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Peroxynitrite-induced oxidation and nitration products of Penciclovir: Structures and mechanisms of product formation

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Abstract

Peroxynitrite is a very good oxidizing agent which is formed by the reaction of nitric oxide with super oxide. There are so many works are reported which clearly indicate that peroxynitrite react with lipid protein and DNA. In our present work we report the oxidation of a very well known antiviral drug penciclovir by peroxynitrite. The oxidation of our selected drug was achieved by refluxing the drug with sodium nitrite, the progress of the reaction was monitored by thin layer chromatography and the product of the reaction was isolated by column chromatography. We also purposed the probable mechanism of the formation of different product.

Key words: Penciclovir, Peroxynitrite, Antiviral drug, Thin layer Chromatography.

1. Introduction

Nitric oxide (NO) plays a pivotal role in many biological process, and is produced primarily by the enzyme nitric oxide synthase (Huie et al 1993, Denicola et al 1996).The expression, regulation, synthesis, and role of NOS and NO in physiologic processes such as vasodilation (Rachmilewitz et al 1993), neurotransmission, inhibition of platelet aggregation, and in proper immunologic function, have been extensively studied and previously reviewed (Mereny et al 1998, Lymar et al 1995).

NO is generally present in our body but as its concentration increases and cross the normal physiological levels it becomes toxic (Nauser et al 2002, Coddington et al 1999). Hence it is very important to control the level of NO to reduce the possibility of undesired effects. In order to control the concentration of NO some pathophysiologic states are disrupted (MacMillan-Crow et al 2000, Soszynski et al 1996). In certain cutenious gastrointestinal inflammatory conditions like the inflammatory bowel disease and chronic Helicobacter pylori infection tissue damaging process are enhanced which potentiate to increases the risk of cancer all these conditions are basically due to increase the concentration of NO and NO derived 8 nitroguanine derivative (8-NO_2G) and 8-oxoguanine (8-oxoG) products (Koppenol et al 1992, Squadrito et al 1995). Thus, understanding the connection between NO and these outcomes requires consideration of the fate of NO in biological systems and the capacity of the associated intermediates to react with various cellular components, especially DNA, since damage to this informational molecule can lead to mutations and ultimately carcinogenesis(Chen et al 2001, Tretyakova et al 2000).

NO itself is relatively uncreative toward DNA, but it can be converted in to several highly reactive species (Weatherly et al 2001, Coddington et al 1999). These include nitrous anhydride (N_2O_3), nitrogen dioxide (NO_2) nitryl chloride (NO_2Cl), and peroxynitrite (ONOO-), and the chemistry underlying the formation and reactivity of these species has been recently reviewed (Burney et al 1999, Sodum et al 2001).

Penciclovir is a potential antiviral drug commonly used in the treatment of herpes viruses initiated diseases (Ahmad et al 2012). It is white colour cream used topically. Chemically Penciclovir is guanine a derivative and its chemical name may be given as9-[4-hydroxy-3-(hydroxymethyl) butyl]

guanine. There are so many works are reported in literature (Singer et al 1996, Dijkstra et al 1996, Yermilov et al 1996,) which clearly indicate that guanine react with peroxynitrite to give 8 nitro and 8 oxo product and our selected drug is a guanine derivative so it may is also react with peroxynitririte to give the 8 oxo and 8 nitro derivative of the penciclovir.

