

MASS SPECTRA OF N-SUBSTITUTED
2,4,4,6-TETRAMETHYL-3,5-DICYANO-1,4-DIHYDROPYRIDINES*

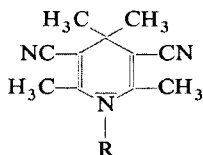
J. PALEČEK and J. KUTHAN

*Department of Organic Chemistry,
Institute of Chemical Technology, 166 28 Prague*

Received November 16th, 1974

In the mass spectra of six N-substituted 2,4,4,6-tetramethyl-3,5-dicyano-1,4-dihydropyridine derivatives *I–VI* most ionic species are formed from the pyridinium cation which results from the molecular ion by splitting off the methyl radical at C₍₄₎. Suggested fragmentation paths were evidenced by the presence of significant metastable ions, by the spectra of some specifically deuterated analogues, and by low-energy electron spectra. The effect of a substituent in the 1-position on the fragmentation is discussed.

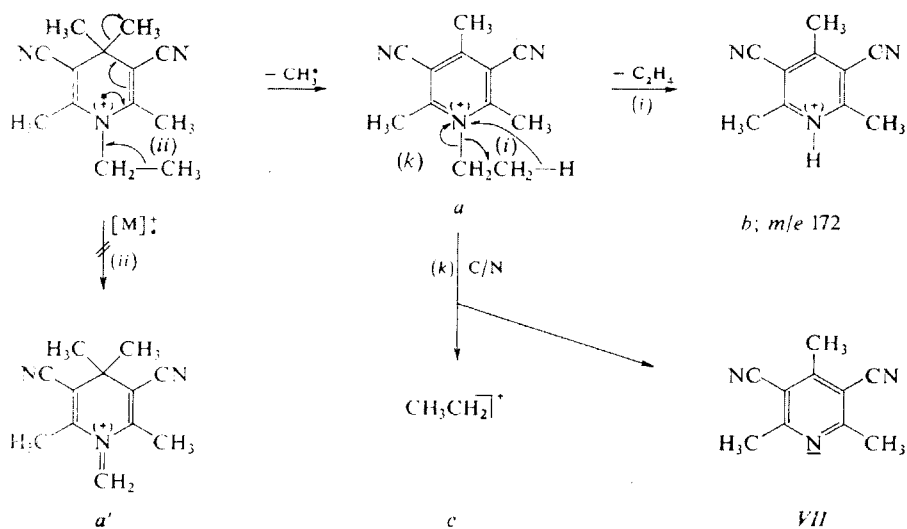
Little attention has been paid to the study of mass spectra of dihydropyridine derivatives. In the interpretation of mass spectra of N-alkyl-3-cyano-1,4-dihydropyridines¹, 3,5-diethoxycarbonyl-(or diacetyl)-1,4-dihydropyridines², N-substituted 2-aryl-5-cyano-1,2-dihydropyridines³, and 3,5-dicyano-2,6-dimethyl-4,4-disubstituted-1,4-dihydropyridines⁴ the authors proved that either hydrogen or a substituent split away from the position 4 or 2 of the molecular ion and the pyridinium cation was formed with a high intensity. In the fragmentation that followed, substituents and functional groups played a significant role. It appeared interesting to investigate — in connection with our systematic study of dihydropyridine derivatives^{5–7} — in which way the fragmentation would be influenced by a substituent on the nitrogen atom.



- | | | |
|--|---|---|
| <i>I</i> , R = CH ₃ | <i>I</i> b, R = CD ₃ CH ₂ | <i>III</i> c, R = CD ₃ CH ₂ CH ₂ |
| <i>I</i> a, R = CD ₃ | <i>III</i> , R = CH ₃ CH ₂ CH ₂ | <i>IV</i> , R = C ₆ H ₁₁ |
| <i>II</i> , R = CH ₃ CH ₂ | <i>III</i> a, R = CH ₃ CH ₂ CD ₂ | <i>V</i> , R = C ₆ H ₅ |
| <i>II</i> a, R = CH ₃ CD ₂ | <i>III</i> b, R = CH ₃ CD ₂ CH ₂ | <i>VI</i> , R = C ₆ H ₅ CH ₂ |

* Part XXXIV in the series On Dihydropyridines; Part XXXIII: This Journal 40, 1892 (1975).

