initial fission at the benzylic carbon-carbon bond (carbon-nitrogen bond for II and IV) and the subsequent cleavage of the amino-side-chain. The fragmentation **a′→c** was documented by the presence of metastable ions at *m/e* 91.6 for I and II. In the case of I′, ions **c′** and **c″** would be formed from ion **c**-I′ and **c′**-I′, methyl homologues of **c** and **c′**, by loss of a methyl radical.

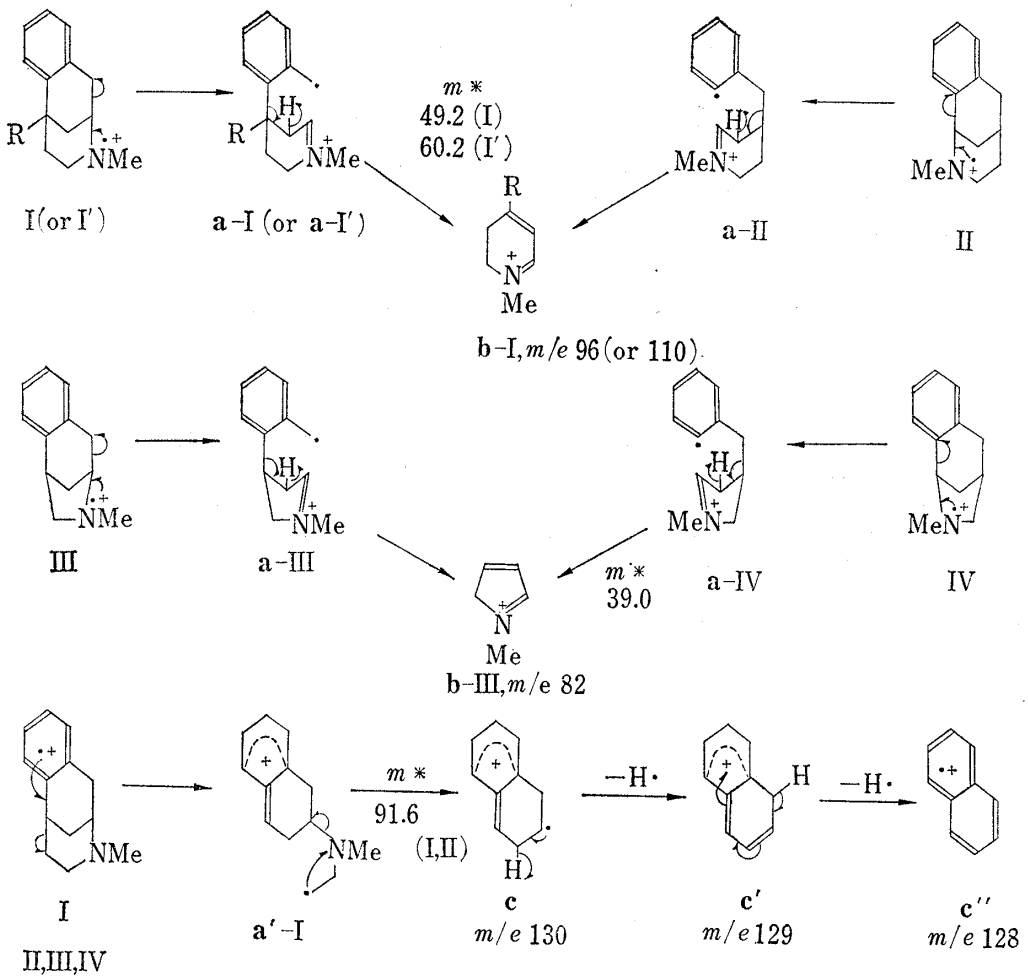


Chart 2

A pair of moderately intense peaks at *m/e* 83 and 82 (ion **d**, C_5H_9N and **d′**, C_5H_8N) in the spectrum of I represents a cleavage specific to the compound I. It is interesting that this pair of the ions or the equivalents are almost neglisible in the spectra of 1-substituted benzomorphans, morphinanes[3] and the other monoaza compounds examined herein. Ion **d** would be formed from the molecular ion by fission of the benzylic carbon-carbon bond with transfer of a hydrogen atom from C-3 to C-1 to give ion **a″**-I and the subsequent cleavage of

the allylic (1—11) bond. Ion **d**′ would be formed from ion **a**″-I by cleavage of the allylic bond with migration of a hydrogen atom at N-methyl, or from ion **d** by loss of a hydrogen atom. The former process (**a**″-I→**d**′) would be ascertained by the presence of a metastable ion at *m/e* 36.0. It is not clear why this fragmentation is almost neglisible for the others.

