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MASS SPECTRA OF 4-SUBSTITUTED 2-PHENYLPIPERIDINES

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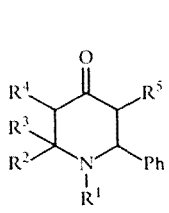
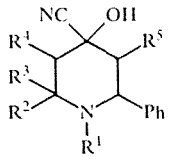
The major transformations in the mass spectral decomposition of 4-substituted 2-phenylpiperidines follow a similar pattern and primarily involve cleavage of the piperidine ring and loss of alkene molecules containing functional groups.

In a continuation of previous studies on the synthesis and properties of 2-phenylpiperidines [1-3], we investigated the mass spectral behavior of 4-substituted 2-phenylpiperidines I-IV. A detailed study of the mass spectra of such compounds has been carried out only for methyl-substituted 4-piperidones [4-10] and several methyl-substituted 4-amino-4-cyano- and 4-hydroxy-4-cyanopiperidines and piperidine-4-spirohydantoins [8, 9]. The formation of strong ion peaks due to the loss of a substituent from the α-position relative to the nitrogen atom of the piperidine ring is characteristic for the fragmentation of the compounds upon electron impact. Data are available on the fragmentation of phenylpiperidines with functional groups at $C_{(4)}$ only for two derivatives of 2,6-diphenyl-4-piperidone [5, 11].

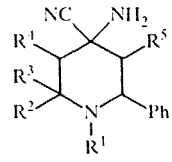
The structures of 2-phenyl-4-piperidone (I), 4-hydroxy-4-cyano-2-phenylpiperidine (II), 4-amino-4-cyano-2-phenylpiperidine (III), and 2-phenylpiperidine-4-spirohydantoin (IV) were established using PMR and ^{13}C NMR spectroscopy [1-3, 12].



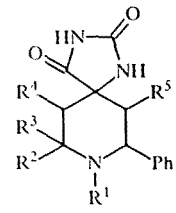
I a–m



II a,b,d,f,h,j,n



III a,b,d-f



IVb,d,f,g,h

I, –m IIa,b,d f n,j,n, III a,b,d-f, IVb,d,f,g,k a R^5 = Me; b $R^1 = R^5$ = Me; c R^4 = Me; d $R^1 = R^4$ = Me; e $R^4 = R^5$ = Me; f $R^1 = R^4 = R^5$ = Me; g $R^2 = R^3$ = Me; h $R^1 = R^2 = R^3$ = Me; i R^2 = Ph, R^5 = Me; j R^2 = =Ph, $R^4 = R^5$ = Me; f R^1 = Me; l R^1 = Et; m R^1 = Pr; n $R^1 = R^5$ = Me, R^2 = Ph, others R = H

The mass spectra of I-IV are given in Table 1. The peaks for the molecular ions (M^+) of 4-piperidones are rather strong and the molecular ion peak is the maximum in the spectrum of 1-methyl-2-phenyl-4-piperidone Ik (Table 1). The decomposition of the M^+ ions of I is in accord with the fragmentation of previously studied 4-piperidones [4-9, 11]. The loss of a hydrogen atom from the α-position relative to the nitrogen atom in the molecular ions of Ia-If and Ik-Im (or of the methyl radical from Ig and Ih) leads to the formation of Φ_1 fragments (Table 2). The ratio of the intensities of the peaks of the M^+ ions and Φ_1 is characteristic for the mass spectra of these compounds (I_{M^+}/I_{Φ_1} is 24.2-27.5 for Ia, Ic, and Ie and 2.7-6.6 for their N-methyl analogs, Ib, Id, and If) and permits us to determine the presence or absence of a methyl group at the nitrogen atom of the piperidine ring. A similar difference in the ratio of the intensities of the peaks of the M^+ and $[M - Me]^+$ (Φ_1) ions is also observed in the case of Ig and Ih. The reverse Diels–Alder decomposition of the Φ_1 ions with loss of the ketone molecule R^5CHCO leads to the formation of Φ_2 fragments, whose mass number indicates the presence of a methyl substituent at $C_{(3)}$ and $C_{(5)}$ of the piperidine ring. The Φ_2 fragments may also be formed directly from M^+ ions. Further fragmentation of the Φ_2 ions proceeds with formation of ions Φ_3-Φ_5.

