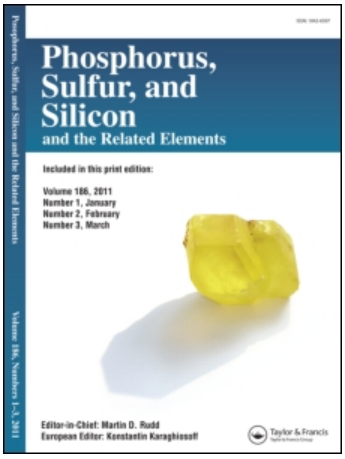

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PHOSPHORYL- AND THIOPHOSPHORYL THIOALKYNES

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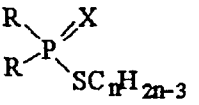
Abstract Syntheses of S-alkynyl derivatives of phosphorus monothioacids with the triple bonds in the α, β, and γ positions are described. Compounds of the type $R_2P(O)SC{\equiv}CR'$ show unusually high anticholinesterase ability ("acetylenic effect").

Key words:thioalkynes, thiophosphorus acid, bromoacetylene.

This communication is devoted to alkynyl esters of thio- and dithiophosphorus acids of the general type



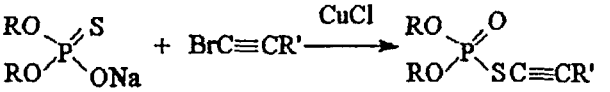
where X is O or S and R is alkyl or alkoxyl.

The triple bond can be located in the α-, β-, or γ-positions relative to the sulfur atom. Earlier this type substances have little been studied but there was reason to look for interesting physiologically active compounds among them. All the literature data indicated the prosperity of the compounds with the triple bond in the β-position relative to the heteroatom, and we performed the synthesis and investigation of physiological action of phosphorylated 2-butynes[1] but all the compounds obtained exhibit a moderate anticholinesretase activity.

We synthesized also the substances with the γ-position of the triple bond relative to the sulfur atom but they appeared to be even less interesting.

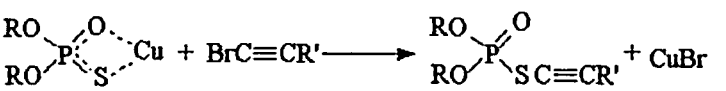
The comparison of the physiological activity, for example, anticholinesterase action, of the compounds studied reveals the following order: compounds with the triple bond in the γ-position have K_{II}s about $10^3 M^{-1}min^{-1}$, those of the butyne derivatives are in the range from 10^4 to 10^5 $M^{-1}min^{-1}$, K_{II}s of propargyl thiol esters slightly exeed $10^5 M^{-1}min^{-1}$. This matching pointed to the advisability of the synthesis and investigation of acetylene thioesters with the triple bond in the α-position

First attempts to alkylate monothiophosphorus acid salts with bromoacetylene, by analogy with the well-known alkylation reaction, were not successful: the reaction did not proceed at all[2]. An attempt to perform the synthesis by the reaction of free acids with bromoacetylene in the presence of pyridine gave also the negative result. At the same time, the Khodkieviez and Cadiot reaction[3] is known where the copper catalyst revives the substitution of bromoacetylene. In our case, the alkylation of the alkaline thiophosphoryl salt was successful when using copper (I) chloride as a catalyst:



(60-80%)

as well as the reaction of a free acid with bromoacetylene and pyridine in the presence of copper (I) chloride. Unlike the Khodkieviez and Cadiot reaction, an equimolar amount of copper (I) chloride was necessary rather than catalytic. That means that the reaction runs through the copper (I) salt of phosphorus thioacid. Indeed, the copper salt reacts readily with bromoacetylene to give the expected thiophosphoryl derivative:



(60-85%)

In doing so, three questions arise as follows: What is the structure of the copper salt of thiophosphorus acid? What is the difference between the reactivity of this salt and that of alkaline metal salts and why they differ? What is the mechanism of the reaction between the copper salt of thiophosphorus acid and bromoacetylenes?

X-ray analysis answered the first question[4]. Copper diethylthiophosphate is tetrameric: copper atoms form a tetrahedral (irregular) cluster. All the bond distances in the complex are typical of covalent (coordination) bonds. Hence, the copper salt is built

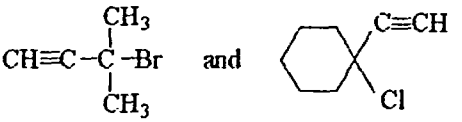
up in the covalent fashion while alkaline metal salts are ionic. This is the answer to the second question.

In order to answer the third question about the mechanism of alkylation of copper (I) thiophosphates, we studied a number of reactions of such copper salts with various alkynyl halides parallel with alkyl halides.

Above we considered reactions with bromoacethylenes. They react with copper (I) salts but do not react with potassium salts. On the contrary, alkyl halides alkylate potassium salts but they do not react with Cu(I) salts.

However, bromoalkynes with the bromine atom in the alkyl part of the molecule react with potassium salts and do not react with copper (I) salt: whereas 1,4-dibromobutyne reacts with both potassium and copper (I) salt but in different fashions. The bromoalkynyl derivatives obtained differ in their ability to react with trimethylamine. The former reacts with trimethylamine to form ammonium derivatives but the second does not react with trimethylamine.

Significantly that both potassium and copper (I) salts react with propargyl bromide. Since the propargylic bromine atoms are sure to exchange with potassium salts according to the mechanism of heterolitic substitution of the S_N2 type, it is reasonable to suppose that copper (I) salts react in the same manner. However, if the S_N2 reaction is inhibited by sterical hindrances, the potassium salt stops reacting but the copper (I) salt continues. For example, the compounds



react only with the copper (I) salt. The problem was solved by NMR and ESR studies[5], which show that we are dealing with the redox transfer of one electron leading to the formation of the free radical •C≡CPh. The free radical formed attacks the sulfur atom in the copper salt to give the reaction products.Both stages are most likely to proceed into the solvent cage. When leaving the cage, the •C≡CPh radicals are dimerized to form diphenyldiacetylene PhC≡C-C≡C-Ph (in our case, 10-15%).

Biochemical experiments on the inhibition of cholinesterases of various origin revealed that the majority of these substances appeared to be anticholineaterases of a great strength with inhibition constants ($K_I M^{-1} min^{-1}$) being tens, hundreds, millions times higher than those of corresponding saturated compounds. We termed the ratio

between the constants of acetylene and saturated compounds (that is $K_{II,acet.}/K_{II,sat}$) the "acetylenic effect" ("AE").

The comparison of anticholinesterase action of $(MeO)_2P(O)SC{\equiv}C\text{-}C_6H_{11}$-c with $(MeO)_2P(O)SCH_2\text{-}CH_2\text{-}C_6H_{11}$-c gives AE of two millions; $K_{II} = 2.0.10^8 M^{-1}min^{-1}$. On butylcholinesterase, AE = $1.5.10^6$ and $K_{II} = 2.2.10^9 M^{-1}min^{-1}$. For cholinesterase of fly heads, AE = $2.7.10^6$ and $K_{II} = 3.0.10^8 M^{-1}min^{-1}$. The presented values are the highest among all obtained but for other compounds, they are also very high.

Unusually high "thionic effect" of α-acetylenic compounds should be specially pointed out consisting in the fact that while changing the P=O group in acetylene compounds for the P=S group, the toxicity is changed very little for arthropoda but sharply decreases for mammals.

The possible mechanisms of the acetylenic and thionic effects are discussed.

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