In this communication we report (Table I) on the mass spectra of six selected derivatives *I–VI*. As substituents representatives of aliphatic, alicyclic, and aromatic series were chosen. To elucidate the particular fragmentation mechanisms, several specifically deuterated analogues were prepared and the spectra were also measured at the energy of ionizing electrons 12 eV. The mass spectra of the compounds *I–IV* (Table I) are characterized by the presence of the molecular ion of medium abundance, while with the derivatives containing the aromatic ring, *V* and *VI*, the abundance of this ion is smaller. The base peak in the spectra of the compounds *I–III*, and *V* corresponds to the pyridinium cation of the type *a* (see Scheme 1) which is formed by dissociation of the methyl radical from the C₍₄₎ atom of the molecular ion, in agreement with the previous findings⁴. This dissociation process is the main fragmentation path and the ionic species represented by *a* dominate the spectra of all studied compounds. In all cases a strong metastable peak was found corresponding to the process $M^+ \rightarrow [M-15]^+$. As it can be seen from the spectra, the character of the substituent R plays a significant role in influencing the abundance of the particular ionic species. Scheme 1 shows, on the example of the ethyl derivative *II*, the formation of various ionic species of a significant abundance. However, in the case of formation of the ion $[M-15]^+$ one may consider another alternative path, besides the above mentioned dissociation of the methyl radical from the position 4 of the molecular ion, namely the α -splitting of the N—CH₂CH₃ group (see *ii* in Scheme 1) and the formation of the fragment *a'*. This type of fragmentation resulting in the formation of the corresponding abundant ions was shown to occur in N-alkyl-3-cyano-1,4-di-



SCHEME 1

TABLE I

Mass Spectra of N-Substituted Dihydropyridines (70 eV and 12 eV)

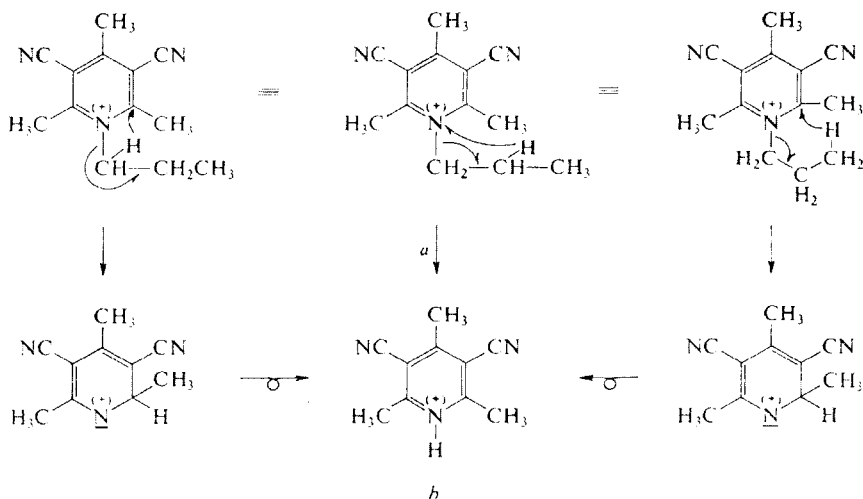
Letters indexing ion species correspond to designation of fragments in Scheme 1. The table lists only the ion species of integral m/e and of abundance higher than 3% of relative intensity.

