# Structure elucidation of new *N*-aminoacetyl-*o*-alkoxymethylanilide type local anaesthetics by mass spectrometry

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Electron impact mass spectra of several newly synthesized aminoacetylanilide type substances have been studied. Using labelling experiment, metastable transition measurements, and high-resolution mass spectrometry, the fragmentation mechanisms of the substances of this class have been elucidated. The information thus obtained is discussed from the point of view of the determination of structure of substances of this type.

Были изучены масс-спектры при ионизации электронами ряда новосинтезированных веществ типа основных аминоацетиланилидов. С использованием меченых соединений, измерением метастабильных переходов и масс-спектрометрией высокого разрешения были найдены механизмы фрагментации этих соединений. Обсуждается использование этих данных при определении структуры веществ указанного типа.

The basic alkoxy-substituted acylanilides originally prepared as potential biologically active substances chiefly with local anaesthetic effects, reviewed elsewhere [1], stimulated the preparation of their alkoxymethyl analogues [2]. This paper is concerned with the mass spectral behaviour of these newly synthesized substances. The practical aim of this study was to apply theoretical information in research and clinical practice for trace amount assay of this class of drugs, and also their metabolites, in biological materials.

## Experimental

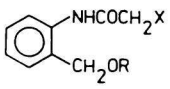
The synthesis of the investigated substances (Table 1) was described earlier [2].

The replacement of the hydrogen atom in the amide group was performed by dissolving the substance *14* in $D_2O$. The obtained degree of deuteration was 65.5%.

The mass spectra (70 eV) were measured with a Jeol JMS-D 100 mass spectrometer, applying the direct sample-introduction technique. The temperature at the site of evapora-

*Table 1*

Compounds studied[a]




| X | R | | | | | |
|---|---|---|---|---|---|---|
| | $CH_3$ | $CH_2CH_3$ | $(CH_2)_2CH_3$ | $(CH_2)_3CH_3$ | $(CH_2)_4CH_3$ | $(CH_2)_5CH_3$ |
| $N(CH_2CH_3)_2$ | *11* | *21* | *31* | *41* | *51* | *61* |
| $N(CH_2CH_2CH_3)_2$ | *12* | *22* | *32* | *42* | *52* | *62* |
| $N(CH_2CH_2CH_2CH_3)_2$ | *13* | *23* | *33* | *43* | *53* | *63* |
| 1-Pyrrolidine | *14* | *24* | *34* | *44* | *54* | *64* |
| 1-Piperidine | *15* | *25* | *35* | *45* | *55* | *65* |
| 1-Perhydroazepine | *16* | *26* | *36* | *46* | *56* | *66* |

*a*) In the denotation the first number stands for the substituent R and the second one for the substituent X.

tion was 175—195°C and the temperature in the ionization chamber was 220°C. The peak intensities (Table 2) are expressed as percentage of total ionization (% $\Sigma_{41}$). The metastable transitions (*) were determined with MS-MT-01 metastable ion detector. Exact mass measurements were done with the accuracy of 2 p.p.m., perfluorokerosene being used as a reference substance.

## Results and discussion

Fifteen compounds from the series of 36 basic acylanilide type substances were selected for the present study. Their mass spectra are given in Table 2. The number of studied substances, together with exact mass measurements of the selected ions, metastable transition measurements, and labelling experiment was sufficient for proposing a general fragmentation scheme for the substances of this type (Scheme 1). According to this scheme, the fission of molecular ions *a* proceeds in four pathways. The McLafferty rearrangement of the hydrogen atom from the $\gamma$ position with respect to the carbonyl group gives rise to weak ions *b* which, after splitting off of the methyl radical, give ions *c*. The benzyl cleavage of the molecular ions yields ions *d* which eliminate a molecule of a secondary amine (HX), giving rise to ions *e*. The most intense pathway is the $\beta$ cleavage with respect to the nitrogen atom in the amine group, enhanced by the presence of the vicinal carbonyl group, giving the *f* type ions. The substituent X appears also in the ions of type *g*. All substances investigated also form ions with $m/z = 132$ and $m/z = 118$. Their