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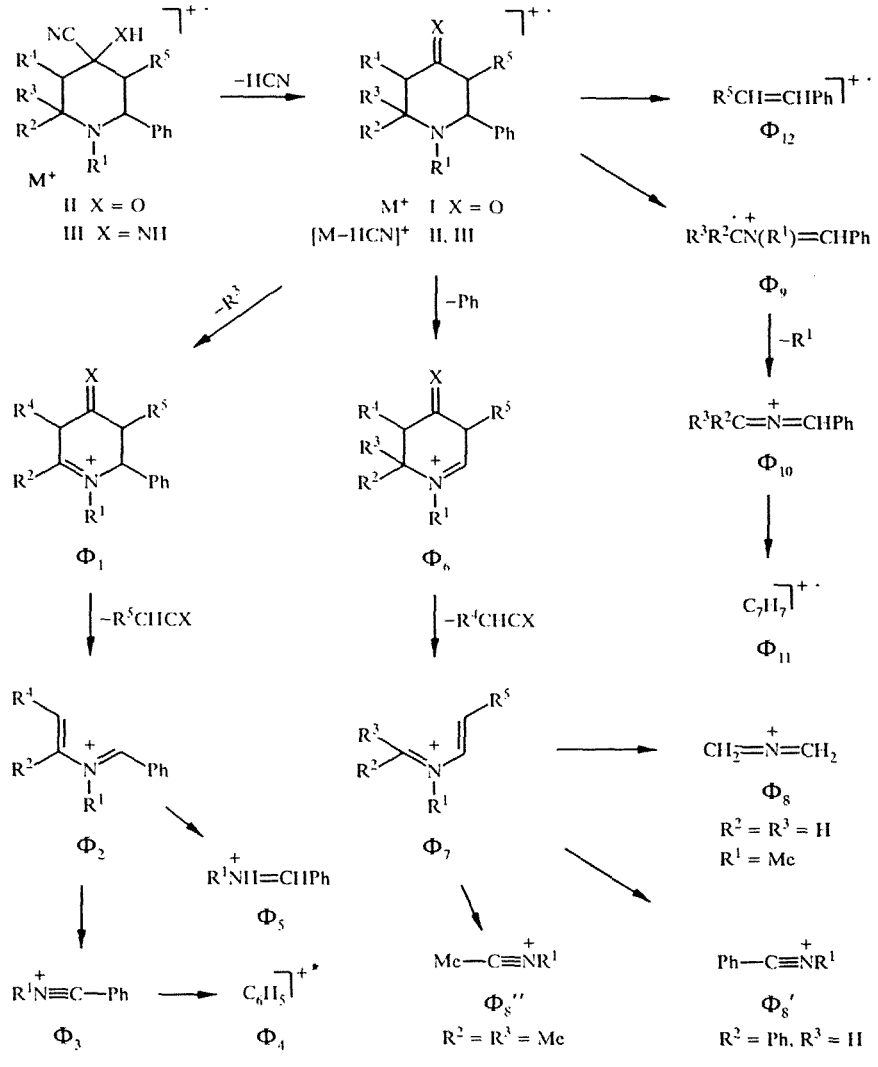


Ermakov and Sheinker [5] studied the mass spectra of 2,6-diphenyl-4-piperidone and showed that despite the loss of a phenyl radical from the M^+ ion, the intensity of the ion formed in this case is much less intense than for the ion due to loss of the methyl radical in analogous methyl-substituted 4-piperidones. The mass spectra of I also show a peak for the Φ_6 ions due to loss of a phenyl radical from the M^+ ion. The intensity of the peak for this ion is much stronger in the spectra of N-alkyl derivatives Ib, Id, If, and Ik-Im than in the spectra of Ia, Ic, and Ie, which are 4-piperidones unsubstituted at the nitrogen atom. The presence of two *gem*-methyl groups at $C_{(6)}$ of the piperidine ring in Ig and Ih suppresses formation of the Φ_6 ion (Table 2) due to the more facile loss of a methyl radical to give the Φ_1 ion. A peak for the Φ_6 ion is hardly observed in the spectra of 2,6-diphenyl derivatives Ii and Ij. The mass number of the Φ_7 ion formed subsequently due to retro-Diels–Alder decomposition of the Φ_6 ion (scheme 1) indicates the presence of a methyl group at $C_{(3)}$ of the piperidine ring.