On the other hand, appearance of moderately intense peaks at *m/e* 59 (ion **e**-II, C_3H_9N) and 44 (ion **e**-IV, C_2H_6N) in the spectrum of II and a peak at *m/e* 44 (ion **e**-IV) in the spectrum of IV is characteristic for II and IV, which suggests the greater facility in fission of the benzylically activated carbon-nitrogen bond of II and IV. Ion **e**-II would be afforded from the molecular ion through the homolytic cleavage of the benzylic carbon-nitrogen bond with rearrangement of the C-11 hydrogen to give **a**″-II intermediate ion,[4] and the successive fission of the allylically activated bond at 4—5 with transfer of the C-6 hydrogen; while ion **e**-IV would be formed by homolytic fission of the carbon-carbon bond β to the nitrogen atom in ion **a**″. The former process would be supported by the presence of a metastable ion at *m/e* 18.7 in the spectrum of II and the shift of ion **e**-II by 2 mass units in the spectrum of II-d_2, and the latter process by the shift of ion **e**-IV in the spectra of II-d_2 and IV-d_2.

The spectrum of V exhibited a different fragmentation pattern from those of the above compounds; that is, the N-methyldihydropyridinium ion is almost neglisible. The most

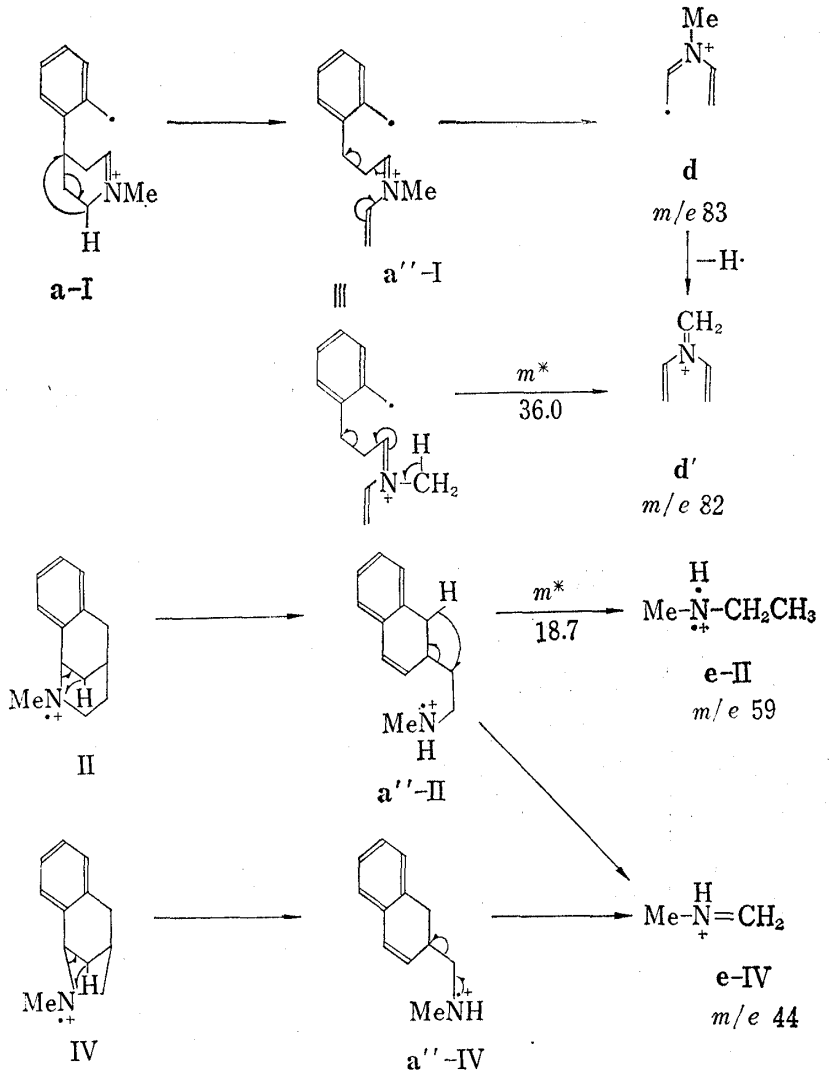


Chart 3

4) J.A. Joule and C. Djerassi, *J. Chem. Soc.*, **1964**, 2777.