2. Experimental

2.1 Chemicals and Reagent

All chemicals used were of analytical grade. Penciclovir was extracted from the commercial medicament denavir (dev chem., Mumbai, India) by very common crystallization method the purity of pure crystal was checked by running CO TLC with authentic pure sample. Acetic Anhydride, Dimethyl Sulfoxide (DMSO), Sodium nitrite were purchased from Sigma Aldrich

2.2 Reaction procedure

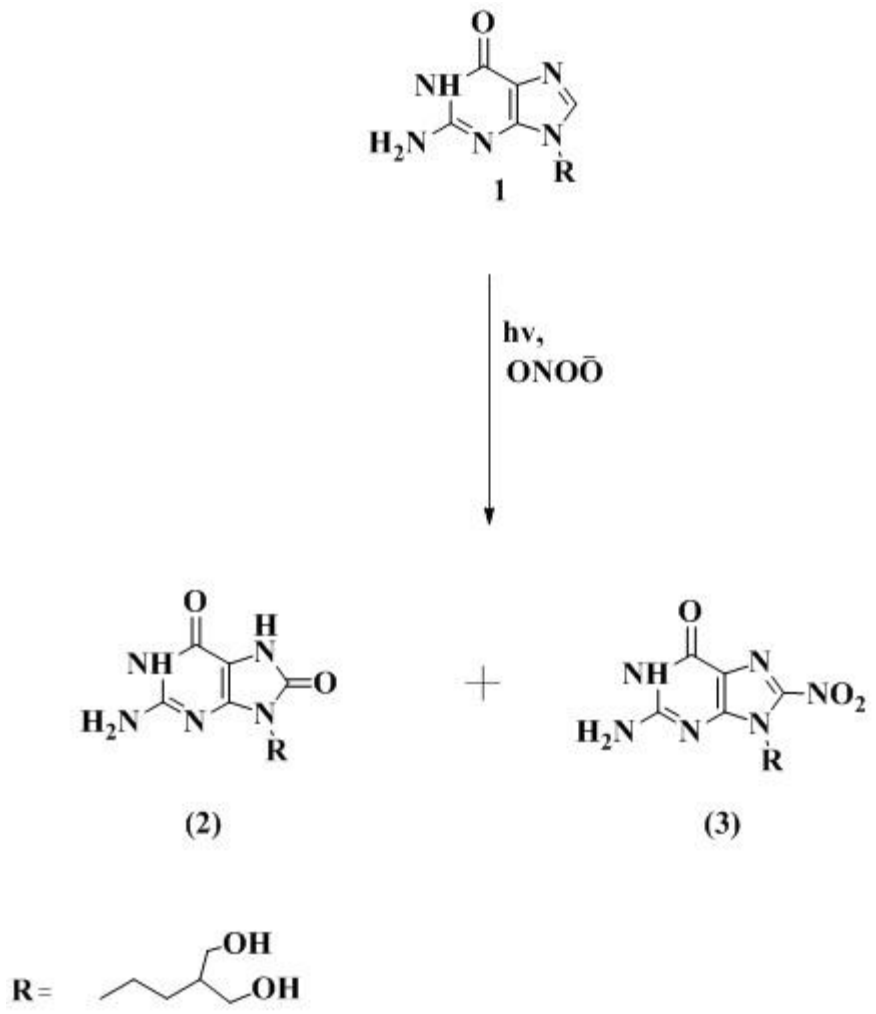
First we isolate the pure crystal of penciclovir from the commercial available drug denavir by crystallization method. After getting the pure crystal of penciclovir we take approximately 1 gm of pure crystal and 0.95 gm of sodium nitrite in round bottom flask containing DMSO. Reflux the reaction mixture overnight at 60 ^{0}C. Progress of the reaction was monitored by thin layer chromatography. The formation of two product confirmed by the thin layer chromatography study.

3. Results and Discussion

The aim our preset study was to established that the penciclovir a potential antiviral drug react with peroxy nitrate to produce two products one is 8 nitro derivative and other is 8 oxo derivative.