The synchronous decomposition of the C_2—C_3 and C_5—C_6 bonds in the M^+ ions of I leads to formation of Φ_9 ions, which then decompose to give Φ_{10} and Φ_{11} ions. The Φ_{11} ion, which probably has tropylium structure, is characteristic for the spectra of alkylbenzenes [13].

The spectra of all the 4-piperidones I studied display a peak for alkenylbenzene ions Φ_{12} due to the simultaneous cleavage of the C_3—C_4 and C_2—N bonds in the M^+ ions. The greatest intensity in the mass spectra of Ib, Ie, If, and Ij is found for *m/z* 118 ions,* while the greatest intensity in the spectra of Ic, Id, Ig, and Ik is found for *m/z* 104 ions (Table 1). Two species, namely, $[C_7H_5NR^1]^+$ (Φ_3 ion) and $[C_8H_7R^5]^+$ (Φ_{12} ion), may correspond to these ions in the case of Ib, Ic, If, and Ii. The relative contribution of isobaric ions Φ_3 and Φ_{12} was established using high-resolution mass spectrometry. The 118 ion

*Here, the *m/z* values are given in the text and schemes, and the intensity of the ion peaks relative to the total ion current ($\%\Sigma_{40}$) is indicated in parentheses.

TABLE 1. Mass Spectra of I-IV*

Compound	m/z (intensity, %)
Ia	189 (97), 133 (34), 132 (100), 119 (27), 118 (84), 117 (33), 105 (47), 104 (91), 91 (59), 78 (17), 77 (25)
Ib	203 (76), 202 (32), 146 (54), 132 (22), 126 (25), 119 (25), 118 (100), 117 (28), 91 (28), 84 (20), 42 (46)
Ic	189 (68), 146 (53), 119 (11), 118 (32), 105 (24), 104 (100), 103 (14), 91 (23), 78 (11), 77 (15), 56 (11)
Id	203 (56), 202 (10), 160 (21), 126 (43), 119 (14), 118 (39), 104 (100), 103 (12), 77 (9), 70 (16), 42 (10)
Ie	203 (79), 146 (92), 133 (24), 132 (20), 119 (28), 118 (100), 117 (37), 105 (28), 104 (53), 91 (59), 77 (18)
If	217 (54), 216 (14), 160 (44), 140 (26), 132 (18), 119 (31), 118 (100), 117 (32), 91 (25), 84 (17), 42 (33)
Ig	203 (50), 188 (50), 160 (25), 146 (39), 131 (78), 106 (40), 104 (100), 103 (29), 77 (29), 58 (40), 42 (47)
Ih	217 (15), 202 (76), 131 (72), 118 (24), 104 (30), 103 (27), 98 (19), 77 (24), 72 (23), 56 (100), 42 (23)
Ii	265 (41), 194 (36), 133 (19), 132 (23), 118 (19), 117 (23), 106 (41), 104 (100), 103 (19), 91 (17), 77 (17)
Ij	279 (51), 195 (20), 194 (82), 146 (26), 133 (52), 118 (100), 117 (83), 115 (21), 106 (41), 104 (21), 91 (38)