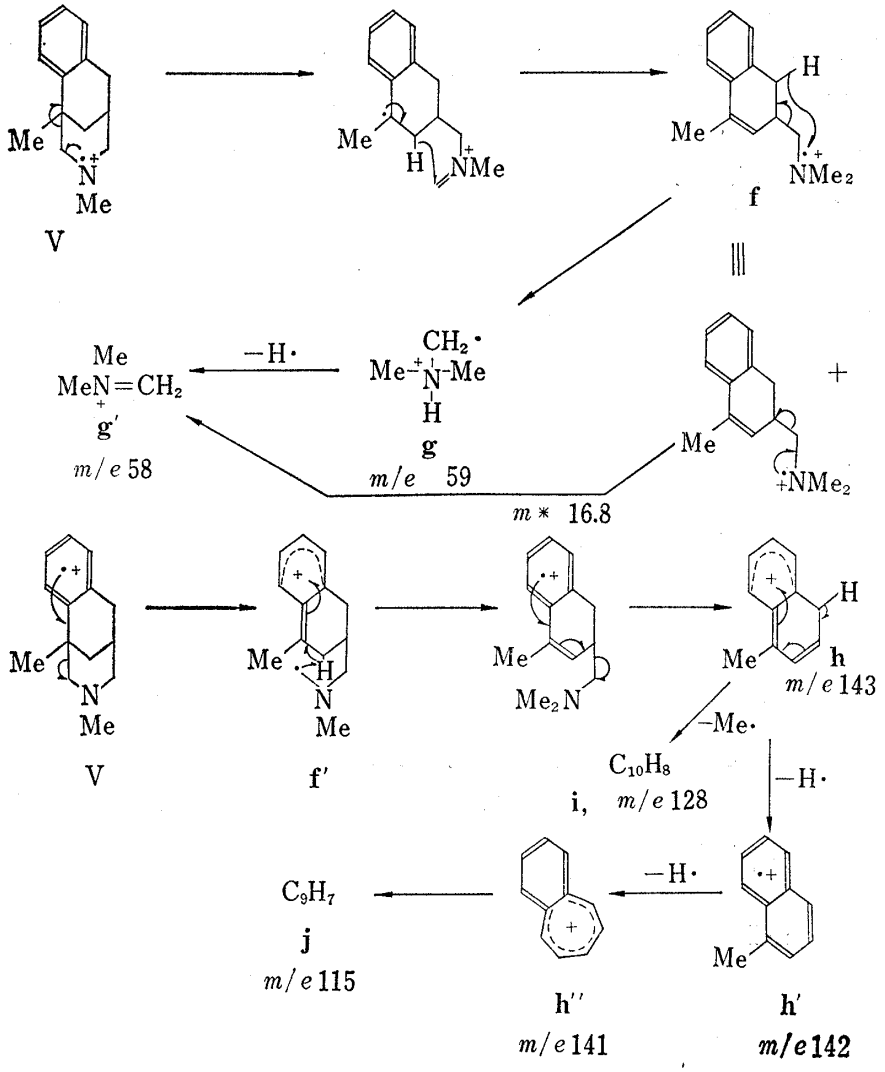


Chart 4

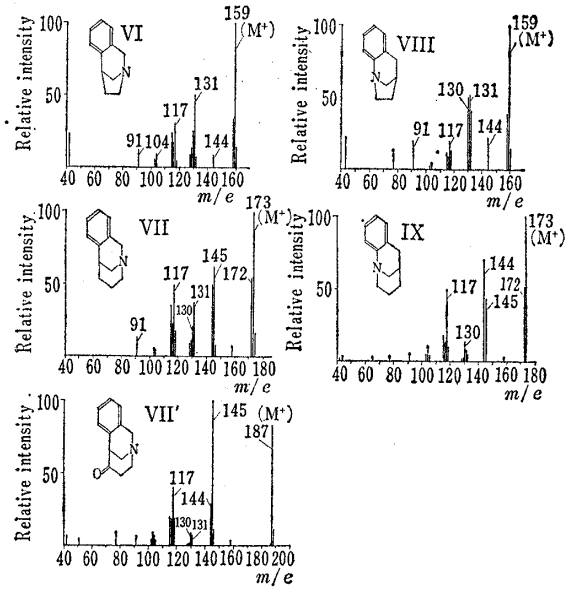


Fig. 2. Mass Spectra of VI, VII, VII', VIII, and IX

intense peak at *m/e* 58 (ion **g'**) might arise from the molecular ion through a cleavage of the benzylically activated carbon-carbon bond β to the nitrogen atom giving an intermediate ion **f** and the subsequent fission at 4—5 bond. Alternatively, cleavage of the 4—5 bond with migration of a hydrogen atom from C-6 to N-3 would give ion **g**, from which ion **g'** would be also formed by loss of a hydrogen atom. The former process is supported by the presence of an appropriate metastable ion at *m/e* 16.8. Ions at *m/e* 143, 142 and 141 (ions **h**, **h'**, and **h''**) would be formed by the similar fragmentation process from the intermediate ion **f'** charged on the benzene ring. These ions would be the progenitors of ions **i** (*m/e* 128) and **j** (*m/e* 115), respectively.

B) Fragmentation of 2,4-Bridged 1,2,3,4-Tetrahydroisoquinolines and 1,3-Bridged 1,2,3,4-Tetrahydroquinolines

The spectra of compounds VI, VII, VII′, VIII and IX indicated that the fragmentations of these four skeletons are considered to be comparable with each other and that the characteristic feature of the compounds is loss of C-ring moiety to give isoquinoline- or quinoline-type fragment ions.

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

Ions	VI (compn.)[a]	VI-d_2	VII	VII′	(compn.)[a]	VIII (compn.)[a]	VIII-d_4	IX
M+	159 ($C_{11}H_{13}N$)	161	173	187	($C_{12}H_{13}ON$)	159 ($C_{11}H_{13}N$)	163	173
M+-1	158 ($C_{11}H_{12}N$)	160	172	—		158 ($C_{11}H_{12}N$)	162 161	172
l	—	—	145	145	($C_{10}H_{11}N$)	—	—	145
m	144 ($C_{10}H_{10}N$)	146	144	144	($C_{10}H_{10}N$)	144 ($C_{10}H_{10}N$)	148 147	144
