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In memoriam prof. I. A. Silberg

THE FORMYLATION OF *BIS*-(N-ALKYL-PHENOTHIAZINYL)-METHANE; A THEORETICAL APPROACH

DAN PORUMB[a], IOAN SILAGHI-DUMITRESCU[a], LUIZA GAINA[a], LUMINITA SILAGHI-DUMITRESCU[a], CASTELIA CRISTEA[a], GABRIELA CORMOS[b]

ABSTRACT. Duff formylation of *bis*-(10-methylphenothiazin-3-yl)-methane obtained by the condensation of phenothiazine with formaldehyde was attempted. Theoretical data based on Density Functional Theory were used in order to explain the reduced reactivity of this substrate, as compared to parent 10-methylphenothiazine. Structural assignments were based on NMR spectroscopy.

INTRODUCTION

Numerous N- or C-substituted phenothiazine derivatives were prepared taking into account the enhanced chemical reactivity of phenothiazine nucleus towards electrophiles. The highest electron density is located at the heterocyclic nitrogen atom (due to its relatively high electronegativity) and consequently many electrophile reagents preferentially attack in position 10 of the phenothiazine nucleus. As a consequence of the transmission of heteroatoms electronic effects, C-substitution of the phenothiazine nucleus occurs readily in positions 3,7 (activated by electronic effects of nitrogen in position *para,* as shown in figure 1*)*, followed by positions 1,9 (*orto* to nitrogen) and then by positions 2,8 and 4,6 respectively (activated by the electronic effects of heterocyclic sulfur atom) [1].

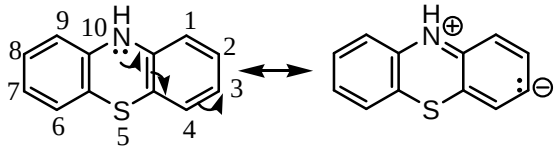


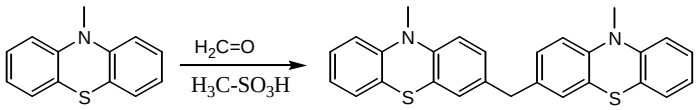
Figure 1. Phenothiazine: IUPAC numbering and resonance structures.

[a] *"Babeş-Bolyai" University, Faculty of Chemistry and Chemical Engineering, Organic Chemistry Department, Cluj-Napoca, RO- 400028, Romania*
[b] *"L. Blaga" University, Faculty of Medicine, Sibiu*

This paper presents the condensation reaction of 10-methylphenothiazine with formaldehyde and the attempts to subsequent formylation of *bis-(*10methylphenothiazin-3-yl)-methane **1** thus obtained. Theoretical data, based on DFT calculations, were used in order to explain the reduced reactivity of substrate **1**.

RESULTS AND DISCUSSIONS

Similarly to the condensation reaction of phenothiazine with formaldehyde, which leads to *bis-(*10*H*-phenothiazin-3-yl)-methane, the condensation of 10-methylphenothiazine with formaldehyde solution in the presence of an acid catalyst generates *bis-(*10-methylphenothiazin-3-yl)-methane **1** (Scheme 1) in good yields.



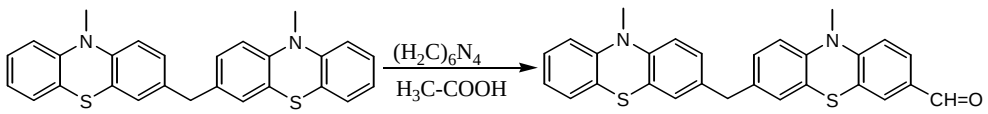
1

Scheme 1

^{1}H-NMR spectroscopy was used in order to completely assign the structure of **1**. Thus, due to the symmetry of the molecule the two methyl groups appear as a singlet signal situated at 3.1 ppm, while a singlet signal situated at 3.8 ppm is assigned to the bridging methylene protons. The protons attached to the two equivalent phenothiazine units generate six multiplet signals which appear in the 6.7-7.2 ppm range.

Duff formylation of 10-methylphenothiazine with urotropine in acidic media generated 3-formyl-10-methylphenothiazine in moderate yields. The electrophilic substitution occurs in position 3, characterized by the highest electron density of the substrate [1]. The reduced reactivity of 10-methylphenothiazine (as compared to 10*H*-phenothiazine), combined with the low reactivity of the electrophile generated by the urotropine in acidic media [2-6], explain the moderate yields.

