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INTRAMOLECULAR INTERACTIONS IN PHOSPHONOHYDROXAMIC ACIDS.

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In recent years the hydroxamic function appears with increasing frequency in biologically active compounds (such as antimalarials, inhibitors of various enzymes, and anticancer agents). However, only few cases are reported in which the hydroxamic and the phosphonic functions are combined in one molecule.

In a program directed towards the synthesis and the study of new types of multifunctional phosphonates, one of our target compounds to synthesize was $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CONHOH}$. In an attempted synthesis of this compound, using the standard approach to hydroxamic acids based on esters, we found that the reaction of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$ with NH_2OH involved dealkylation, and gave $(\text{EtO})(\text{O}^-)\text{P}(\text{O})\text{CH}_2\text{CONHOH}$ and $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COO}^-$ as byproduct. Monitoring the reaction of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$ ($\delta_{\text{P}} = 23.1$ ppm) with NH_2OH by ^{31}P nmr spectroscopy we found that it led first to the transient formation of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CONHOH}$ ($\delta_{\text{P}} = 26.2$ ppm), which was subsequently transformed to $(\text{EtO})(\text{O}^-)\text{P}(\text{O})\text{CH}_2\text{CONHOH}$ ($\delta_{\text{P}} = 17.1$ ppm). In contrast, reaction of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$ with NH_2OMe gave $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CONHOMe}$ ($\delta_{\text{P}} = 25.7$ ppm) and $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COO}^-$ ($\delta_{\text{P}} = 27.3$ ppm) as byproduct. Upon extended standing in NaHCO_3 solution, the methyl hydroxamate hydrolyzed to $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COO}^-$. No P-monoethyl ester was observed at all in the latter reaction. In control experiments we found that neither $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOMe}$ nor $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COO}^-$ underwent deethylation under the reaction conditions. These results indicate that the OH group of the hydroxamic function has a role in the deethylation during the attempted synthesis of diethylphosphinylacethydroxamic acid. The mechanism suggested (see scheme) involves intramolecular attack of the hydroxamate anion on the phosphorus, leading to a pentacoordinated intermediate which loses an ethoxy group and then opens to the final product. (Only the first step of the mechanism is shown.)

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