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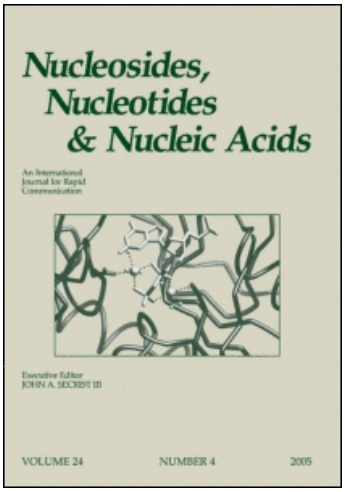

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Oxidation of Guanine Nucleosides to 4-Amidinocarbamoyl-5-hydroxyimidazoles by Dimethyldioxirane

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ABSTRACT

Final oxidation products generated from guanosine and 2′-deoxyguanosine by reaction with dimethyldioxirane have been identified as 4-amidinocarbamoyl-5-hydroxyimidazoles.

Key Words: Deoxyguanosine; Dimethyldioxirane; Guanosine; Oxidation.

The cyclic peroxide dimethyldioxirane (DMD) is a very powerful oxidant capable of inserting oxygen atoms into a wide variety of organic molecules. On reaction with DNA, it generates alkali-labile cleavage sites exclusively at the positions of guanine bases and has thus been proposed as a G-specific chemical sequencing agent.[1]

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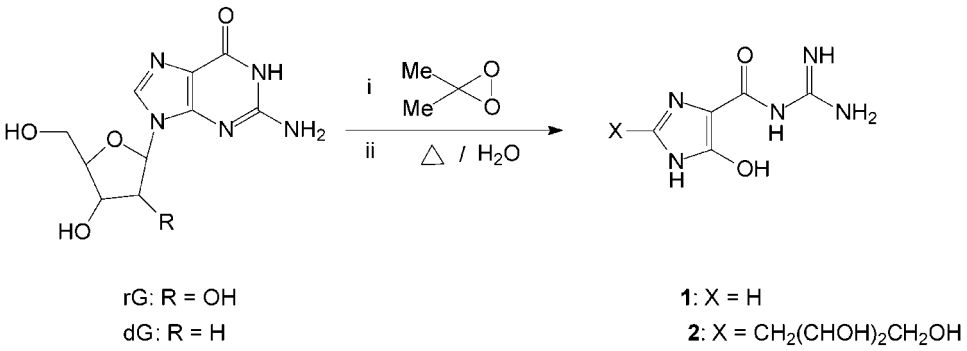

rG: R = OH
dG: R = H

1: X = H
2: X = $CH_2(CHOH)_2CH_2OH$

Scheme 1.

With the aim of identifying the oxidative lesions responsible for DNA cleavage, we have examined the reaction of DMD with guanosine (rG) and 2′-deoxyguanosine (dG) as model compounds (Sch. 1). When treated with excess DMD in aqueous solution, both nucleosides rapidly lose their UV-absorbing chromophore – probably reflecting initial epoxidation of the central 4,5-double bond of the guanine nucleus. However, if the reaction mixture is subsequently incubated at 90°C for 5 h there is gradual formation of a product species absorbing maximally at 302 nm. The products derived from rG and dG were purified to homogeneity by successive chromatography on Sephadex® G-10 and reversed-phase HPLC. Spectroscopic characterization by tandem mass spectrometry, combined with one and two-dimensional NMR, established that the end-product of DMD oxidation of rG is 4-amidinocarbamoyl-5-hydroxyimidazole (compound **1**, Sch. 1). Its identity was confirmed[2] by the X-ray crystal structure of its perchlorate salt in which the molecules exist as imidazolium-5-olate zwitterions. Remarkably, the corresponding oxidation product from dG proved to be 2-(2,3,4-trihydroxybutyl)-4-amidinocarbamoyl-5-hydroxyimidazole (compound **2**, Sch. 1) where a 4-carbon fragment derived from the deoxyribose moiety is incorporated at C(2) of the imidazole ring. The (multi-stage) mechanism responsible for this unusual transformation remains to be elucidated but it is evidently quite distinct from the pathways that are currently known to be involved in guanine oxidation. If it is operative at the polynucleotide level, the lesions produced by DMD in DNA will constitute interesting new substrates for studies of molecular mutagenesis and DNA repair.

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