

Original article

Synthesis of some *N*-substituted nitroimidazole derivatives
as potential antioxidant and antifungal agentsDorota Olender^a, Justyna Żwawiak^a, Victor Lukianchuk^b, Roman Lesyk^c,
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Abstract

Some new nitroimidazole derivatives have been synthesized by treating 4,5-dinitro- and 2-methyl-4,5-dinitroimidazoles with epoxyp propane, epichlorohydrin or phenacyl bromide in alkylation reactions. The nitro group in *N*-substituted 4,5-dinitro- and 2-methyl-4,5-dinitroimidazoles has been replaced with primary and secondary amines to afford 4-amino-5-nitroimidazole derivatives. Some of the compounds have been tested for their antioxidant and antifungal properties against fungi species acting on timber. Nearly all of them have shown significant antioxidant activity in comparison with that of tocopherol, which is used as a reference substance. Two compounds from those tested have revealed very strong fungistatic activity against *Sclerophoma pityophila*.

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1. Introduction

For a few decades, nitroimidazoles have been the subject of much interest because of their properties. Depending on the nature of substituents and the position of the nitro group, the nitroimidazole derivatives can show various pharmacological activities [1]. The compounds with nitro group at position 4 are usually less active than the corresponding 5-nitro derivatives. Nitroimidazoles, such as metronidazole, misonidazole, ornidazole, secnidazole, etanidazole and tinidazole, are commonly used as therapeutic agents against a variety of protozoan and bacterial infections of humans and animals [2–4]. It has been suggested by many authors that nitroimidazoles containing nitroimidazooxazole or nitroimidazooxazine

structures (CGI-17341, PA-824) might be potential antitubercular agents [5–7]. Derivatives of 5-nitroimidazoles have been tested in cell-based assays and in enzyme assays against HIV-1 recombinant reverse transcriptase [8,9]. 2-Nitroimidazoles play a major role as bioreductive markers for tumour hypoxia and as radiosensitizers [10–12]. Some of them demonstrate antiprotozoan activity [4].

Our earlier investigations have provided evidence of the antifungal and antibacterial properties of *N*-phenacyl-4,5-dinitroimidazole derivatives [13]. Some dinitro- and mononitroimidazole derivatives have been predicted as notable radiosensitizers, antiprotozoal and antibacterial or antiepileptic agents [14].

Antifungal agents are regarded as efficient drugs with relatively low toxicity. New, effective antifungal substances are still being sought because of the increasing number of resistant fungi being isolated.

Antioxidants play a significant role in several important biological processes such as immunity, protection against tissue

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damage, reproduction and growth or development. They preserve adequate function of cells against homeostatic disturbances such as those caused by septic shock, aging and, in general, processes involving oxidative stress. These substances are classified according to their mode of action. Important antioxidants include the chain-breaking or scavenging substances (vitamins E, C and A, bilirubin), preventative (albumin, lactoferrin, haptoglobin) and enzyme antioxidants (catalase and glutathione peroxidase) [15]. They reduce damage to cells and biochemicals caused by free radicals, which are normal products of metabolism. Antioxidants can prevent cardiovascular disease, cancer, cataracts and various other ailments associated with aging [16,17]. The studies suggest that supplementation with antioxidants may be useful in the prevention and treatment of Parkinson's disease [18,19]. Oxidative stress is also important in the pathogenesis of Alzheimer's disease. The studies suggest that supplementation with vitamin E might delay the development of Alzheimer's disease [20,21].

The broad spectrum of biological activity of nitro compounds was the inspiration to test them for antioxidant and antifungal activities. The results obtained in this study can be useful for the design and synthesis of new substances with antioxidant and antifungal activities.

The aim of this study was to determine in vitro the antioxidant properties of some *N*-substituted 4,5-dinitroimidazoles and their 2-methyl derivatives as well as respective compounds with primary or secondary amino group in *C*-4 position of the nitroimidazole ring. In addition some derivatives were tested for their antifungal activity against fungi species attacking timber. Wood can be protected from the attack of fungi decay by applying suitable chemical preservatives. The antioxidative activity experiments were carried out in comparison with tocopheryl acetate.

