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Nucleotides Bearing a Cleavable Genotoxic Group on the Phosphate*

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N–Nitrosopyrrolidine (NPYR), a rodent carcinogen, is a promutagen requiring enzymic conversion, presumably to its α–hydroxylated derivative, to exhibit its mutagenic activity. Earlier studies from our laboratory have shown that NPYR and *N*–nitrosomorpholine can be converted into their α–phosphate esters on near–ultraviolet (UVA) irradiation in the presence of inorganic phosphate and that these α–phosphate derivatives are directly mutagenic toward bacteria. Furthermore, direct mutagenicity was observed for UVA–irradiated mixtures of *N*–nitrosomorpholine and nucleotides (in place of inorganic phosphate), and the mutagenic components formed were found in distinctive zones in paper chromatography depending on the nucleotides linked to the *N*–nitrosodialkylamine at the α–carbon. Such compounds seemed to be worthy of exploration for their properties. We report here the synthesis of this new class of nucleotide derivatives by the reaction with NPYR. These nucleotides are directly mutagenic to *Salmonella*, and they can be cleaved *in vitro* under mild conditions at the phosphoester–NPYR linkage. The product, thymidine 5'–phosphate mono(1–nitroso–2'–pyrrolidinyl)ester, was isolated by use of TLC on cellulose followed by paper chromatography. The NMR spectra (^{1}H, ^{31}P, ^{1}H–^{1}H COSY, and ^{1}H–^{31}H HSQC) of this material supported the expected structure and its diastereomeric mixture. The proton–detected ^{1}H–^{31}P heteronuclear two–dimensional correlation spectrum (^{1}H–^{31}P HSQC) confirmed the assignment that the phosphate is linked to the α–carbon of NPYR. With near–ultraviolet irradiation, this cleavage takes place and, when a strand of DNA is present in the reaction mixture, the DNA undergoes single strand breaks.

The NPYR moiety may be incorporated into oligonucleotides having terminal phosphomonoester groups. Such oligonucleotides would be useful in specific cleavage of nucleic acids and in targeted gene–manipulation. This new class of nucleotide derivatives may also be useful in studies of mutagenesis and carcinogenesis mechanisms of *N*–nitrosodialkylamines. 2–Butenal, and moiety from the NPYR nucleotides, should be reactive not only to DNA but also to nucleophilic groups in proteins and other biological substances.

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