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MASS SPECTROMETRY OF SOME NEW 10-PENTYL-10*H*-PHENOTHIAZINE DERIVATES

FLORIN IRIMIE[1], CSABA PAIZS[1], MONICA TOŞA[1], CORNELIA MAJDIK[1], MIHAELA CĂPRIOARĂ[1], MĂDĂLINA NEACŞU[2], PETER VEGH[3]

[1]Department of Biochemistry and Biochemical Engineering,
"Babeş-Bolyai" University of Cluj-Napoca, ROMANIA
[2]"Bios" Center of development and production", Cluj-Napoca, ROMANIA
[3]"ITIM' Research Center", Cluj-Napoca, ROMANIA

ABSTRACT. The fragmentation processes of ten new phenothiazine derivatives **1-10** have been investigated. The main decomposition rutes consist of losses of small neutral groups (O, OH, SO, SO_2, CO, CH_2=CO) and/or fragments of the alkyl substituent.

INTRODUCTION

The importance and widespread use of different phenothiazine derivatives in medical practice gave rise to a continuous interest in their mass spectromeric behaviour, resulting a well-documented mass spectrometry of these compounds [1-5]. However, the same is not true for phenothiazine S-oxides and S,S-dioxides, although the significance of these derivatives is now also evident: the metabolic oxidation of phenothiazine drugs to cyclic S-oxides has been postulated repeatedly [6] and the metabolic formation of sulfone derivatives from chlorpromazine has been shown recently in man [7].

These facts prompted us to study the details of the electron-impact induced fragmentation of some phenothiazine derivatives.

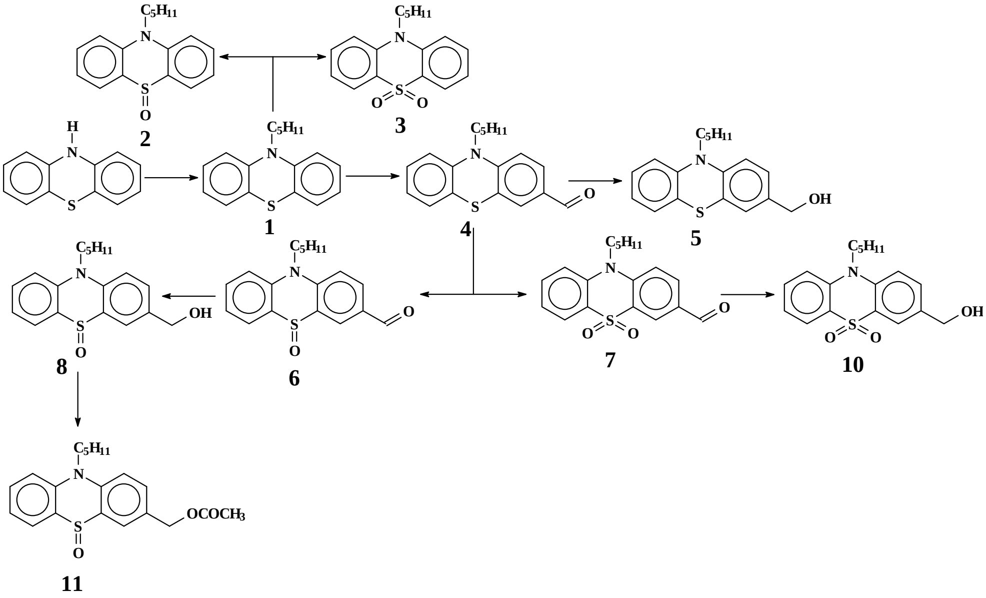
In this paper is presented the mass spectral behaviour of ten new phenothiazine based structures **1-11**. 10-Pentyl-10*H*-phenothiazine was recently synthetized [8] and functionalized at C-3 atom (Scheme 1) as reported previously [9-12].

