Mass spectrometry of basic alkoxy carbanilates having local-anaesthetic properties

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Received 12 March 1980

New basic alkoxy carbanilates having local-anaesthetic properties have been studied by 70 eV e.i. mass spectrometry. Fragmentation mechanisms for the series of studied substances have been elucidated by applying labelling experiments, metastable transition measurements, and high-resolution mass spectrometry. The information obtained can be used for identification of this class of substances.

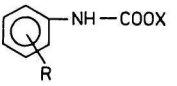
С помощью масс-спектрометрии изучены новые основные алькоксикарбанилаты с локаланестетическими действиями. Апликацией меченных экспериментов, измерений метастабильных переходов, как и высоко разрешающей масс-спектрометрии были объяснены механизмы фрагментации в серии изучаемых веществ. Полученные информации могут служить для определения веществ этой группы.

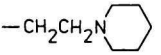
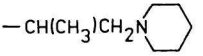
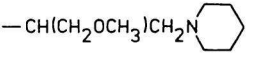
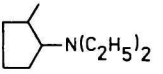
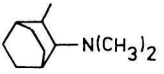
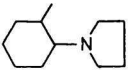
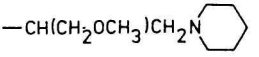
Within our previous studies on local anaesthetics several highly effective drugs with gradual onset and protracted effect have been discovered. One of these, pentacaine (*VII*, [1]) is being tested clinically and others, *e.g.* heptacaine (*I*, [2]), compounds *II*, *III* [1], *IV*, *VIII* [3], *V* [4], *VI* [5] (Table 1), as to their pharmacological and toxicological properties, have been shown to be more advantageous than substances used so far.

A key problem in evaluating long-term effects of local anaesthetics, during which process application is followed by slow absorption and degradation of the drug, is the determination of the amount of unaltered and metabolized substance in an organism. After their application in therapeutical amounts, the level of drugs in biological fluids and tissues lies usually below the sensitivity of modern analytical methods. Among these, owing to its high sensitivity and universal applicability, mass spectrometry is outstanding particularly in combination with gas—liquid chromatography. Mass spectrometry of simple carbanilates has been published [6—11]. In the present work mass spectral behaviour of local anaesthetics *I*—*VIII*

Table 1

Studied substances



Compound	X	R
I		*o* – OC_7H_{15}
II		*o* – OC_7H_{15}
III	$-CH(CH_3)CH_2N(C_2H_5)_2$	*o* – OC_7H_{15}
IV		*o* – OC_7H_{15}
V		*o* – OC_7H_{15}
VI		*o* – OC_6H_{13}
VII		*m* – OC_5H_{11}
VIII		H

has been studied with the purpose to apply the obtained information in identification and quantitative determination of this class of drugs and their metabolites in biological materials by mass fragmentography.

Experimental

Compounds under investigation (Table 1) were prepared by addition reactions of basic alcohols to the corresponding phenyl isocyanates [12]. The deuterio analogues of *I* and *VII* were prepared by dissolving substances in D_2O; the achieved degree of deuteration for heptacaine and pentacaine was 57.5 and 65%, respectively.

Table 2

Mass spectra (rel. int. % Σ_{41}) of the studied carbanilates

m/z	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
406				0.07				
390					0.06			
388						0.13		
376		0.09						
375					0.16			
374							0.12	
364			0.05					
362	0.10							
361				0.11	0.02			
349			0.07					
335			0.03					
322				0.03				
318					0.35			
303							0.04	
292		0.09	0.35					0.03
280							0.41	
278	0.13							
274					0.16			
264				0.05				
260							0.10	
247								0.19
234	0.14			0.27				
233	1.26	0.37	0.30	1.44	0.43			
219						2.19		
208				0.11				
207	0.10	0.19	0.15	0.59	0.40			
206							0.27	
205							1.63	
194		0.01	0.02					
193						0.20		
187							0.12	
180	0.12							
179							0.85	
173				0.16				
170							1.05	
169						3.54	2.43	
168							1.46	
157					0.50			
156	0.04			1.01	3.08			0.76
155				6.93				5.38
152						6.44	2.52	
151						30.35	12.55	
149							5.12	0.57

