AMINO α-OXO PHOSPHONIC ESTERS

(UDC 542.91 + 661.718.1)

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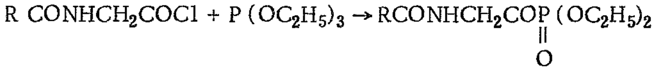
M. I. Kachnik and P. A. Rossiiskaya [1] showed that by the action of acid chlorides on phosphorous triesters, α-oxo phosphonic esters are obtained. Attempts that we made to carry out the reaction of acid chlorides of dibasic acids with trialkyl phosphites were not successful. It was therefore considered to be of interest to determine the effect of the presence of various functional groups in the hydrocarbon group of the acid chloride of a monobasic acid on the course of its reaction with a trialkyl phosphite. We chose the acid chlorides of amino acids for examination. The preparation of amino α-oxo phosphonic esters presented interest for its own sake, because compounds of this type have not been described in the literature*.

Our experiments showed that hippuroyl (R = C_6H_5) and aceturoyl (R = CH_3) chlorides react normally with triethyl phosphite with formation of substituted glycylphosphonic esters (I)



$$RCONHCH_2COCl + P(OC_2H_5)_3 \rightarrow RCONHCH_2CO\underset{\overset{\|}{O}}{P}(OC_2H_5)_2 \quad \text{(I)}$$

N-Unsubstituted amino acid chlorides, in the form of their hydrochlorides, react with triethyl phosphite with formation of amino α-oxo phosphonic ester hydrochlorides, as was shown for the case of the hydrochlorides of glycyl, alanyl, and β-alanyl chlorides. The resulting diethyl amino α-oxo phosphonates and their derivatives, with the exception of diethyl hippuroylphosphonate which is a liquid, are crystalline solids. The properties of the compounds obtained are given in Table 1.

To prove the structure of the compounds obtained, one of them (No. 5) was synthesized by an independent method. From acryloyl chloride and triethyl phosphite we prepared diethyl acryloylphosphonate [9], which by the addition of ammonia was converted into diethyl β-alanylphosphonate (Table 1, No. 6). Its hydrochloride melted at 340°, undepressed by admixture with product No. 5. Amino α-oxo phosphonic esters have the properties of ketones

TABLE 1

No.	Formula	M. p., °C	Found, %			Calculated, %			Yield, %
			P	C	H	P	C	H	
1	$C_6H_5CONHCH_2COP(O)(OC_2H_5)_2$ *		10,50	51,9	6,15	10,36	52,1	6,00	48
2	$CH_3CONHCH_2COP(O)(OC_2H_5)_2$	155	13,10	—	—	13,0	—	—	42
3	$Cl[NH_3CH_2COP(O)(OC_2H_5)_2]$	129	13,48	—	—	15,8	—	—	38
4	$Cl[NH_3CH(CH_3)COP(O)(OC_2H_5)_2]$	124	12,60	—	—	12,7	—	—	30
5	$Cl[NH_3CH_2CH_2COP(O)(OC_2H_5)_2]$	340	12,60	34,6	6,7	12,7	34,1	6,8	35
6	$NH_2CH_2CH_2COP(O)(OC_2H_5)_2$	52							
7	$CH_2OHCOP(O)(OC_2H_5)_2$ †		15,2	—	—	15,3	—	—	

*b.p. 107-109°(1 mm); n_D^{20} 1.4658.
†b.p. 115-120° (6 mm); n_D^{20} 1.4498.

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*A number of papers have appeared on the preparation of substituted amides of phosphonoformic esters [2-8].

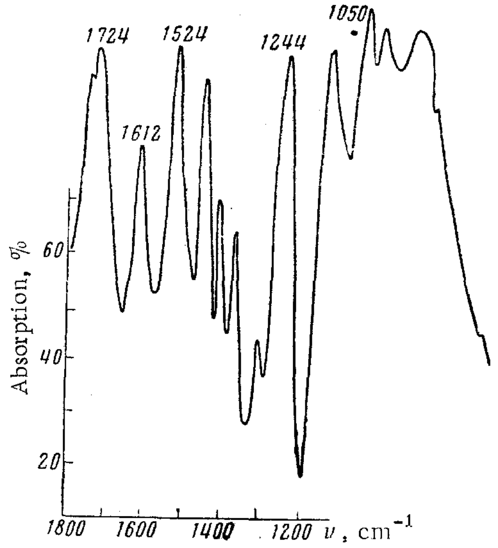
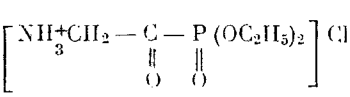