Substance R	eV	Fragments											
<i>I</i> CH_3	70	m/e	202	201 ^M	187	186 ^a	172 ^b	56	42	15 ^c			
	70	% r.i.		7.6	14.3	100	3.6	3.6	3.7	3.1			
	12	% r.i.	4.6	31.6	14.4	100							
<i>Ia</i>	70	m/e	204 ^M	190	189 ^a	188	172 ^b	67	56	43	42	41	18 ^c
		% r.i.	5.7	13.4	100	3.4	3.6	3.9	2.8	4.8	6.2	5.9	6.2
		% r.i.											
<i>II</i> CH_3CH_2	70	m/e	216	215 ^M	201	200 ^a	173	172 ^b	171	55	42	29 ^c	27
		% r.i.		9.7	14.5	100	6.1	50.0	7.4	3.8	7.9	25.0	8.7
	12	% r.i.	4.9	30.0	15.0	100							
<i>IIa</i> CH_3CD_2	70	m/e	217 ^M	203	202 ^a	201	173 ^b	172 ^b	171	44	43	42	41
		% r.i.	7.7	14.6	100	8.4	16.9	46.7	6.4	4.0	4.0	10.3	4.0
	70	m/e	31 ^c	30	29	27							
<i>IIb</i> CD_3CH_2	70	m/e	218 ^M	204	203 ^a	201	174	173 ^b	172 ^b	171	44	43	42
		% r.i.	7.1	14.2	100	5.1	5.0	41.3	31.4	5.1	9.2	7.6	8.3
	70	m/e	32 ^c	31	30	29							
<i>III</i> $\text{CH}_3\text{CH}_2\text{CH}_2$	70	m/e	230	229 ^M	215	214 ^a	173	172 ^b	171	43 ^c	42	41	39
		% r.i.	3.3	11.2	15.9	100	7.3	59.3	8.6	57.9	8.3	24.0	7.7
	12	% r.i.	5.0	29.7	15.9	100	12.8						

TABLE I
(Continued)

Substance R	eV	Fragments															
<i>IIIa</i> CH ₃ CH ₂ CD ₂	70	<i>m/e</i>	231 ^M	217	216 ^a	215	174	173 ^b	172 ^b	171	45 ^c	44	43	42	41		
		% r.i.	7.9	15.4	100	7.9	2.9	23.9	60.9	6.5	70.5	6.7	15.2	15.8	4.2		
		<i>m/e</i>	39	29	27												
<i>IIIb</i> CH ₃ CD ₂ CH ₂	70	<i>m/e</i>	231 ^M	217	216 ^a	215	173 ^b	172 ^b	171	45 ^c	44	43	42	41	40		
		% r.i.	10.6	16.4	100	13.3	19.4	51.5	6.1	63.6	9.5	16.4	20.3	6.4	6.4		
		<i>m/e</i>	39	29	27												
<i>IIIc</i> CD ₃ CH ₂ CH ₂	70	<i>m/e</i>	232 ^M	218	217 ^a	174	173 ^b	172 ^b	171	46 ^c	44	43	42	41	40		
		% r.i.	11.1	15.8	100	3.1	26.3	41.1	7.0	61.6	8.6	13.6	9.2	5.0	15.6		
		<i>m/e</i>	39	29	27												
<i>IV</i> C ₆ H ₁₁	70	<i>m/e</i>	269 ^M	255	254 ^a	173	172 ^b	171	84	83 ^c	67	56	55	54	53		
		% r.i.	9.0	4.8	24.8	13.2	100	5.9	6.7	96.6	5.0	3.1	71.4	4.4	5.7		
		<i>m/e</i>	43	42	41	39	29	27									
<i>V</i> C ₆ H ₅	70	<i>m/e</i>	3.8	5.9	38.7	9.2	8.8	7.1									
		% r.i.	263 ^M	249	248 ^a	77 ^c	51										
		<i>m/e</i>	5.2	18.4	100	17.2	6.9										
<i>VI</i> C ₆ H ₅ CH ₂	70	<i>m/e</i>	278	277 ^M	263	262 ^a	92	91 ^c	65	51	39						
		% r.i.	3.1	12.0	100	11.3	3.2	4.1									
		<i>m/e</i>	5.8	26.2	21.8	100	6.9	85.5									