Ik	189 (100), 188 (30), 146 (42), 119 (21), 118 (82), 112 (79), 104 (65), 103 (21), 77 (25), 70 (48), 42 (67)
Il	203 (73), 160 (31), 132 (49), 126 (72), 104 (79), 103 (36), 91 (29), 84 (100), 77 (35), 56 (54), 42 (88)
Im	217 (13), 188 (60), 117 (18), 104 (29), 103 (16), 91 (16), 84 (81), 77 (16), 43 (28), 42 (100), 41 (17)
IIa	216 (0,7), 189 (100), 133 (30), 132 (89), 119 (25), 118 (79), 117 (26), 105 (39), 104 (76), 91 (49), 77 (19)
IIb	230 (4), 203 (100), 202 (41), 146 (58), 132 (28), 126 (31), 119 (27), 118 (98), 91 (23), 84 (22), 42 (60)
IId	230 (29), 203 (38), 160 (26), 153 (72), 132 (26), 126 (31), 119 (33), 118 (57), 104 (100), 70 (32), 42 (48)
IIf	244 (8), 217 (65), 160 (50), 140 (28), 132 (22), 119 (40), 118 (100), 117 (27), 91 (20), 84 (19), 42 (37)
IIh	244 (0,3), 217 (16), 202 (78), 131 (61), 118 (24), 104 (24), 98 (18), 77 (15), 72 (25), 56 (100), 42 (22)
IIj	306 (0,9), 279 (54), 195 (20), 194 (84), 146 (25), 133 (53), 118 (100), 117 (75), 106 (48), 104 (19), 91 (34)
IIn	306 (3), 279 (51), 146 (29), 120 (79), 119 (18), 118 (100), 117 (24), 104 (90), 91 (23), 77 (16), 42 (45)
IIIa	215 (3), 199 (51), 133 (29), 132 (44), 119 (57), 118 (100), 117 (29), 105 (45), 104 (92), 91 (79), 70 (35)
IIIb	229 (5), 203 (35), 202 (37), 159 (60), 158 (53), 146 (39), 132 (39), 125 (96), 118 (100), 117 (33), 91 (43)
IIId	229 (11), 159 (43), 158 (44), 125 (55), 120 (100), 119 (36), 118 (73), 104 (68), 70 (49), 44 (38), 42 (87)
IIIe	229 (2), 203 (22), 147 (21), 146 (55), 119 (61), 118 (100), 117 (28), 105 (32), 104 (58), 91 (73), 84 (23)
IIIf	243 (7), 173 (35), 160 (40), 139 (38), 132 (28), 119 (52), 118 (100), 117 (31), 91 (33), 84 (28), 42 (51)
IVb	273 (25), 196 (14), 160 (31), 155 (44), 146 (31), 132 (29), 119 (45), 118 (100), 117 (22), 91 (21), 42 (46)
IVd	273 (29), 196 (58), 169 (100), 160 (36), 154 (32), 146 (54), 119 (49), 118 (76), 104 (66), 70 (61), 42 (64)
IVf	287 (21), 169 (40), 161 (34), 160 (93), 119 (78), 118 (100), 117 (29), 91 (25), 84 (35), 44 (20), 42 (53)
IVg	273 (0,3), 258 (63), 217 (79), 160 (56), 154 (44), 146 (59), 106 (64), 104 (100), 58 (80), 44 (53), 42 (94)
IVk	259 (18), 182 (41), 155 (100), 146 (67), 132 (23), 119 (23), 118 (60), 104 (28), 70 (41), 44 (23), 42 (58)

