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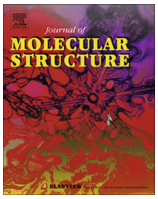

Theoretical and experimental NMR data of 3,5-dinitro-2-(2-phenylhydrazinyl) pyridine and of its 4- and 6-methyl derivatives

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HIGHLIGHTS

- The NMR spectra of 3,5-dinitro-2-(2-phenylhydrazinyl)-pyridine and its methyl derivatives are discussed.
- GIAO/DFT procedure is used for calculation of shielding constants.
- Correlations between calculated and experimental chemical shifts are demonstrated.
- Molecular structures of above pyridine compounds are determined.

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ABSTRACT

3,5-Dinitro-2-(2-phenylhydrazinyl)pyridine and its methyl derivatives: 4-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine and 6-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine were synthesized and characterized by ^{1}H NMR and ^{13}C NMR. Calculations were also performed where the above molecules were optimized using the methods of density functional theory (DFT) with 6-31G(d,p) and 6-311G(d,p) basis sets. For all molecules studied, the lowest energy was obtained using the 6-311G(d,p) basis set. The GIAO/DFT (Gauge Invariant Atomic Orbitals/Density Functional Theory) calculations on the 6-311G and 6-311++G and 6-311G** basis sets were carried out to determine proton and carbon chemical shifts and to find they were close to the experimental values.

It has been also found that intramolecular hydrogen bonding exists between hydrogen atom (in 2-NH group) and oxygen atom (pyridine-3-NO_2). Moreover, resonances between pyridine ring and electron withdrawing 3-nitro group as well between that ring and the lone electron pair of NH group favor a co-planarity of the structure; this means a chelate ring created by above-mentioned intramolecular hydrogen bond is almost co-planar with pyridine ring.

1. Introduction

Pyridine compounds and their derivatives such as N-oxides are a compound class of great scientific and practical importance. A vast number of those compounds are used in pharmaceutical research and industry but practical uses in the production of dyestuffs, antioxidants or copolymers are also known [1]. Biological activities of heterocyclic compounds including nitro pyridines, such as antibacterial or antifungal potency, have been the subject of many studies [2]. In recent years, ruthenium complexes of o-tolylazopyridine and 4-methyl-2-phenylazopyridine have been synthesized and investigated due to their potential anticancer activity [3–7]. An invention was reported [8], related to special 3-nitropyridine derivatives and their salts which, due to their inhibitory activity against the proliferation of human immunodeficiency virus (HIV) as well as of hepatitis B virus (HBV), could be used as therapeutic or preventive agents for hepatitis B and acquired immune deficiency syndrome (AIDS).

Nitration of pyridine as electrophilic aromatic substitution proceeds with a great difficulty and only low yields of nitro pyridines can be obtained by this way. However, novel methods developed by Bakke [9] (using N_2O_5 dissolved in liquid SO_2) and Katritzky et al. [10] (with nitric acid in trifluoroacetic anhydride) made possible to generate the desired products with reasonable or even high yields.

Hydrazinopyridines and their derivatives constitute a subclass of pyridine compounds which may be interesting from scientific point of view and, again, may be useful as pharmaceutical intermediates. Syntheses of *ortho*-vanillin-2-hydrazinopyridine (a compound created by condensation of 2-hydroxy-3-methoxybenzaldehyde i.e. *ortho*-vanillin with 2-hydrazinopyridine) and of organotin(IV) complexes of that compound as a ligand have been carried out by Sam et al. [11]; those products showed moderate

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or high activity against such types of bacteria as *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Enterobacter aerogenes*.

Pyridines with NH—X substituents in the two-position of the ring may show tautomerism, i.e. they can exist in both amino and imino forms [12]. While for NH_2 and NH-alkyl groups the amino form is predominant, the importance of imino form increases considerably for electron-withdrawing X groups, especially such as NO_2 or CN. In the paper cited, the tautomerism and rotamerism of 2-(2-phenylhydrazinyl)pyridine has been confirmed using NMR technique.

In modern investigations of pyridine compounds, GIAO DFT computational methods in the GAUSSIAN package are widely used for theoretical calculations of molecules properties to confirm their experimental NMR data [13–31].

Synthesis and molecular structure investigations of pyridine compounds were being undertaken by the authors for many years [32]. In most recent study [33], the molecular structure and ^1H and ^{13}C NMR spectra of the 4,4′(or 6,6′)-dimethyl-3,3′-dinitro-2,2′-azo- and hydrazo-pyridine in the solid state and solution have been discussed. The present paper shows the results of $^1H/^{13}C$ NMR investigations and theoretical studies on the structure of 3,5-dinitro-2-(2-phenylhydrazinyl)pyridine and of its methyl derivatives.

