SYNTHESES OF PHOSPHORUS CONTAINING HETEROCYCLES BY THE OZONOLYSES OF ALKENYLPHOSPHORAMIDATES (2). SYNTHESES OF THE SUGGESTED ACTIVE METABOLITE OF ISOPHOSPHAMIDE AND SOME RELATED COMPOUNDS

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Ozonolysis of O-3-butenyl-N,N'-bis(2-chloroethyl)phosphorodiamidate afforded 2-[(2-chloroethyl)amino]-3-(2-chloroethyl)-4-hydroperoxytetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide(4-hydroperoxyisophosphamide), which on deoxygenation with triethyl phosphite yielded 4-hydroxyisophosphamide, the suggested active species of the antitumor agent isophosphamide. Similarly, a number of related 1,3,2-oxazaphosphorinanes and 1,3,2-diazaphosphorinanes were prepared. Among them, both 4-hydroperoxy- and 4-hydroxyisophosphamide exhibited the most pronounced cytostatic activities in in vivo and in vitro experiments, confirming that they are indeed the active species.

The NMR studies on the stereochemistry of 4-hydroperoxy-1,3,2-oxazaphosphorinanes revealed that the C-4 hydroperoxy group is axially oriented and perhaps has trans disposition to the phosphorus alkylamino substituent.

As one of the urinary metabolites of 4-hydroperoxyisophosphamide in rabbits was isolated 2-[2-(2-chloroethylcarbamoyl)ethoxy]-1,3,2-oxazaphosphorolane-2-oxide which was synthesized by a new alkali-catalyzed ring contraction reaction of 4-keto-1,3,2-oxazaphosphorinane to 1,3,2-oxazaphosphorolane.