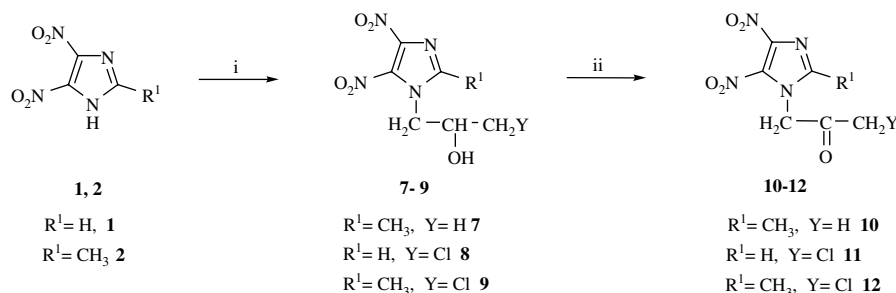
2. Results and discussion

2.1. Chemistry

As starting materials 4,5-dinitroimidazole **1** and 2-methyl-4,5-dinitroimidazole **2** were used [22]. 4,5-Dinitro-1-phenacylimidazole derivatives **3–6** of above-mentioned dinitroimidazoles are known substances [13]. *N*-Hydroxypropyl derivatives **7–9** were synthesized by the reaction of dinitroimidazoles **1** or **2**

with propylene oxide or with epichlorohydrin without solvent or in alcoholic solutions (Scheme 1). The reagents were heated under reflux for about 3 h. The treatment of **2** with an excess of epoxypropane (1:2) led to new *N*-(2-hydroxypropyl) derivative **7**. While reacting **1** with epoxypropane in ethanol or without solvent, formation of respective hydroxypropyl derivative of 4,5-dinitroimidazole was not observed. Dinitroimidazoles **1** and **2** alkylated with epichlorohydrin formed compounds **8** and **9**, respectively [13]. If a methyl group at *C*-2 position of dinitroimidazole ring was present, the solvent was not necessary but formation of **8** in the reaction without solvent was not observed. Thus, the presence of a methyl group at *C*-2 position of the imidazole ring significantly influenced *N*-alkylation and other substitution reactions. Subsequently, derivatives **7–9** were transformed into new *N*-(2-oxopropyl)-4,5-dinitroimidazoles **10–12** (Scheme 1). The process was carried out using Jones reagent in the oxidation reaction, at room temperature and by using acetone as a solvent. From this reaction mixture the isolated and purified derivatives of ketones were readily obtained. ¹H NMR spectra of **10–12** showed only methyl and methylenic protons assigned to the side chains or proton at *C*-2 position of the imidazole ring, but no signals of the hydroxyl groups. IR spectra of the compounds prepared showed strong bands in the region 1725–1720 cm⁻¹ attributed to the carbonyl group.

Derivatives **3–11** were applied to obtain some new products in the reaction with primary and secondary amines such as *o*-toluidine, morpholine, pyrrolidine, piperidine and *N*-methylpiperazine. These reactions were carried out in THF, at room temperature [23]. The treatment of **3–6** with the above-mentioned amines, even at molar ratio 1:5 led to the respective 4-amino-5-nitroimidazole derivatives **13–29** only (Scheme 2). Formation of aminonitro compounds occurs very easily and often with high yield. The other solvents (ethanol, acetonitrile, methylene chloride) were unsuitable for the reaction. Under these conditions, the amino products were formed in longer time and often with poor yields and purity. With ethanol being used as a solvent, the reaction led to a mixture of both possible isomers: 4-amino-5-nitro- and 5-amino-4-nitroimidazoles. Moreover, elevated temperatures favour the formation of by-products. Derivatives **13–17**, **20**, **22–24**, **27** and **29** are newly synthesized substances but products **18**, **19**, **21**, **25**, **26** and **28** have been described earlier [23]. IR spectra of some newly synthesized aminonitroderivatives



Scheme 1. Synthesis of *N*-substituted 4,5-dinitroimidazole derivatives. Reagents and conditions: (i) epoxypropane or epichlorohydrin, without solvent or in EtOH, boiling, 2.5–3.5 h; (ii) Jones reagent, acetone, r.t.

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