EXPERIMENTAL

The mass spectra were recorded on double focussing Varian Matt 312 mass spectrometer, with electron impact source at 70 eV and 300 mA. The source temperature was 170 °C.

10-Pentyl-phenothiazine **1** was prepared by alkylation of phenothiazine with pentylbromide in the presence of sodium amide [8]. 10-Pentyl-*10H*-phenothiazine-3-carbaldehyde **4** was obtained by Vilsmeier-Haack formilation from **1** [9]. Sulfoxides (**2**, **6**) and sulfones (**3**, **9**) were prepared using selective oxidative methods [8]. 3-Hydroxymethyl compounds (**5**, **8**, **10**) were synthetised from the corresponding carbaldehydes by Bakers' yeast mediated reductions [9], ester **11** was obtained by enzymatic esterification of the appropriate alcohol **8** [10,11].

Scheme 1. Reaction pathway for synthesis of compounds **1-11**

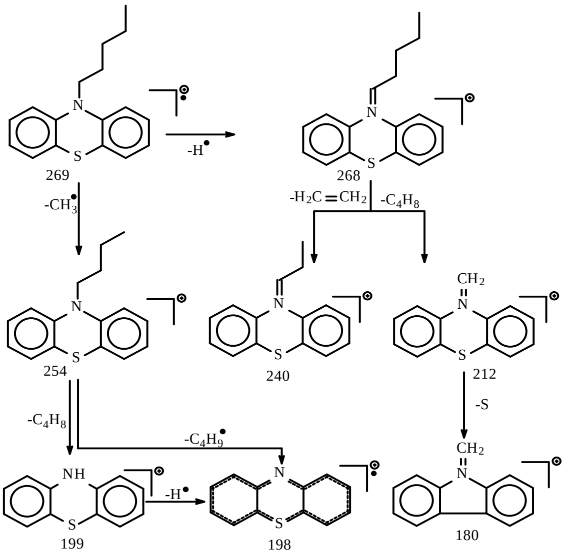


RESULTS AND DISCUSSION

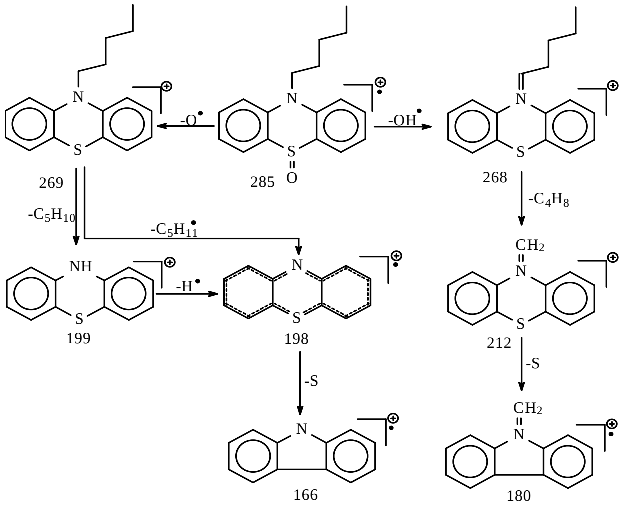
In mass spectrum of 10-Pentyl-10*H*-phenothiazine **1** (scheme 2), the base peak corresponds to the elimination of the alkyl substituent by formation of phenazathionium cation as fragment. Molecular peak was relatively stable, with 60% abundance.

α, β and δ-clevages in the alkyl substituent appeared, but only α-clevage conduct to the formation of a m/z=212 fragment with high relative intensity (58%).