hydropyridines¹. However, the absence of the ionic species $[M-CD_3]^+$ at m/e 200 in the spectrum of the 2,2,2-trideuterioethyl derivative *I**b*** excludes the latter mechanism. This conclusion is in agreement with the virtual absence of the ionic species $[M-C_2H_5]^+$ in the N-propyl derivative *III* and of the corresponding ionic species in the deuterated analogues *IIIa-IIIc*. Fragmentation of the pyridinium cation represented by *a* continues then along two significant paths $a \rightarrow b$ and $a \rightarrow c$. In the first case, in agreement with the finding of the above mentioned authors¹, a prominent ionic species *b* of m/e 172 is formed upon breaking off one ethylene molecule (or an alkene) and a simultaneous transfer of hydrogen into the pyridinium core (see *i*, Scheme 1). This process is energetically inconvenient with the derivatives *I*, *V*, and *VI* (it assumes a dissociation of methylene, dehydrobenzene, or dehydropropylum), and thus the abundance of the ionic species of m/e 172 is in the respective spectra very low, in agreement with the suggested fragmentation mechanism. The origin of the transferred hydrogen in the step $a \rightarrow b$ was determined from the mass spectra of the deuterium labelled compounds *IIa*, *IIb*, and *IIIa-IIIc* (Table II). As it can be seen from this table, the hydrogen transfer does not occur exclusively from one particular carbon atom of the aliphatic chain. In the case of the ethyl derivatives *II* the hydrogen transfer occurs preferentially from the β -carbon, while with the propyl derivatives *III* the transfer is practically equally probable from all positions of the chain, if we consider statistical abundances. Therefore, it may be assumed that in the hydrogen transfer a four-membered or a six-membered mechanism plays a role (see the analogy in the fragmentation of amines⁸), as shown in Scheme 2. Relative increase of the abundances of the ion peaks at m/e 172–174 in the deuterated



SCHEME 2

analogues is only apparent, as in fact no change of $\sum_{172}^{174}/\sum_{29}^*$ occurs with respect to the basic non-deuterated derivative. As one can see from Table I, the relative abundance of the ion represented by *b* increases in the compounds *II–IV* with the size of the substituent R and in the spectrum of the N-cyclohexyl derivative it amounts to 100% of the relative intensity (base peak).

In the second fragmentation path $a \rightarrow c$ heterolytic splitting of the C—N bond occurs (see *k*, Scheme 1). This process is favoured through the formation of the stable 3,5-dicyano-2,4,6-trimethylpyridine molecule (*VII*). The splitting of this bond is further positively influenced by the thermodynamic stability of the fragment $[R]^+$. In agreement with this conclusion, the base peak in the spectrum of the N-benzyl derivative *VI* is the tropylium ion of m/e 91. An increase of the $[M 15]^+$ fragment abundance (type *a*, relative intensity 100%, Scheme 1) and a decrease of the tropylium cation abundance (relative intensity 85.5%) in the spectrum obtained when ionizing with 12 eV electrons supports the suggested fragmentation mechanism. By the direct analysis of daughter ions⁹ (DADI), the process $a \rightarrow c$ was definitely confirmed by the presence of the metastable transition $[262]^+ \rightarrow [91]^+ + 171$. Other ionic species, m/e 65, 51, and 39, result from the fragmentation of the tropylium cation. An analogous change of the spectra (70 eV and 12 eV) can be seen in the N-cyclohexyl derivative *IV*. The region of the spectrum below m/e 83 (ion $[C_6H_{11}]^+$) represented by *c* is qualitatively identical with the spectrum of cyclohexane¹⁰. Therefore, ionic species m/e 55, 54, 53, 42, 41, 39 and 29 are for the greatest part obviously products of the cyclohexyl radical fragmentation. The fragmentation path $a \rightarrow c$ plays a significant role in the compound *III*, with a lesser importance in the ethyl *II* and phenyl *V* derivatives,

TABLE II

Deuterium Transfer in the Fragmentation Process $a \rightarrow b$ (see Scheme 1)Calculation carried out as described in ref.¹

Substance	R	% of rel. int. m/e 173	% of rel. int. m/e 172	% Deuterium transferred
<i>II</i>	CH ₃ CH ₂	6.1	50.0	—
<i>IIa</i>	CH ₃ CD ₂	16.9	46.7	19.3
<i>IIb</i>	CD ₃ CH ₂	41.3	31.2	54.6
<i>III</i>	CH ₃ CH ₂ CH ₂	7.3	59.3	—
<i>IIIa</i>	CH ₃ CH ₂ CD ₂	23.3	60.9	20.6
<i>IIIb</i>	CH ₃ CD ₂ CH ₂	19.4	51.5	20.2
<i>IIIc</i>	CD ₃ CH ₂ CH ₂	26.4	41.1	34.1

* Values of the total ion current were calculated from all ion currents of the mass spectrum

TABLE III
Physico-Chemical Properties of N-Alkyl-1,4-dihydropyridines Labelled by Deuterium

