



# The double Smiles rearrangement in neutral conditions leading to one of 10-(nitropyridinyl)dipyridothiazine isomers<sup>☆</sup>



Beata Morak-Młodawska<sup>a</sup>, Krystian Pluta<sup>a,\*</sup>, Kinga Suwińska<sup>b,c</sup>, Małgorzata Jeleń<sup>a</sup>

<sup>a</sup> Department of Organic Chemistry, School of Pharmacy with the Division of Laboratory Medicine in Sosnowiec, Jagiellońska 4, 41-200, Sosnowiec, Medical University of Silesia, Katowice, Poland

<sup>b</sup> Faculty of Mathematics and Natural Sciences, Cardinal Stefan Wyszyński University, Wóycickiego 1/3, PL-01 938, Warszawa, Poland

<sup>c</sup> A. M. Butlerov Institute of Chemistry, Kazan Federal University, Kremlevskaya 18, 420008, Kazan, Russia

## ARTICLE INFO

### Article history:

Received 14 July 2016

Received in revised form

16 November 2016

Accepted 22 November 2016

Available online 26 November 2016

### Keywords:

Phenothiazines

Dipyrido-1,4-thiazines

Double Smiles rearrangement

Thiazine ring formation

2D NMR spectra

X-ray analysis

## ABSTRACT

Phenothiazines are reported to exhibit very promising anticancer, antibacterial, antifungal, anti-inflammatory activities, reversal of multidrug resistance and many other actions. Synthesis of phenothiazines is mostly carried cyclization of *o*-aminodiphenyl sulfides proceeded through the Smiles rearrangement. The modifications of the phenothiazine structure via the substitution of the benzene ring with the pyridine ring gave various pyridobenzothiazines and dipyridothiazines. The reaction of 3-amino-3'-nitro-2,2'-dipyridinyl sulfide with 4-chloro-3-nitropyridine in sole DMF led to one of four possible isomeric nitropyridinyl dipyridothiazines. Two-dimensional <sup>1</sup>H and <sup>13</sup>C NMR experiments (COSY, ROESY, HSQC and HMBC) were used to reveal the right product structure as 10-(3'-nitro-4'-pyridinyl)dipyrido[2,3-b; 2',3'-e] [1,4]thiazine (10-(3'-nitro-4'-pyridinyl)-1,6-diazaphenothiazine). The final structure confirmation came from a single crystal X-ray analysis. This structure is the result of very rare reaction mechanism involving the double Smiles rearrangement of the S–N type. The tricyclic dipyridothiazine system is unexpectedly almost planar, with the butterfly angle of 176.39(4)° between two pyridine rings and 174.17(6)° between the halves of the thiazine ring (the NCCS) planes. The pyridinyl substituent is rotated about N10–C11 bond and oriented almost perpendicularly to the tricyclic ring system with the dihedral angle between the two planar systems of 94.93(3)°. The nitropyridinyl substituent is located quasi-equatorially with the S···N10–C11 angle of 176.92(8)°. The nitro group is tilted from the pyridine ring by 128.44(8)°.

© 2016 Elsevier B.V. All rights reserved.

## 1. Introduction

Phenothiazines are known as tricyclic fused heterocyclic compounds of the dibenzo-1,4-thiazine structure exhibiting important biological actions and interesting chemical properties. Classical phenothiazines with the dialkylaminoalkyl substituents at the thiazine nitrogen atom show neuroleptic, antihistaminic, antitussive and antiemetic activities [1]. The chemical modifications of the phenothiazine structures have been carried out mainly by introduction of new substituents at the thiazine nitrogen atom and by replacement of one or two benzene rings with the naphthalene and azine rings to form benzophenothiazines and azaphenothiazines

(azinobenzothiazines and diazinobenzothiazines) containing additional nitrogen atoms. New phenothiazines are reported to exhibit very promising anticancer, antibacterial, antifungal, anti-inflammatory activities, reversal of multidrug resistance and many other actions [2–11].

The Smiles rearrangement is the intramolecular aromatic nucleophilic substitution named after Samuel Smiles who published over ten papers in 1930s on the rearrangements of sulfides, sulfoxides, sulfones and ethers. As nucleophilic group most often the amino acylamino groups were used but thiol, hydroxyl, amide, sulfonamide and methyl groups are also found [12–16]. In the phenothiazine synthesis the rearrangement is most often observed when *o*-aminodiphenyl sulfide **I** containing the halogen or nitro groups (in *o*-position) as leaving groups is heated in the basic conditions (ethanol, DMSO, NaOH, KOH) [1,17,18]. The reaction may run through the Ullmann cyclization to form 1,4-thiazine ring and the product **II** or through the Smiles rearrangement to *o*-

<sup>☆</sup> Part CL in the series of Azinyl Sulfides.

\* Corresponding author.

E-mail address: [pluta@sum.edu.pl](mailto:pluta@sum.edu.pl) (K. Pluta).