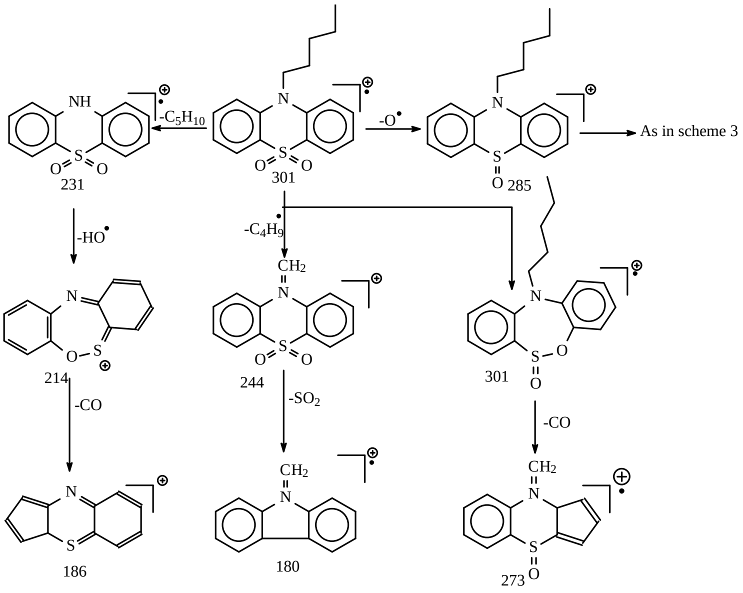
The mass spectral behaviour of 10-pentyl-10*H*-phenothiazine-5-oxide is very dissimilar to that of phenothiazine sulfoxide [5], which gives the m/z=269 base peak fragment (Scheme 3). Any further fragmentation of the $(M\text{-}OH)^+$ ions has been found almost negligible. Elimination of an O atom from the molecular ion resulted in low abundant $(M\text{-}O)^+$ peaks, their main further fragmentation, consisting of the loss of the alkylic substituent, leading to abundant $(M\text{-}O\text{-}C_5H_{11})^{+\cdot}$ peak.



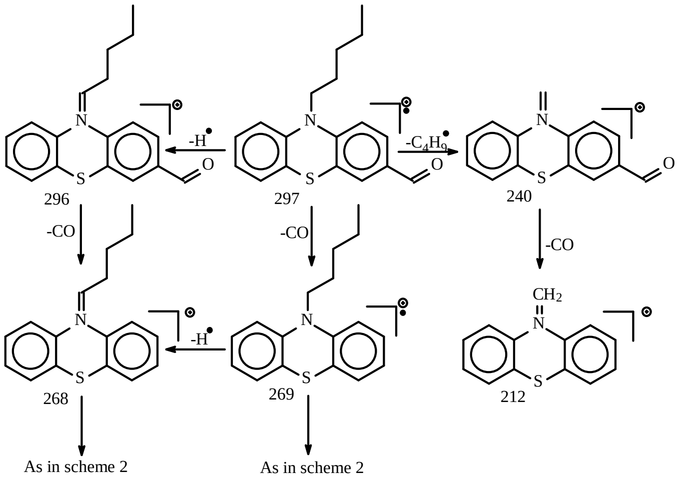
Scheme 2. Fragmentation scheme of 10-Pentyl-10*H*-phenothiazine **1**



Scheme 3. Fragmentation scheme of 10-Pentyl-10*H*-phenothiazine-5-oxide **2**



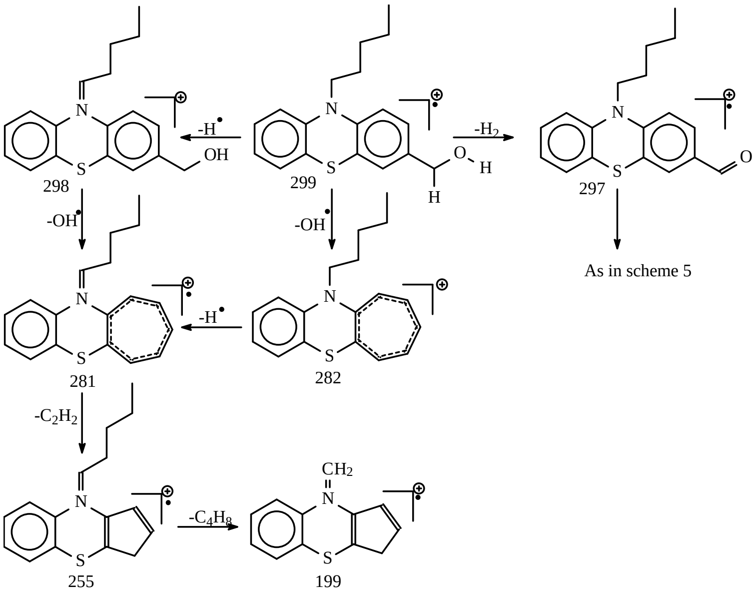
Scheme 4. Competing routes in fragmentation of 10-Pentyl-10*H*-phenothiazine-5,5-dioxide **3**