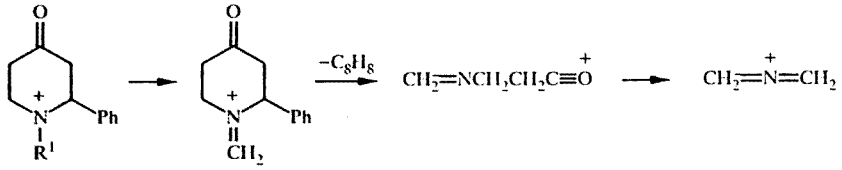
*The molecular ion peak and 10 strongest peaks are given.

TABLE 2. Intensity of the Peaks of Characteristic Ions in the Mass Spectra of I-IV

Compound	W_M	Intensity (% of total ion current) W_M													
		$[M-HX]^+$	$[M-HCN]^+$	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	$\Phi_8-\Phi^*_8$	Φ_9	Φ_{10}	Φ_{11}	Φ_{12}
Ia	12,1	—	—	0,5	10,9	9,9	2,7	1,6	0,3	0,8	—	2,9	7,6	6,4	1,5
Ib	12,3	—	—	4,5	7,6	12,0	2,0	0,8	3,5	2,8	6,5	0,7	Φ_3	3,9	2,1
Ic	14,6	—	—	0,6	10,0	6,3	2,8	1,0	0,9	2,1	—	2,1	6,0	4,3	12,5
Id	13,2	—	—	2,0	4,3	7,9	1,9	0,4	8,7	3,3	2,0	0,3	Φ_3	1,5	20,4
Ie	11,0	—	—	0,4	11,0	6,4	2,2	1,3	0,3	0,8	—	3,4	10,0	7,1	2,0
If	10,4	—	—	2,3	7,3	14,2	1,6	0,8	4,3	0,6	5,5	0,7	Φ_3	4,1	2,3
Ig	6,4	—	—	5,5	4,3	3,8	3,2	4,4	0,3	2,6	5,2	0,6	Φ_2	1,6	7,2
Ih	2,4	—	—	10,6	0,2	3,3	3,3	0,9	0,7	2,6	13,9	—	1,3	1,7	4,2
Ii	8,8	—	—	—	1,1	5,9	3,0	7,3	—	0,5	Φ_3	6,4	6,4	3,0	11,8
Ij	7,4	—	—	—	0,8	2,4	1,9	4,8	—	3,0	Φ_3	2,3	9,5	4,4	11,6
Ik	11,7	—	—	3,1	4,3	8,4	2,6	0,3	8,1	4,9	6,9	0,3	Φ_3	1,6	6,7
Il	7,7	—	—	2,0	2,8	4,4	3,2	0,2	6,5	9,0	4,9	0,1	2,3	2,6	7,1
Im	2,4	—	—	0,3	0,7	1,9	2,5	—	1,6	1,7	1,5	—	1,7	2,5	4,5
IIa	0,1	0,3	12,7	0,6	11,3	9,7	2,4	1,7	—	0,9	—	3,2	8,7	6,2	1,4
IIb	0,6	1,2	12,7	5,2	7,4	10,7	1,5	0,8	0,3	2,8	7,6	0,8	Φ_3	2,9	1,8
IId	3,8	0,7	4,3	0,7	2,9	6,4	2,0	0,6	8,1	3,6	5,4	0,8	Φ_3	1,7	11,2
IIf	1,5	0,8	10,0	2,4	7,6	13,0	1,2	1,0	0,9	2,9	5,6	1,2	Φ_3	3,0	2,2
IIh	0,05	—	2,7	13,1	0,1	3,4	2,5	0,9	—	3,0	16,8	—	0,6	1,3	4,0
IIj	0,1	—	6,7	0,1	0,9	2,4	1,4	6,0	—	3,1	Φ_3	2,5	10,4	4,2	12,4
IIo	0,5	0,3	6,7	0,2	0,5	11,3	2,1	10,4	0,2	0,8	Φ_3	0,2	0,2	3,0	1,9
IIIa	0,3	4,3	1,4	0,4	3,7	7,8	2,4	1,4	—	3,0	—	4,8	7,3	6,7	1,2
IIIb	0,5	2,0	2,8	0,9	3,0	6,6	1,6	1,2	0,2	2,3	6,2	0,6	Φ_3	3,3	1,1
IIId	1,0	0,4	1,5	1,1	1,6	5,2	2,3	7,1	1,7	3,5	6,2	0,4	Φ_3	2,1	4,8
IIIe	0,2	1,4	1,4	0,4	5,7	6,0	1,9	2,1	—	0,8	—	6,3	9,0	7,5	1,5
IIIf	1,9	0,9	1,7	0,7	4,3	9,1	1,3	2,7	0,5	3,0	5,4	0,7	Φ_3	3,5	1,5
IVb	3,6	—	—	0,6	8,8	10,2	1,0	0,9	1,7	1,9	5,5	0,7	Φ_3	2,5	1,7
IVd	2,7	—	—	0,6	2,8	6,0	1,4	1,3	4,5	4,8	5,0	0,3	Φ_3	1,7	5,2
IVf	2,7	—	—	0,3	10,0	9,3	1,1	1,4	1,8	3,8	5,7	0,5	Φ_3	2,7	1,5
IVg	0,02	—	—	4,2	3,9	2,2	2,1	4,3	—	2,9	6,3	0,9	Φ_2	1,3	4,4
IVk	2,2	—	—	0,9	6,9	6,2	1,6	0,6	4,2	4,2	6,0	0,4	Φ_3	1,5	2,9

in the spectra of Ib and If corresponds to species $[C_8H_8N]^+$ and $[C_9H_{10}]^+$ with 6:1 intensity ratio, while $[C_7H_6N]^+$ and $[C_8H_8]^+$ with 1:2 intensity ratio correspond to the 104 ion in the spectra of Ic, Ig, and Ii.