Table 2 (Continued)

m/z	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
142		0.28		0.43	0.75			0.57
141								0.87
140				0.27	6.21			
139					32.96			
136	1.33	0.84	1.18	1.22	1.08	2.06	1.07	
135	6.65	2.79	3.37	12.25	3.51	12.23	11.00	
128	0.74			0.96				0.87
126		3.44						
125		21.41		0.48				
124		0.74		3.52	3.13	2.77		3.56
123						21.89	1.30	
120	0.31	0.37	0.39		0.43			0.57
119				0.37				4.71
113			15.17		1.03			
112	4.44	0.65			12.43			
111	25.15				5.67		1.53	
110	1.25	1.39		0.59	2.21	0.77	21.92	0.67
109	0.89	0.93	1.68	3.68	1.84	0.83	3.65	
99	3.55	2.70		2.13				3.56
98	34.03	45.62	2.52	35.97	2.16			56.23
97	0.52						2.92	
96	3.33	0.56		0.53	1.13		1.17	
93								1.15
91	0.26							2.01
86			62.39					
84	1.11	0.47			2.27	4.18	3.29	1.06
83	0.81							
80		0.56						
79	0.81			0.64		2.83		
77								0.87
71	1.18					2.70		1.63
70	2.14	0.93		0.69			4.87	
69		1.12		1.12		1.67		2.50
58			4.04			5.15		
57	3.69	2.51	3.70	5.32	3.89		2.43	2.11
56	1.99				3.13			
55	2.96	2.70		2.82			2.92	3.36
45								2.50
44				8.52				
43		2.51		2.93	3.34	1.21	7.80	
41	1.14	4.56	4.38	4.80	5.94		5.12	4.42

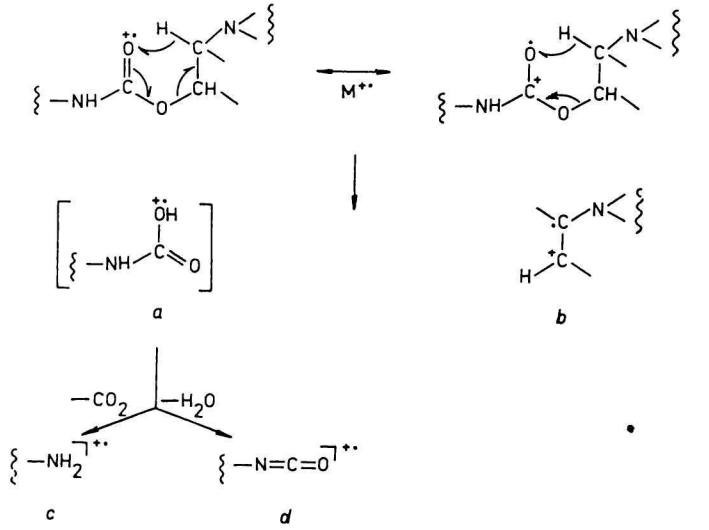
Mass spectra (70 eV) were measured with a Jeol JMS-D 100 spectrometer using direct sample-introduction technique. The temperature at the site of evaporation was 150—200°C, and that in the ionization chamber was 220°C. The peak intensities (Table 2) are expressed

in per cent of total ionization (% Σ_{41}). Metastable transitions (*) were measured with an MS-MT-01 metastable ion detector. Exact mass measurements were done with an accuracy of 2 p.p.m. using perfluorokerosene as a reference substance.

Results and discussion

Mass spectra of *I*—*VIII* are summarized in Table 2. It has been found by comparison of the spectra and from shifts of *m/z* values of isotopically labelled (—ND—) analogues of *I* and *VII*, and brominated (*o*-Br) analogue of *VII*, as well as by metastable transition and elemental composition measurements for characteristic ion fragments that the disintegration of molecular ions occurs at two ionization centra in the molecule.