2. Experimental

2.1. Synthesis

Compounds studied in this work i.e. 3,5-dinitro-2-(2-phenylhydrazinyl)pyridine and its methyl derivatives were synthesized by the authors by methods published previously by Talik and Talik [34,35]. The syntheses included several consecutive steps as presented in Scheme 1 for the first compound:

(A) Synthesis of 3 or 5-nitro-2-aminopyridine (or 4 or 6-methyl derivatives) from 2-amino pyridine (or its 4 or 6-methyl derivatives).
(B) Synthesis of 3,5-dinitro-2-aminopyridine (or 4 or 6-methyl derivatives) from 5-nitro 2-aminopyridine (or 4 or 6-methyl derivatives).
(C) Synthesis of 2-fluoro-3,5-dinitropyridine (or 4 or 6-methyl derivatives) from 3,5-dinitro-2-aminopyridine (or 4 or 6-methyl derivatives).
(D) Synthesis of 3,5-dinitro-2-(2-phenylhydrazinyl)-pyridine (or 4 or 6-methyl derivatives) from 2-fluoro-3,5-dinitropyridine (or 4 or 6-methyl derivatives).

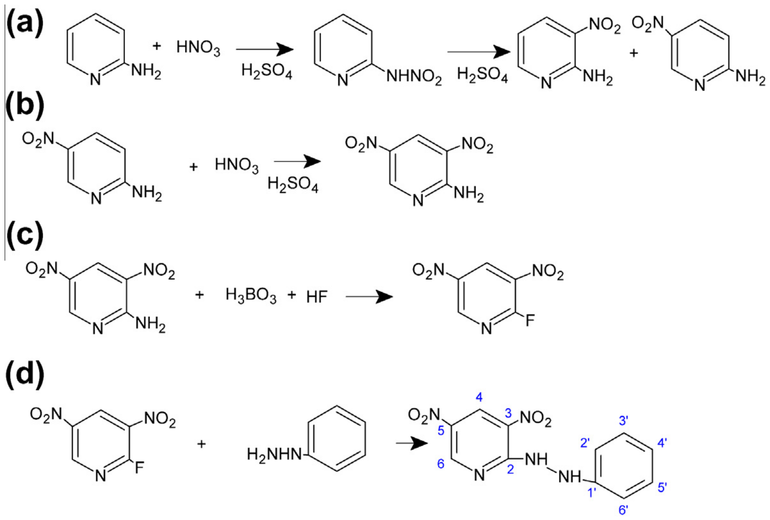
Syntheses were carried out using 2-aminopyridine or its 4 or 6-methyl derivatives (Fluka, purum, >99%) as initial compounds. The product yields, referred to the substrate used in each step and to the reaction stoichiometry, were as follows (for 2-aminopyridine, 2-amino-4-methylpyridine and 2-amino-6-methylpyridine as primary compounds, respectively):

Step (A) 48.3%, 42.1% and 56.1%.
Step (B) 63.0%, 60.1% and 74.1%.
Step (C) 44.3%, 44.3% and 41.1%.
Step (D) 72.1%, 45.3% and 42.6%.

The last step (D) i.e. syntheses of 3,5-dinitro-2-(2-phenylhydrazinyl)pyridine, 4-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine and 6-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine has been carried out as condensations of 2-fluoro-3,5-dinitropyridine or its 4-methyl or 6-methyl derivatives with phenylhydrazine. 0.01 mol of 2-fluoro-3,5-dinitropyridine or its methyl derivative was dissolved in 10 ml of methanol; to this solution 0.02 mol of phenylhydrazine (Sigma–Aldrich, purum, >95%) was added. The reaction mixture was heated for 2 min at 60 °C and then allowed to stand at room temperature for 24 h. Then, the solvent was distilled off under reduced pressure and the residue was extracted with hot chloroform. The chloroform extract was evaporated to obtain a dry residue which, subsequently, was treated with a small amount of pharmaceutical petrol to remove traces of phenylhydrazine. The insoluble reaction product was filtered off, dried and recrystallized.

The elemental analyses and melting points were:

- For 3,5-dinitro-2-(2-phenylhydrazinyl)pyridine (recrystallized from ethanol): C: 48.40 (calc. 48.00) H: 3.18 (calc. 3.30) N: 25.20 (calc. 25.45) 155 °C.
- For 4-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine (recrystallized from methanol): C: 50.30 (calc. 49.82) H: 3.80 (calc. 3.83) N: 24.48 (calc. 24.21) 131 °C.
- For 6-methyl-3,5-dinitro-2-(2-phenylhydrazinyl)pyridine (recrystallized from methanol and acetonitrile): C: 50.20 (calc. 49.82) H: 3.83 (calc. 3.83) N: 24.21 (calc. 24.21) 164 °C.



Scheme 1. Scheme of synthesis of 3,5-dinitro-2-(2-phenylhydrazinyl)pyridine and atom numbering of the final structure.