SYNTHESES AND STEREOCHEMISTRY OF THE ANTITUMOR ALKYLATING AGENTS RELATED TO 4-HYDROPEROXYISOPHOSPHAMIDE

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A number of 4-hydroperoxy-1,3,2-oxazaphosphorinane-2-oxides having different alkylating functionalities at the 2- and 3-positions on the ring were synthesized. The syntheses were simply performed by the ozonolysis reactions of O-(3-butenyl)-phosphorodiamidates bearing two ethylamino groups whose β-positions are unsymmetrically substituted by Cl, Br, CH_3SO_2O, $C_2H_5SO_2O$ or (p)-CH_3-C_6H_4-SO_2O groups. Among the compounds synthesized so far, 2-[N-methyl-N-(2-chloro)ethyl]amino-3-(2-methylsulfonyloxy)ethyl-4-hydroperoxy-1,3,2-oxazaphosphorinane-2-oxide was found to exhibit the highest lifespan activity against L1210 leukemic mice.

An acid-catalyzed isomerization of 4-hydroperoxyisophosphamide, as well as its derivative bearing modified alkylating group(s), produced a stereoisomer having an inverted stereochemistry at the phosphorus atom. The stereochemistries of these epimeric compounds were elucidated by chemical and spectroscopic investigations. The two epimers of 4-hydroperoxyisophosphamide were found to exhibit essentially the same cytotoxicity and antileukemic activity, suggesting that the inverted stereochemistry of the alkylating group at the phosphorus atom is also effective in promoting the tumor inhibitory action of the 1,3,2-oxazaphosphorinane antitumor alkylating agents.