Fig. 1. Infrared spectrum of



$\left[NH_3^+CH_2-\underset{O}{\underset{\|}{C}}-\underset{O}{\underset{\|}{P}}(OC_2H_5)_2\right]Cl^{\ominus}$ in oil.

and of amines. Thus, diethyl glycylphosphonate hydrochloride (No. 3) gives a p-nitrophenylhydrazone. When treated with nitrous acid it forms diethyl glycoloylphosphonate (Table 1, No. 7). Table 2 gives values of the infrared frequencies of the substances obtained. The infrared spectra of hydrochlorides of three amino α-oxo phosphonic esters are presented in Figures 1-3.

The spectra contain frequencies characteristic for the P = O group (1244-1250 cm^{-1}), the C = O group (1720-1728 cm^{-1}), and the NH_3^+ group (1520-1528 cm^{-1}). The 1612-1617 cm^{-1} frequencies probably also belong to the NH_3^+ group [10].

EXPERIMENTAL

Action of Hippuroyl Chloride on Triethyl Phosphite. 16.6 g of triethyl phosphite was added dropwise to 19 g of hippuroyl chloride in a three-necked flask provided with stirrer, dropping funnel, thermometer, and reflux condenser. The temperature rose from 20 to 50°, and the acid chloride dissolved with a pinkish-violet coloration. Fractionation gave 14 g (48%) of diethyl hippuroylphosphonate; b. p. 107-109° (1 mm), n_D^{20} 1.4657; d_4^{20} 1.0550; found: MR 78.39. $C_{13}H_{18}O_5NP$. Calculated: MR 78.32.

Action of Aceturoyl Chloride on Triethyl Phosphite. 9 g of triethyl phosphite was added dropwise to 7.5 g of aceturoyl chloride [11] in a three-necked vessel provided with stirrer, dropping funnel, thermometer, and reflux condenser. The temperature rose to 65°, and ethyl chloride was liberated. After five months, the viscous mass in the flask crystallized. The crystalline mass was washed with ligroin, and we obtained 5.2 g (42%) of crystals. After several crystallizations from a mixture of ether and alcohol it had m. p. 155°. Found: P 13.15%. $C_7H_{16}O_4PN$. Calculated: P 13.00%.

Action of Glycyl Chloride Hydrochloride on Triethyl Phosphite. 6 g of glycyl chloride hydrochloride [12] and 16.6 g of triethyl phosphite were introduced into the flask described for the first experiment. The temperature rose from 19 to 69°, and the mixture became pinkish yellow. After a time, the thick oil formed crystallized. Recrystallization from alcohol and hot ether gave 3.5 g (33%) of crystals of m. p. 129°. The product was sparingly soluble in alcohol and ether, but readily soluble in water. Treatment with p-nitrophenylhydrazine gave the p-nitrophenylhydrazone, m. p. 127° (decomp.).

Action of Nitrous Acid on the Product of M. P. 129°*. With cooling with snow, a saturated aqueous solution of 5 g of sodium nitrite was added to an aqueous solution of 8 g of the product, and with vigorous shaking, hydrochloric acid was added dropwise. The course of the reaction was followed with the aid of starch-iodide paper. Water was then added, and the solution was refluxed for 48 h. Water was driven off. Distillation of the residue gave a fraction of b. p. 115-120° (6 mm); n_D^{20} 1.4498. A glassy residue remained in the flask.

The same product was obtained by the action of glycoloyl chloride on triethyl phosphite. 0.1 mole of triethyl phosphite was added cautiously with stirring to an ethereal solution of 0.1 mole of glycoloyl chloride [13]. Ethyl

TABLE 2

Hydrochlorides of amino α-oxo phosphonic esters	ν, cm^{-1}
$[NH_3^+CH_2COP(O)(OC_2H_5)_2]Cl^{\ominus}$	1724, 1612, 1524, 1244, 1050
$[NH_3^+CH(CH_3)COP(O)(OC_2H_5)_2]Cl^{\ominus}$	1720, 1717, 1524, 1250, 1052
$[NH_3^+CH_2CH_2COP(O)(OC_2H_5)_2]Cl^{\ominus}$	1728, 1617, 1520, 1245, 1048

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*As in Russian Original-Publ. note.