Scheme 5. Fragmentation routes in the case of 10-pentyl-10*H*-phenothiazine-3-carbaldehyde **4**

The molecular ion of 10-Pentyl-10*H*-phenothiazine-5,5-dioxide **3** form the base peak of the spectrum and decompose in competing routes. Molecular ion undergoes rearrangement [14], with the formation of C-O bond. Elimination of an O atom gives the corresponding sulfoxidie fragment. Expulsion of SO_2 from the fragment generated by the α-cleveage of the alkyl-substituent (m/z=244) was also appeared. Base peak fragment (m/z=231) was formed by elimination of C_5H_{10}. Further elimination of O atom produced rearangement which gives the possibility of elimination of an CO molecule.

In case of 10-pentyl-10*H*-phenothiazine-3-carbaldehyde **4**, molecular ion was the base ion. Its fragmentation undergoes predominantly in two ways: *via* α-cleveage of the pentyl substituent or *via* elimination of an CO molecule characteristic for aromatic and heteroaromatic compounds. β,γ,δ-cleveage of the alkyl substituent generated fragments with low stability which were not mentioned in the fragmentation scheme 5.

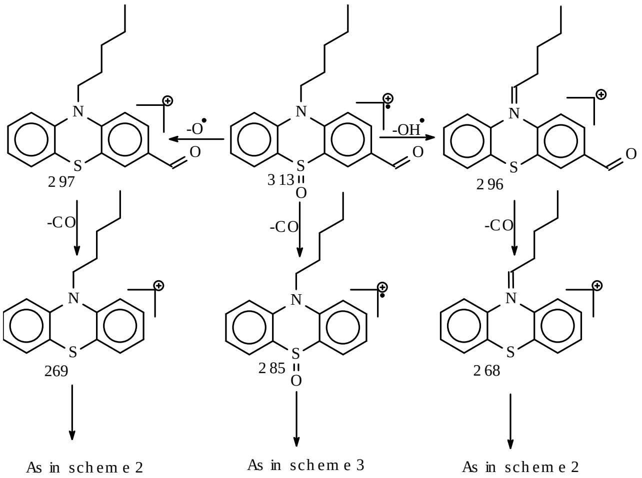


Scheme 6. Fragmentation of (10-Pentyl-10*H*-phenothiazine-3-yl)methanol **5**

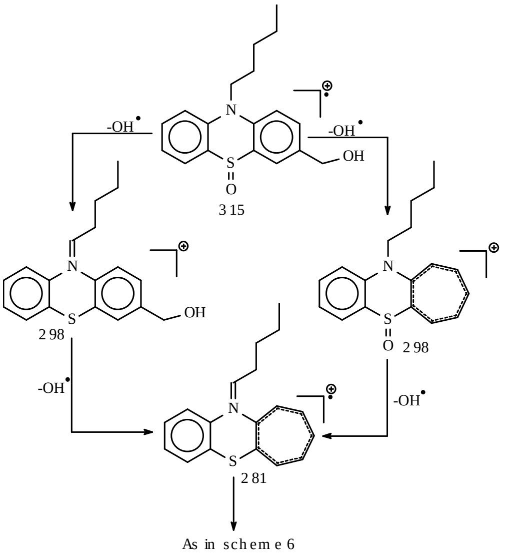
Fragmentation of (10-Pentyl-10*H*-phenothiazine-3-yl) methanol **5** undergoes in two ways: elimination of a H_2 molecule generating the aldehyde fragment, or elimination of an OH fragment which conducts by a ring rearrangement to the m/z= 282 fragment. Fragmentation of molecular ion by cleveage of the alkyl substituent was not observed.