Substance R	M.p., °C (yield, %)	Formula (m.w.)	Calculated/Found			Deuterium content ^c	UV-spectrum (ethanol c 4, 10^{-5} M)	
			% C	% H + D	% N		λ_{\max}	(log ϵ)
<i>Ia</i> CD ₃	172–173 (87.5 ^a)	C ₁₂ H ₁₂ D ₃ N ₃ (204.3)	70.55	8.88	20.57	d_3 99.8	219	343
			70.34	8.67	20.72	d_2 —	(4.17)	(3.44)
<i>Ila</i> CH ₃ CD ₂	156–157 (80.3 ^a)	C ₁₃ H ₁₅ D ₂ N ₃ (217.3)	71.85	8.81	19.34	d_2 93.5	223	345
			71.89	8.63	19.52	d_1 5.7	(4.17)	(3.42)
<i>Ilb</i> CD ₃ CH ₂	159–160 (76.3 ^a)	C ₁₃ H ₁₄ D ₃ N ₃ (218.3)	71.52	9.23	19.25	d_3 87.4	222	345
			71.30	9.17	19.41	d_2 7.6	(4.16)	(3.34)
<i>IIIa</i> CH ₃ CH ₂ CD ₂	115–116 (78.5 ^b)	C ₁₄ H ₁₇ D ₂ N ₃ (231.3)	72.67	9.15	18.17	d_2 93.1	222	341
			72.57	9.06	18.40	d_1 5.6	(4.17)	(3.42)
<i>IIIb</i> CH ₃ CD ₂ CH ₂	113–114 (83.3 ^b)	C ₁₄ H ₁₇ D ₂ N ₃ (231.3)	72.67	9.15	18.17	d_2 86.0	223	343
			72.35	8.87	18.32	d_1 12.3	(4.16)	(3.30)
<i>IIIc</i> CD ₃ CH ₂ CH ₂	113–114 (87.1 ^b)	C ₁₄ H ₁₆ D ₃ N ₃ (232.3)	72.37	9.54	18.09	d_3 97.7	222	343
			72.44	9.38	18.16	d_2 2.3	(4.17)	(3.38)

^a Crystallized from ethanol; ^b from the mixture benzene-hexane; ^c calculation carried out from the spectra measured at electron energy 12 eV.

TABLE IV
 $^1\text{H-NMR}$ Spectra and Infrared Spectra of N-Alkyl-1,4-dihydropyridines Labelled by Deuterium

Substance R	$^1\text{H-NMR}$ spectrum (δ) in CDCl_3^a			IR-spectrum in CCl_4					
	$\text{CH}_3\text{C}=\text{C}$	$(\text{CH}_3)_2\text{C}$	NCH_2	$-\text{CH}_2-$ $-\text{CH}_3$	$\nu(\text{CH}_3)$	$\nu(\text{C}=\text{N})$	$\nu(\text{CD})$	$\nu(\text{C}=\text{C})^b$	$\delta(\text{CH}_3)$
<i>Ia</i> CD_3	2.24 s	1.36 s	—	—	2.962 2.920	2.200	2.080 (2.120)	1.648 1.585	1.432 1.388 1.358
<i>IIa</i> CH_3CD_2	2.24 s	1.38 s	—	— 1.18 s	2.970 2.930	2.200	2.082 (2.150)	1.648 1.585	1.457 1.443 1.389 1.360
<i>IIb</i> CD_3CH_2	2.24 s	1.37 s	3.55 s	—	2.963 2.920	2.200	2.082	1.650 1.585	1.457 1.442 1.389 1.360
<i>IIIa</i> $\text{CH}_3\text{CH}_2\text{CD}_2$	2.23 s	1.37 s	—	— 1.55 k 0.93 t	2.960 2.925 2.880	2.200	2.155	1.648 1.582	1.458 1.440 1.395 1.380
<i>IIIb</i> $\text{CH}_3\text{CD}_2\text{CH}_2$	2.23 s	1.37 s	3.43 s	— 0.93 s	2.965 2.930 2.880	2.200	2.128	1.645 1.582	1.456 1.450 1.395 1.373
<i>IIIc</i> $\text{CD}_3\text{CH}_2\text{CH}_2$	2.23 s	1.37 s	3.44 t	— 1.53 t	2.965 2.937 2.876	2.200	2.120 2.070	1.645 1.582	1.458 1.427 1.398 1.382