n	117 (C_9H_9)	118	117	117	(C_9H_9)	117 (C_9H_9)	120	117
n′	116 (C_9H_8)	117	116	116	(C_9H_8)	116 (C_9H_8)	)	116
n″	115 (C_9H_7)	116	115	115	(C_9H_7)	115 (C_9H_7)	115	115
n‴	—	—	118	118	(C_9H_{10})	—	—	118
o	131 (C_9H_9N)	131	131	131	(C_9H_9N)	131 (C_9H_9N)	132	131
o′	130 (C_9H_8N)	130	130	130	(C_9H_8N)	130 (C_9H_8N)	131	130

a) Composition of each fragment peak was determined by high resolution mass spectrometer (JEOL Model JMS-01SG).

A peak at *m/e* 144 (*m/e* 146 for VI-d_2, and *m/e* 147 and 148 for VIII-d_4) common to all these compounds was found to be $C_{10}H_{10}N$ and would be formulated as type **m** ion. In the case of VI and VIII having five-membered C-ring, type **m** ion would be formed by loss of a methyl radical from type **k** intermediate ion which is caused by fission of C-ring carbon–carbon linkage at the position β to the nitrogen atom, whereas in the case of VII and IX having six-membered C-ring, two pathways were observed for the formation of type **m** ion: the first is continuous loss of an ethylene (ketene for VII′) giving type **l** ion (*m/e* 145) and a hydrogen atom, and the second is loss of a hydrogen atom from the side-chain in type **k** intermediate ion giving (M+-1) ion and loss of an ethylene from (M+-1) ion. Each of the pathways is supported by the presence of the corresponding metastable ion as shown in Chart 5 and the shifts of ion **m**-VI and ion **m**-VIII in the spectra of VI-d_2 and VIII-d_4 (2 mass units higher for VI-d_2, and 3 and 4 for VIII-d_4, respectively). The pathway for the formation of type **m** ion of VII and IX through (M+-1) ion could be also supported by the fact that (M+-1) peak was neglisible in the spectrum of VII′.