Fragmentation of 10-Pentyl-10*H*-phenothiazine-3-carbaldehyde-5-oxide **6** udergoes by elimination of characteristic fragments for phenothiazine-5-oxides and aromatic aldehydes. M-O-CO, M-OH-CO, M-CO-OH peaks appeared in the mass spectrum of **6** (Scheme 7), together with the fragmentation of molecular ion *via* cleveage of the alkyl group.

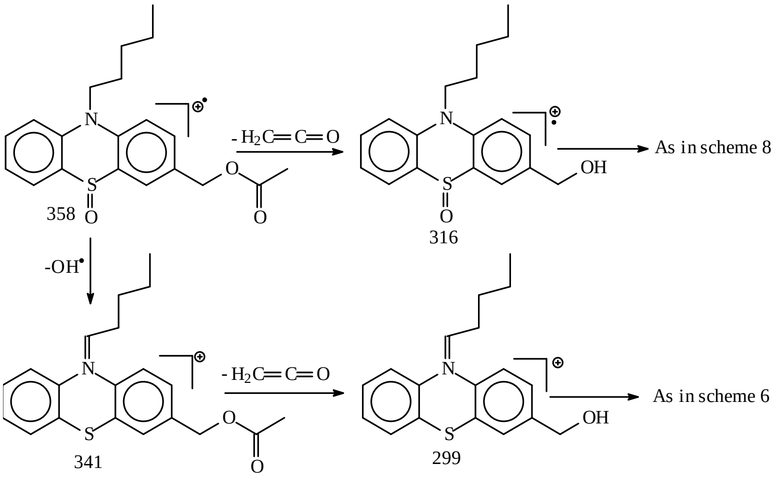
Fragmentation of (10-Pentyl-10*H*-phenothiazine-3-yl)-methanol-5-oxide **7** (Scheme 8) undergoes only by elimination of OH, which is characteristic for benzyl type alcohols and phenothiazine-sulfoxides too, any other peaks on the spectra appeared from the cleveage of the fragment with m/z=282. No other path for fragmentation was observed. The corresponding acetate **8** (Scheme 9), by elimination of cetene, generated the alcohol-sulfoxid fragment. No M-29 or M-43 peaks which are characteristic for ester appeared.



Scheme 7. Fragmentation routes in the case of 10-pentyl-10*H*-phenothiazine-3-carbaldehyde-5-oxide **6**