*Table 2*

Mass spectra of the compounds studied (70 eV)
(Relative intensity % $\Sigma_{41}$)

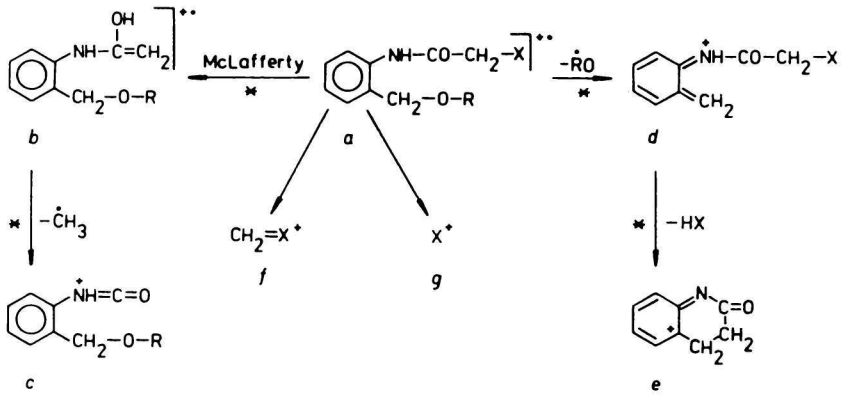
| *m/z* | *11* | *12* | *13* | *14* | *15* | *16* | *22* | *25* | *32* | *35* | *42* | *45* | *52* | *55* | *65* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 334 | | | | | | | | | | | | | 0.19 | | |
| 332 | | | | | | | | | | | | | | | 0.32 |
| 320 | | | | | | | | | | | 1.02 | | | | |
| 306 | | | 0.32 | | | | | | 0.41 | | | | | | |
| 305 | | | | | | | | | | | | 0.10 | 0.29 | | |
| 304 | | | | | | | | | | | | 0.48 | | | |
| 292 | | | | | | | 0.38 | | | | 0.07 | | | | |
| 291 | | | 0.03 | | | | | | | 0.09 | 0.36 | | | | |
| 290 | | | | | | | | | | 0.57 | | | | | |
| 278 | | 0.55 | | | | | | | 0.05 | | | | | | |
| 277 | | | | | | 0.08 | | 0.16 | 0.23 | | | | | | |
| 276 | | | | | | 0.43 | | 0.87 | | | | | | | |
| 275 | | | 0.15 | | | | | | | | | | | | |
| 263 | | 0.03 | 0.41 | | 0.13 | | 0.31 | | 0.11 | | 0.14 | | 0.19 | | |
| 262 | | | | | 0.53 | | | | | | | | | | |
| 261 | | | | | | 0.05 | 0.05 | | 0.02 | | | | | | |
| 250 | 2.49 | | | | | | | | | | | | | | |
| 249 | | 0.32 | | 0.14 | | | | | | | | | | | |
| 248 | | | | 0.93 | | | 0.05 | 0.07 | 0.09 | 0.07 | 0.11 | 0.05 | | | |
| 247 | | 0.20 | | | 0.08 | | 0.28 | 0.33 | 0.46 | 0.32 | 0.55 | 0.36 | 0.69 | 0.48 | 0.42 |
| 245 | | | | | | 0.15 | 0.03 | | 0.02 | | 0.07 | 0.02 | | | |
| 235 | 0.08 | | | | | | | | | | | | | | |
| 233 | | | | 0.14 | | | | | | | | | | | |
| 231 | | | 0.77 | | 0.18 | | | 0.26 | | 0.48 | | 0.48 | | 0.73 | 0.53 |
| 221 | | | | | | | | | | | 0.04 | 0.08 | | | |
| 219 | 0.25 | | | | | | | | | | | | | | |
| 218 | | | | | | | 0.12 | | 0.16 | | 0.14 | | | | |