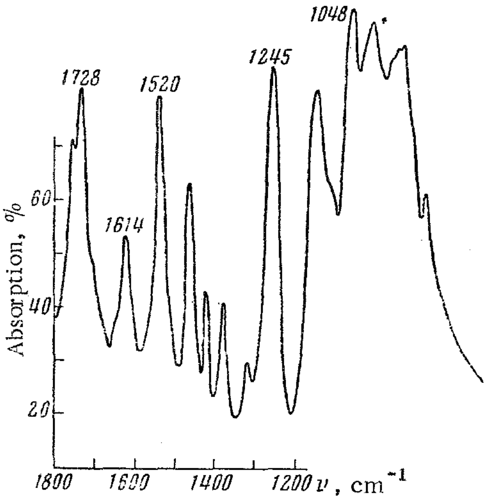
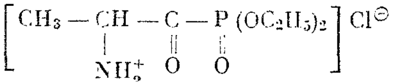


Fig. 2. Infrared spectrum of



$$\left[CH_3-\underset{NH_3^+}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-\underset{O}{\underset{\|}{P}}(OC_2H_5)_2\right]Cl^{\ominus}$$

in oil.

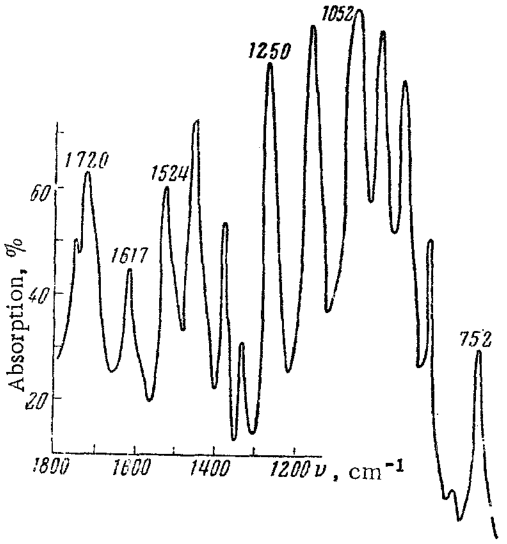
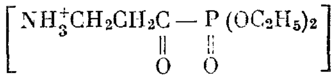


Fig. 3. Infrared spectrum of



$$\left[NH_3^+CH_2CH_2\underset{O}{\underset{\|}{C}}-\underset{O}{\underset{\|}{P}}(OC_2H_5)_2\right]Cl^{\ominus}$$

in oil.

chloride was liberated. Toward the end of the reaction the flask was heated so that the ether boiled. Ether was driven off, and distillation then gave a fraction of b. p. 125° (10 mm); n_D^{20} 1.4501. Found: P 15.12%. $C_6H_{13}O_5P$. Calculated: P 15.30%.

Reaction of β-Alanyl Chloride Hydrochloride with Triethyl Phosphite. The reaction was carried out under the conditions described for glycyl chloride hydrochloride. We took 14.4 g of the acid chloride [14] and 16.6 g of triethyl phosphite. The temperature rose to 42°. After treating the contents of the flask with alcohol and ether,we isolated 8.5 g (35%) of a finely crystalline substance, m. p. 340° after recrystallization from acetone. Found: P 12.48%. $C_7H_{17}O_4NPCl$. Calculated: P 12.60%.

Action of Ammonia on Diethyl Acryloylphosphonate. A mixture of 10 g of diethyl acryloylphosphonate and 25% aqueous ammonia (a small excess) was heated in a sealed tube for 7 h at 150°. Water was driven off, leaving a viscous oil, which on treatment with hydrochloric acid (sp. gr. 1.18) gave a crystalline product of m. p. 340° (from acetone), undepressed by admixture of the product of the preceding experiment.

Reaction of Alanyl Chloride Hydrochloride with Triethyl Phosphite. The reaction was carried out under the conditions described for glycyl chloride hydrochloride. We took 10 g of the acid chloride and 23 g of triethyl phosphite (2 moles per mole of the acid chloride). The temperature rose to 40°. The crystalline product was filtered from the excess of the phosphorous ester. Yield 5.4 g (30%). After recrystallization from a mixture of alcohol and ether it had m. p. 124° (decomp.).

SUMMARY

1. Hydrochlorides of amino acid chlorides react with triethyl phosphite with formation of the hydrochlorides of the corresponding amino α-oxo phosphonic esters.

2. The hydrochlorides of diethyl glycylphosphonate, diethyl alanylphosphonate, and diethyl β-alanylphosphonate were prepared.

3. Diethyl aceturoylphosphonate and diethyl hippuroylphosphonate are described.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.