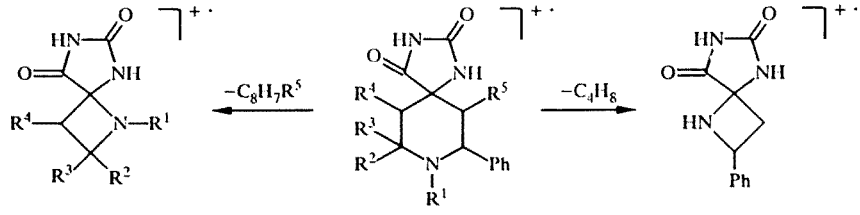
The features established for the decomposition of the M^+ ions of Ia-Ik are also found in the case of N-alkyl-4-piperidones *Il* and Ii. However, the predominant pathway for the fragmentation of the M^+ ions for these compounds is the loss of a portion of the alkyl substituent at the nitrogen atom and then of an alkenylbenzene molecule. The high intensity of the 188 ions is typical for amine fragments formed in the loss of substituents from the α-position relative to the radical–ion site [14].



M^+ I *l*, m 188(2, 3) I *l* 84(9, 0) I *l* 42(7, 9) I *l*
188(9, 4) I m 84(12, 7) I m 42(15, 6) I m

The mass spectra of 4-hydroxy- (II) and 4-amino-4-cyanopiperidines (III) have weak M^+ ion peaks (Table 1). Fragmentation with formation of $[M - Me]^+$ and $[M - Me - HCN]^+$ ions is most characteristic for their 2-methylpiperidine analogs [8, 9]. The $[M - HCN]^+$ ion peaks in the spectra of these compounds have low intensity. On the other hand, the major direction for the decomposition of the M^+ ions for II and III is the loss of an HCN molecule. Loss of the phenyl radical from the M^+ ions of II and III occurs but the peaks of the ions formed are either weak, with the exception of IId, or entirely absent. The subsequent fragmentation of the $[M - HCN]^+$ ion proceeds through decomposition of the M^+ ions of 4-piperidones (Table 2). The loss of the functional substituent (OH or NH_2) as a radical with formation of an $[H - HX]^+$ ion is common for the fragmentation of the M^+ ions of II and III, respectively. The loss of NH_3 or the CN radical is possible for III as for methyl-substituted 4-amino-4-cyanopiperidines [9]. Peaks for the analogous ions in the spectra of II are lacking in their mass spectra. All these features of the fragmentation of the M^+ ions of I related to the position of the methyl groups in the piperidine ring, are also seen in the mass spectra of II and III.

The mass spectra of piperidine-4-spirohydantoins IV show strong M^+ ion peaks (Table 1). The major decomposition processes of the M^+ ions of these compounds completely correspond to the mass spectral fragmentation of the 4-piperidones studied (Table 2). On the other hand, the presence of a spirohydantoin ring at $C_{(4)}$ of the piperidine ring leads to an additional channel for the decomposition of M^+ ions in comparison with 4-piperidones. One of these pathways for the mass spectral decomposition of IV is the elimination of the alkenylbenzene molecule from the M^+ ion leading to a strong ion peak, which is the predominant peak for IVd and IVk. The loss of an alkene molecule by the M^+ ion is most characteristic for IVg. Furthermore, we find $[M - Me]^+$ ions in the spectra of IVb, IVd, IVf, and IVk. Analogs of these peaks are lacking in the spectra of the corresponding 4-piperidones I.



M^+ IV 217(15.2) IV*ж*

IVb 155 (5,2), IVd 169 (7,8), IVf 169 (4,3), IVg 169 (0,3), IVk 155 (10,3)

Thus, the mass spectrometric study of 2-phenylpiperidines IV, which feature a functional group at $C_{(4)}$, showed that the electron impact fragmentation is monotypical and related largely to the cleavage of the piperidine ring and loss of alkene molecules containing the functional group. The presence of a phenyl substituent in I-IV leads to the circumstance that their strongest mass spectral peaks contain an aromatic ring. The mass spectra of 2-phenylpiperidines I-IV provide complete information on the number and position of the methyl substituents in the piperidine ring and permit us to distinguish between structural isomers of this class.

EXPERIMENTAL

The preparations of I-IV are described in our previous work [1-3, 15].

The low- and high-resolution mass spectra were obtained on a Finnigan MAT-90 spectrometer at 70 eV by direct inlet into the source. The temperature of the ionization chamber was 150°C and the injection temperature of the samples ranged from 25 to 120°C. The resolution $M/\Delta M = 8500$.

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