*Table 2* (Continued)

| *m/z* | *11* | *12* | *13* | *14* | *15* | *16* | *22* | *25* | *32* | *35* | *42* | *45* | *52* | *55* | *65* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 217 | 0.06 | 0.73 | 0.06 | 0.17 | | | 1.32 | | 1.37 | | 0.95 | | 0.99 | | |
| 207 | | | | | | | | | 0.03 | 0.09 | | | | | |
| 179 | 0.14 | 0.06 | 0.03 | 0.74 | 0.06 | 0.02 | | | | | 0.04 | 0.02 | | | |
| 175 | | | | | | | | | | | | | 0.19 | | |
| 164 | 0.08 | 0.06 | 0.06 | 0.13 | 0.06 | 0.05 | 0.16 | 0.13 | 0.09 | 0.14 | 0.07 | 0.01 | | 0.12 | 0.11 |
| 149 | | | | | | | | 0.40 | | 0.09 | | 0.08 | | | |
| 147 | | 0.32 | | | | | 0.35 | 0.20 | 0.27 | 0.12 | 0.25 | 0.22 | 0.39 | | |
| 146 | 0.19 | 0.58 | 0.30 | 0.14 | 0.13 | 0.18 | 0.59 | | 0.50 | | 0.47 | | 0.59 | | |
| 144 | | | | | 0.16 | | | 0.20 | | 0.17 | | 0.15 | | 0.24 | |
| 142 | | | 47.30 | | | | | | | | | | | | |
| 132 | 1.66 | 0.73 | 0.83 | 0.91 | 1.13 | 0.80 | 1.15 | 1.01 | 0.66 | 0.62 | 0.76 | 0.99 | 1.18 | 0.85 | 0.86 |
| 128 | | | 2.66 | | 0.10 | | | | | | | | | | |
| 122 | | | | 0.43 | | | | 0.39 | | 0.35 | | 0.28 | | | |
| 119 | | | | | 0.29 | | | 0.38 | | | | 0.28 | | | |
| 118 | 0.83 | 2.33 | 2.96 | 0.55 | 0.52 | 0.67 | 2.47 | 0.49 | 2.28 | 0.46 | 1.82 | 0.43 | 1.78 | 0.60 | 0.53 |
| 115 | | 7.00 | | | | | 7.08 | | 7.33 | | 7.27 | | 5.63 | | |
| 114 | | 58.32 | | | | | 60.96 | | 61.80 | | 61.84 | | 54.89 | | |
| 113 | | | | | | 5.89 | | | | | | | | | |
| 112 | | 0.87 | | | | 51.20 | | | | | | | 0.69 | | |
| 106 | 0.48 | | | 0.33 | | | 0.82 | | | 0.28 | | 0.28 | 0.79 | | |
| 104 | 0.68 | 0.46 | 0.48 | 0.67 | 0.65 | 0.56 | 0.66 | 0.46 | | 0.55 | | 0.48 | 0.69 | 0.79 | 0.64 |
| 100 | | 2.62 | 9.64 | | | | | | 3.20 | | 4.00 | | 2.47 | | |
| 99 | | | | | 5.50 | | 0.99 | 6.23 | | 6.00 | | 6.70 | | 5.10 | 5.24 |
| 98 | | | 2.07 | | 56.66 | 6.65 | | 56.53 | | 60.06 | | 59.35 | 0.69 | 0.73 | 58.88 |
| 96 | | | | | | | | 1.74 | | 1.23 | | 1.65 | | 1.34 | 1.28 |
| 94 | | | | | | | | | 0.39 | | 0.33 | | | | |
| 93 | | | | 0.77 | | 0.66 | | | | | | | | | |
| 91 | | | | 0.60 | | 0.61 | 0.99 | | 0.57 | | 0.58 | | | | |
| 86 | 72.60 | 3.20 | 9.16 | | | | 3.29 | | 2.75 | | 2.18 | | 2.57 | | |