Type **l** and **m** ions could undergo further decomposition initiated by loss of a hydrogen cyanide. Loss of HCN unit from type **m** ion would give a moderately intense ion **n** (*m/e* 117, C_9H_9), which would lose hydrogen atoms successively to give ions **n′** (*m/e* 116, C_9H_8) and **n″** (*m/e* 115, C_9H_7). In the case of VII, VII′, and IX, ion **n** would also arise from ion **l** by loss of HCN and a hydrogen atom through ion **n‴** (*m/e* 118, C_9H_{10}), and the process would be documented by the presence of metastable ions at *m/e* 96.0 in the spectra of VII and VII′. Metastable ions observed in the spectra of VII and VII′ at *m/e* 93.0 would suggest another process for the formation of ion **n′** from ion **l** involving loss of $HN{=}CH_2$ unit.

An alternative mode of fragmentation of VI, VII, VII′, VIII, and IX involved loss of C-ring moiety to afford type **o** (*m/e* 131, C_9H_9N) and **o′** (*m/e* 130, C_9H_8N) ions, which is initiated by fission of carbon-nitrogen bond (1—2 bond for VIII and IX, 2—3 bond for VI, VII, and VII′) in C-ring, and the pathway shown in Chart 6 would be plausible. Metastable ions at *m/e* 108.0 in the spectra of VI and VIII are appropriate to the process **k′**→**o**.