3.1 Mechanistic Study

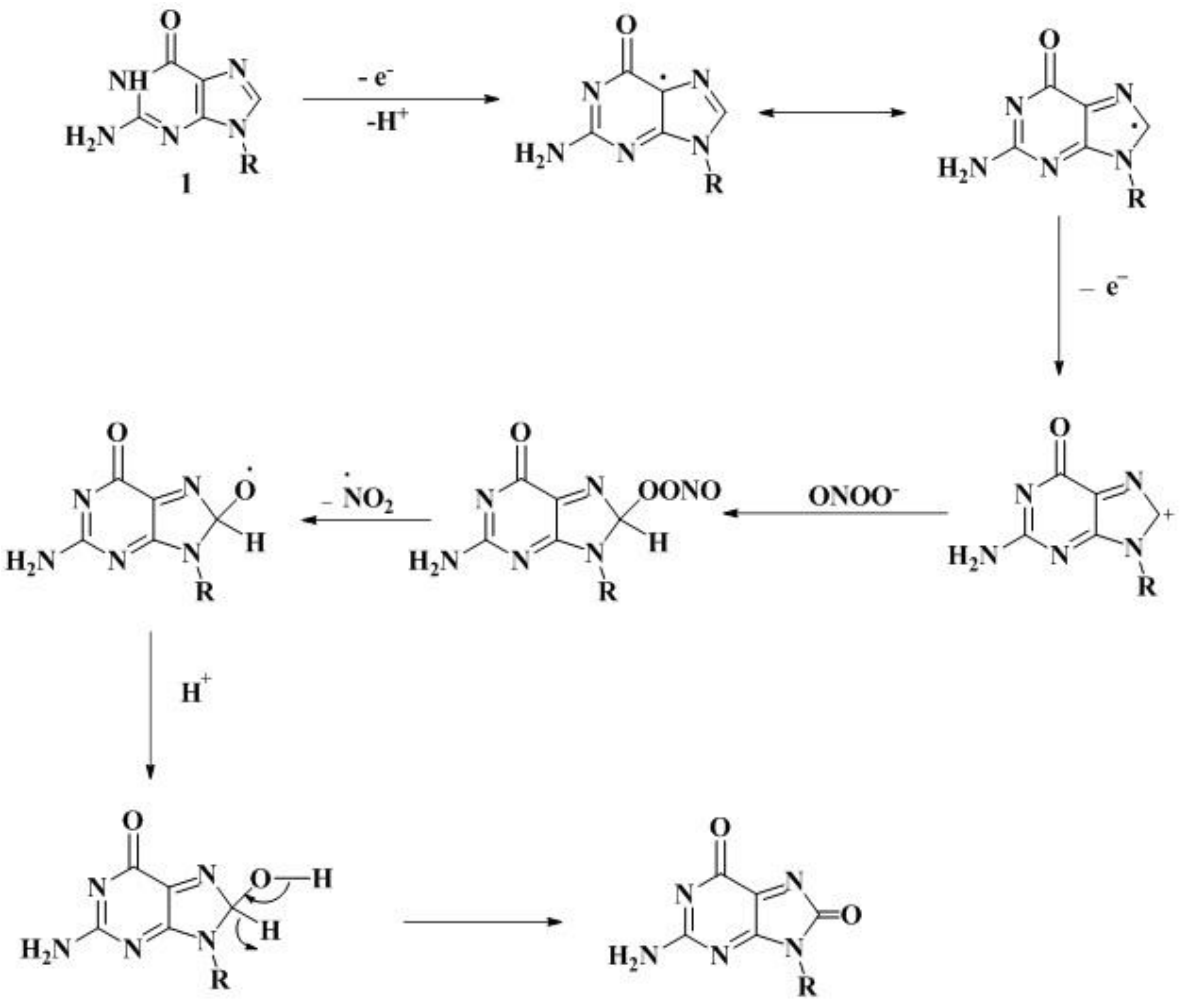
When we reflux the penciclovir with sodium nitrite in presence of DMSO we get two reaction products as given in scheme -1