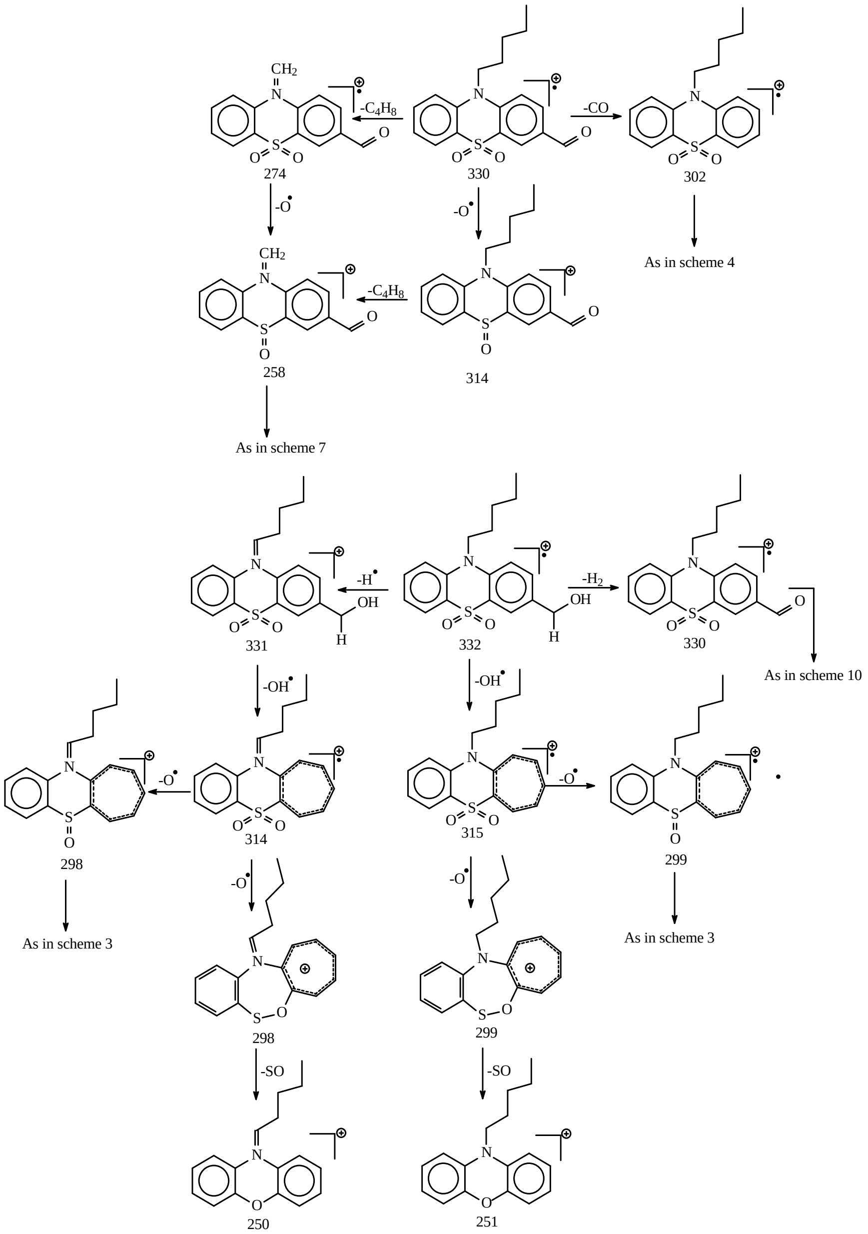


Scheme 8. Fragmentation routes in the case of (10-pentyl-10*H*-phenothiazine-3-yl)-methanol-5-oxide **7**



Scheme 9. Fragmentation routes in the case of (10-pentyl-10*H*-phenothiazine-3-yl) methyl acetate **8**

Decomposition processes of sulfonealdehyde **9** and sulfonealcohol **10** (Scheme 10) were in agreement with those presented for 10-alkyl-10*H*-phenothiazine-5,5-sulfone (**3**), 10-alkyl-10*H*-phenothiazine-3-carbaldehyde (**4**), respectively (10-alkyl-10*H*-phenothiazine-3-yl)methanol (**5**), the observed fragmentation processes lead to stable ionic structures *via* heteroaromatization, or by extension of the π-conjugation.



Scheme 10. Fragmentation routes in case of 10-pentyl-10*H*-phenothiazine-3-carbaldehyde-5,5-dioxide **9** and (10-pentyl-10*H*-phenothiazine-3-yl)-methanol-5,5-dioxide **10**

CONCLUSION

Fragmentation scheme of ten new phenothiazine compounds were presented. Molecular peaks were clear, the characteristic fragments in each case were observed. For sulfoxides and sulfones, ring rearangement paths were proposed in according with literature data.

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