^a s denotes a singlet, t a centered triplet, k a centered quartet; ^b in DHP.

and it does not occur practically in the compound *I*. To confirm these conclusions, deuterium-labelled compounds were used. As it is clear from Table I, in the N-propyl derivative *III* the *c*-type ion (m/e 43) shifts almost quantitatively to m/e 45 in the spectra of dideuterated compounds *IIIa*, *IIIb*, and to m/e 46 in the spectrum of the trideutero derivative *IIIc*. An analogous shift from m/e 29 to m/e 31 (or m/e 32) is clearly visible also in substance *II*. An apparent increase of the relative intensity of the peaks in the m/e region 29 to 32 in the deuterated compounds *IIa*, *IIb*, and in the region of m/e 41 to 46 in the substances *IIIa*–*IIIc* is only fictitious, as the ratio $\sum_{27}^{32}/\sum_{27}^*$ and $\sum_{41}^{46}/\sum_{27}^*$ practically does not change.

EXPERIMENTAL

Temperature data are not corrected. Melting points were determined in the Boetius block. Infrared spectra were measured on a Perkin-Elmer 325 instrument, in tetrachloromethane. Ultraviolet spectra were obtained with the use of a Specord UV Vis (Zeiss, Jena) instrument, in ethanol. Proton NMR spectra were measured on a Varian XL 100 device, in deuteriochloroform, with tetramethylsilane in the capacity of the internal standard. Mass spectra were recorded on a LKB 9000 gas chromatograph-mass spectrometer unit using the energy of ionizing electrons 12 eV and 70 eV, ionizing current 60 μ A, ionizing chamber temperature 230°C, and the direct inlet system. The metastable transition by the DADI method was determined on a Varian MAT 311 instrument. Preparative chromatography of the alcohols was carried out on Fractovap Carlo Erba, Milano (column length 2 m, diameter 1 cm, 15% Carbowax 400 on Celite, column temperature 95°C, evaporator temperature 270°C, carrier gas helium — flow 60 ml/min, feed 0.1–0.13 ml).

Chemicals

1,1-Dideuterioethanol (b.p. 78–79°C, yield 66.3%) and 1,1-dideuteriopropanol (b.p. 97–98°C, yield 56.5%) were prepared from the corresponding acid chlorides in the usual way¹¹ by lithium–aluminium deuteride reduction in ether. The ether residue was separated by preparative chromatography, the alcohol was dried by potash and distilled again. 2,2,2-Trideuterioethanol (b.p. 78–79°C, 54.5%) and 2,2-dideuteriopropanol (b.p. 97–98°C, 63.3%) was obtained by an analogous procedure from chlorides of trideuterio-acetic acid and 2,2-dideuteriopropionic acid, respectively, by lithium-aluminium hydride reduction. The specifically deuterated acids and their chlorides were prepared by the known procedures^{11,12}. 3,3,3-Trideuteriopropanol (b.p. 97.5 to 99°C, 38.4%) was prepared from trideuteriomethyl magnesium iodide and ethylene oxide, and after the usual preparation procedure the product was isolated by preparative gas chromatography. Perdeuteriomethanol was a commercial product (Merck). Deuterated alkyl iodides were obtained from the corresponding alcohols by the reaction with iodine and red phosphorus¹³. N-substituted 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines were prepared by alkylation of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine sodium salt by the corresponding alkyl iodide in dimethylformamide according to the procedure described by us earlier^{6,7}. The yields, physico-chemical properties, and spectra of the new compounds are summarized in Tables III and IV.

We are indebted to Dr P. Sedmera, Institute of Microbiology, Czechoslovak Academy of Sciences, Prague, for measuring the metastable transition by the DADI method. We wish to express our thanks to Dr E. Janečková, Dr A. Kohoutová, Dr P. Trška, Dr P. Zachař, and Dr L. Helešić,

Central Laboratories, Institute of Chemical Technology, Prague, for careful spectra measurements and elemental analyses. Technical help of Mrs M. Lutišánová, Mrs Z. Donnerová and Mr J. Vaňura is gratefully acknowledged.

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Translated by Z. Herman.