Peroxy nitrite induced Photodegradtion of Penciclovir

3.2 Formation of 8 oxo Product:

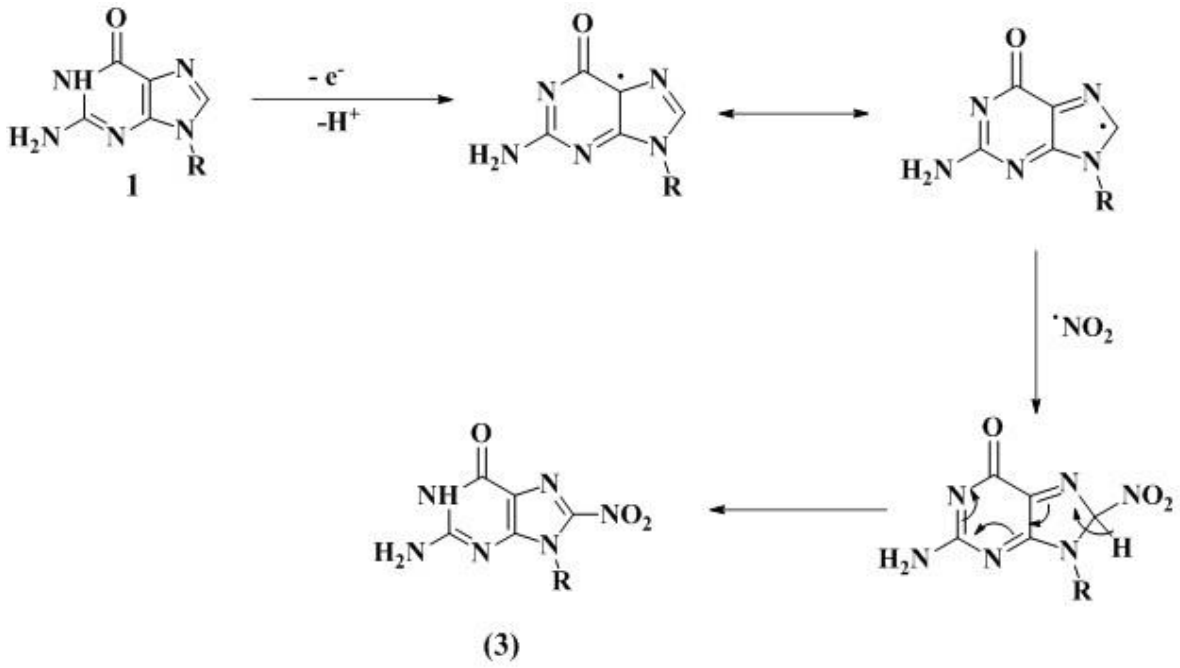
The formation of these products most probably explains by the following mechanism. As we reflux the reaction mixture first pencilovir loses proton and one electron after losing proton and electron it rearrange to give a radical intermediate 2. These radical intermediates in next step loses one electron and give carbocation intermediate which in next step combine with peroxinitrite anion to give an intermediate compound. In the next step this intermediate compound loses NO_2 free radical and generates another free radical intermediate which abstract a proton to give hydroxyl derivative this hydroxyl derivative finally loses H_2 molecule to give 8oxo derivative.



Mechanistic Pathway of the formation of Product-2

3.3 Formation of 8 Nitro derivatives

This product is also formed by the similar mechanism in the first step first step PC loses one electron and proton to generate free radical which on rearrangement give another free radical intermediate this free radical combine with another NO_2 free radical to give a reaction intermediate this reaction intermediate loses a proton and udergo rearrangement to give the final 8 nitro derivative of penciclovir



Mechanistic Pathway of the formation of Product-3

4. Conclusion:

Under chronic inflammation and infection various reactive oxygen and nitrogen species are produced in body which is directly or indirectly react with several biomolecules such as Protein DNA and sugar etc. In the view of these reported facts here in we have investigated the peroxy nitrate induced chemistry of very well known antiviral drug Pencilovir and the finding of our present investigation established that the penciclovir react with peroxynitrite under go nitration and oxidation to give a 8 nitro and 8 oxo derivative product.

Conflict of interest:

Authors declare that they have no conflict of interest.

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