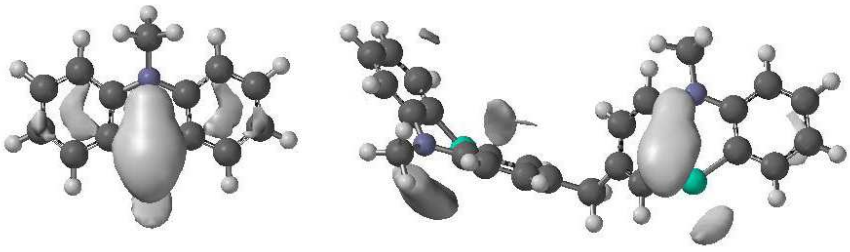
The same formylation reaction was attempted by using **1** as a substrate. The expected (10-methylphenothiazin-3-yl)-(7-formyl-10-methylphenothiazin-3-yl)-methane **2** (Scheme 2) was obtained in extremely low yields.



1 **2**

Scheme 2

A theoretical explanation for this difference of reactivity between the two similar substrates: 10-methylphenothiazine and *bis-(*10-methylphenothiazin-3-yl)-methane **1**, has been attempted. Based on DFT calculations, Figure 2 shows the electrostatic potential surfaces generated on the lowest energy conformer of 10-methylphenothiazine and **1**, using Spartan software [7].



a **b**

Figure 2. Electrostatic potential surfaces generated for:
a)10-methylphenothiazine and b)*bis-(*10 methylphenothiazin-3-yl)-methane **1**

The mild electrophile $H_2C{=}N^+{<} \leftrightarrow H_2C^+{-}N{<}$ [2] generated by the urotropine during the Duff formylation reaction may selectively be attached in position 3 of the 10-methylphenothiazine substrate, but it is not capable to interact with the carbon atom in position 7 of **1** substrate, as it can be observed from the electrostatic potential surface in figure 2a (there is no electrostatic potential surface covering carbon atom in position 7).

Stronger electrophiles may be required in order to perform the same substitution reaction of **1**, so Vilsmeier [8,9], Reimer-Tiemann [10-12] or Gattermann [13-15] formylation procedures are to be tested.

CONCLUSIONS

As a consequence of the moderate reactivity of 10-methylphenothiazine substrate, reaction with electrophiles generated by formaldehyde or urotropine in acidic media proceeds selectively in position 3 (*para* to heterocyclic nitrogen atom). Further electrophilic substitution reactions occur only in the presence of stronger electrophiles, so that the formylation of *bis-(*10-methylphenothiazin-3-yl)-methane was not observed under the present conditions. Comparison between generated electrostatic potential surfaces using Spartan software, for *bis-(*10-methylphenothiazin-3-yl)-methane and 10-methylphenothiazine suggest that the mild electrophile generated by the urotropine in the Duff formylation reaction is not able to interact with the heterocycle carbon atoms.

EXPERIMENTAL PART

The chemical reagents and the solvents were purchased from Merck (for synthesis purity)
The H-NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer.

*Bis-(*10-methylphenothiazin-3-yl)-methane 1

10-methylphenothiazine 0,5g (2,5mmol) was solved in acetic acid (50 mL), methanesulfonic acid (0.5 mL) was added and then formaldehyde (4mmol, 0.32 mL aqueous solution 36%) was added drop wise under vigorous stirring at room temperature. After refluxing for 1 hour, a white-pink precipitate started to accumulate and the reaction was perfected for 3 hours. The precipitate was filtered and washed several times with warm methanol; 0.4g white-pink powder was obtained, yield 65%, m.p. = 248 ^{o}C.
^{1}H-NMR (300MHz, DMSO-d_6**):** δ=3.10 ppm (s, 6H), 3.80 ppm (s, 2H), 6.70 ppm (d, 2H), 6.75 ppm (d, 2H), 6.8 ppm (t, 2H), 6.85 ppm (s, 2H), 6.90 ppm (d, 2H), 7.02 ppm (d, 2H), 7.12 ppm (t, 2H).

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