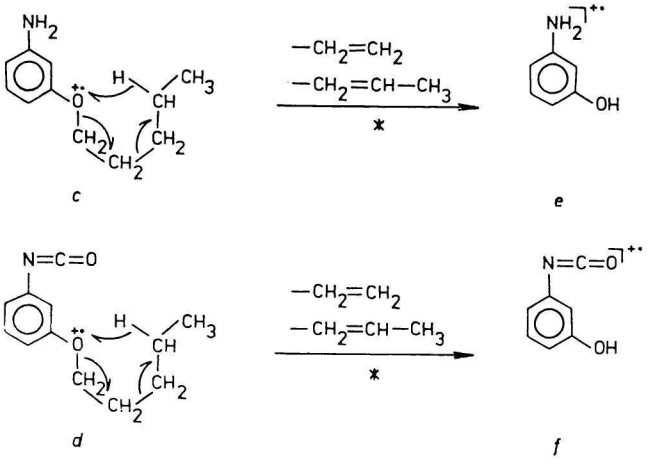
The carbamate function is responsible for McLafferty rearrangement of molecular ions [9] giving rise to a pair of ion radicals *a* and *b*, depending upon the site of charge localization. The disintegration of unstable ions *a* results in the formation of amine and isocyanate ion radicals *c* and *d* (Scheme 1). According to *Hammerum*



Scheme 1

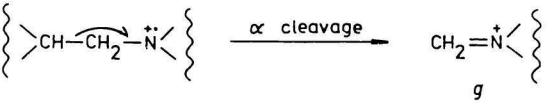
[11] ions *c* can be formed also by a one-step transfer of hydrogen to a nitrogen atom in the six-membered transition state, with simultaneous elimination of an olefin and carbon dioxide.

In the case of compounds *I*—*VII*, containing in the substituent R at least four carbon atoms, ions of *c* and *d* series eliminate olefins to give the corresponding intense particles *e* and *f*, as shown in Scheme 2 for pentacaine (*VII*).



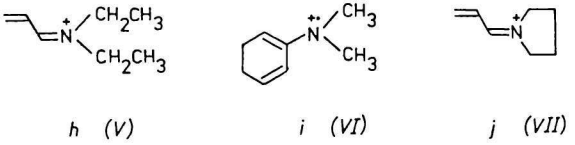
Scheme 2

The ionization of nitrogen in the substituent *X* is followed by α cleavage. With the exception of compounds *V—VII*, branched at α carbon with respect to the amine nitrogen, ions *g* are formed in the way shown in Scheme 3.



Scheme 3

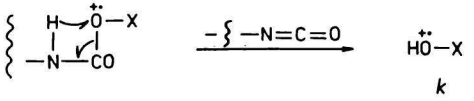
The α cleavage in *V—VII* gives rise merely to variously rearranged molecular ions from which, probably, the intense ions *h*, *i*, and *j* are formed (Scheme 4).



h (*V*) *i* (*VI*) *j* (*VII*)

Scheme 4

Another cleavage of molecular ions, occurring with lesser probability, was observed with compounds *V—VII*. It gives rise to HO-X alcohol ions by transfer of a hydrogen atom from the —NH— carbamate group with concurrent elimination of an isocyanate (Scheme 5).



Scheme 5

Table 3
Characteristic ions formed in mass spectral fragmentation of studied carbanilates

Compound	Ion (*m/z*)							
	$M^{+\bullet}$	*b*	*c*	*d*	*e*	*f*	*g*—*j*	*k*
I	362	111	207	233	109	135	98	—
II	376	125	207	233	109	135	98	—
III	364	113	207	233	109	135	86	—
IV	406	155	207	233	109	135	98	—
V	390	139	207	233	109	135	112	156
VI	388	151	193	219	109	135	123	169
VII	374	151	179	205	109	135	110	169
VIII	292	155	93	119	—	—	98	—

The *m/z* values of ions characteristic of the studied mass spectral fragmentation are given in Table 3. Best suitable for structural characterization of the studied class of substances are ions *b*, *d*, *f*, and *g*—*j*. The *m/z* values of ions *b* and *g*—*j* characterize the X portion of the molecule, whereas *m/z* values of fragments *d* and *f* (or the difference between their values) characterize its R portion.

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Translated by P. Kováč