*Table 2* (Continued)

| *m/z* | *11* | *12* | *13* | *14* | *15* | *16* | *22* | *25* | *32* | *35* | *42* | *45* | *52* | *55* | *65* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 84 | | 1.75 | | 64.60 | 8.09 | 0.61 | 1.84 | 8.70 | 2.06 | 9.36 | 2.18 | 9.40 | 1.87 | 8.50 | 7.49 |
| 77 | 2.28 | | | 2.39 | 1.94 | 1.80 | | | | 1.23 | | | | 0.97 | 0.75 |
| 72 | 5.80 | 7.58 | | | | | 7.91 | | 7.33 | | 5.82 | | 5.24 | | |
| 70 | | | | 8.37 | 1.78 | | | | | | 1.45 | 1.15 | 1.28 | 1.46 | 0.98 |
| 69 | | | | | 1.94 | | | 4.78 | | 2.77 | | 1.65 | | 1.58 | 1.60 |
| 58 | 7.88 | | | | | 6.10 | | | | | | | | | |
| 55 | | | | 6.46 | 4.53 | 5.38 | | 5.50 | | 4.06 | | 3.96 | 0.79 | 3.89 | 3.53 |
| 46 | | | | | | | | | | | | | 1.68 | 2.06 | 1.93 |
| 45 | | | | | | | | | | | | | 2.96 | 3.65 | 2.89 |
| 44 | | | 9.45 | | | 4.10 | | | | | | 5.77 | 3.36 | 2.55 | 6.10 |
| 43 | | 7.58 | | | | | 7.74 | | 7.33 | | 6.54 | | 6.92 | 2.43 | 2.46 |
| 42 | 3.94 | 4.95 | | 11.48 | 7.12 | 7.17 | | | | 4.60 | | | | | |
| 41 | | | | | 6.96 | 6.15 | | 6.30 | | 5.65 | | 5.60 | | | |




*Scheme 1*
Fragmentation scheme of *N*-aminoacetyl-*o*-alkoxymethylanilides

*Table 3*

Diagnostic data for the determination of structure of *N*-aminoacetyl-*o*-alkoxymethylanilides

| Compound | Base peak (*f* ions) *m/z* | Molecular peak (*a* ions) *m/z* |
|---|---|---|
| *11* | 86 | 250 |
| *21* | 86 | 264 |
| *31* | 86 | 278 |
| *41* | 86 | 292 |
| *51* | 86 | 306 |
| *61* | 86 | 320 |
| *12* | 114 | 278 |
| *22* | 114 | 292 |
| *32* | 114 | 306 |
| *42* | 114 | 320 |
| *52* | 114 | 334 |
| *62* | 114 | 348 |
| *13* | 142 | 306 |
| *23* | 142 | 320 |
| *33* | 142 | 334 |
| *43* | 142 | 348 |
| *53* | 142 | 362 |
| *63* | 142 | 376 |

*Table 3* (Continued)

| Compound | Base peak (*f* ions) *m/z* | Molecular peak (*a* ions) *m/z* |
|---|---|---|
| *14* | 84 | 248 |
| *24* | 84 | 262 |
| *34* | 84 | 276 |
| *44* | 84 | 290 |
| *54* | 84 | 304 |
| *64* | 84 | 318 |
| *15* | 98 | 262 |
| *25* | 98 | 276 |
| *35* | 98 | 290 |
| *45* | 98 | 304 |
| *55* | 98 | 318 |
| *65* | 98 | 332 |
| *16* | 112 | 276 |
| *26* | 112 | 290 |
| *36* | 112 | 304 |
| *46* | 112 | 318 |
| *56* | 112 | 332 |
| *66* | 112 | 346 |

elemental composition is $C_8H_6NO$ and $C_7H_4NO$, respectively, and they are likely to have the structure of isocyanates. However, we were unable to ascertain their precursors by metastable peak measurements.

The fragmentation scheme (Scheme 1) shows that the determination of the *m/z* values of molecular and base peaks in the spectrum is sufficient for structural characterization of aminoacetyl-*o*-alkoxymethylanilides (Table 3). Because of its simplicity Table 3 can be successfully used not only for the proof of the structures of synthesized products of this type, but also for the mass fragmentographical detection of substances of this type in biological material.

## References

1. Beneš, L. and Linhart, M., *Acta Fac. Pharm. Univ. Comenianae 26,* 195 (1974).
2. Mapunda, P., Beneš, L., Švec, P., Pešák, M., and Borovanský, A., *Česk. Farm.,* in press.

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