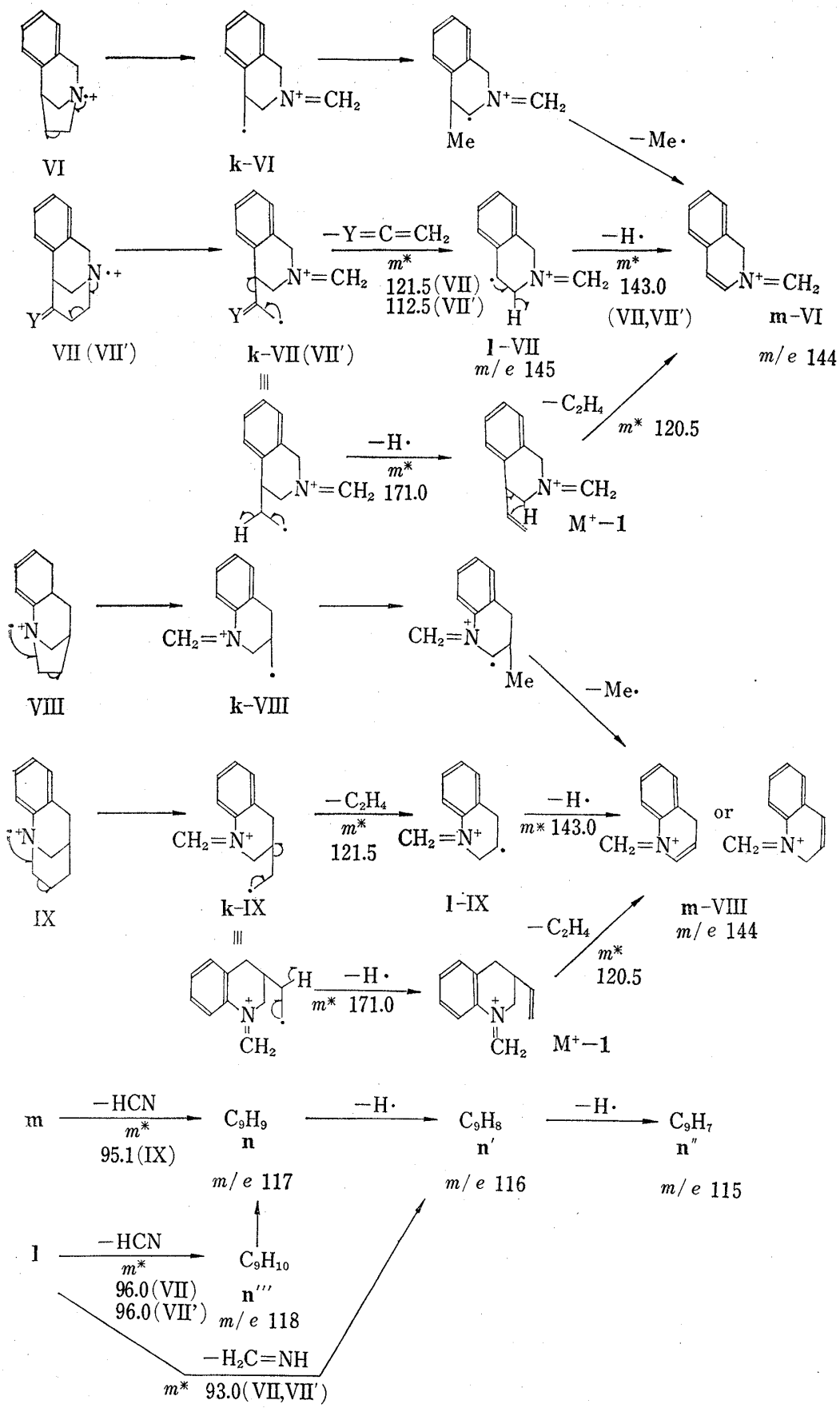


Chart 5

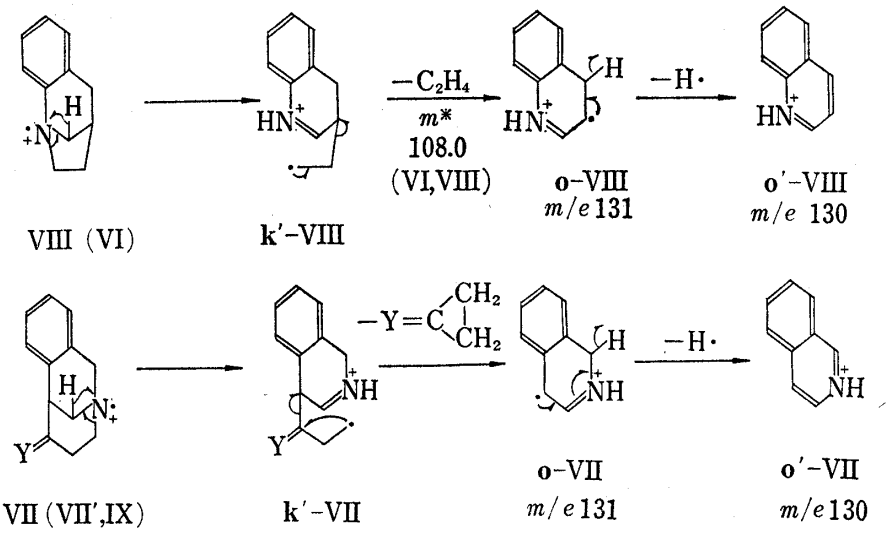


Chart 6

Experimental

Compounds——a) II-d_2 was prepared by reduction of 1,2,3,4-tetrahydro-1,5-methano-2-benzazocin-3(4*H*)-one[5] with $LiAlD_4$ and the subsequent methylation by a Clarke-Eschweiler reaction.[5]

b) IV-d_2 was prepared by reduction of 4,5-dihydro-4,5-methano-1*H*-2-benzazepin-3(2*H*)-one[5] with $LiAlD_4$ and the subsequent methylation by a Clarke-Eschweiler reaction.[5]

c) VI-d_2: Methyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate[5] was reduced with $LiAlD_4$ to give 2-benzyl-4-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-β,β-d_2, which was then derived to VI-d_2 by our method described in the previous paper.[5]

d) VIII-d_4: Methyl 3,4-dihydrocarbostyril-3-acetate[5] was reduced with $LiAlD_4$ to give 3-(β-hydroxyethyl)-1,2,3,4-tetrahydroquinoline-2,2,β,β-d_4, which was derived to VIII-d_4 by our method described in the previous paper.[5] The other compounds used in the present work were prepared by the methods described in our previous paper.[5]

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-01SG. The ionizing voltage was maintained at 70 eV for single-focussing measurement, 75 eV for double-focussing measurement. The sample heating temperature varied between 30° to 70°.

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5) K. Mitsuhashi, S. Shiotani, R. Oh-uchi, and K. Shiraki, *Chem. Pharm. Bull.* (Tokyo), **17**, 434 (1969).