

***O*-Alkylhydroxylamides of the phosphoric acid**

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By condensation of *O*-alkylhydroxylamines with chlorides of diphenylphosphoric and phenylphosphoric acids and with phosphorus trichloride oxide the corresponding mono-, bis-, and tris(*O*-alkylhydroxylamides) of these acids have been prepared. Mono-*O*-alkylhydroxylamides were also synthesized in the reaction of free bases of *O*-alkylhydroxylamines with diethyl or diphenyl esters of hydridophosphoric acid in the presence of carbon tetrachloride. In acid medium the *O*-alkylhydroxylamides hydrolyze to form *O*-alkylhydroxylammonium salts. In base medium the ester groups are saponified, and, moreover, in bis- and tris(*O*-alkylhydroxylamides) a partial cleavage of P—N bonds takes place.

Моно-, бис- и трис(*O*-алкилгидроксилами́ды) были приготовлены конденсацией соответствующих *O*-алкилгидроксилами́нов с хлоридами дифенилфосфорной и фенилфосфорной кислот и с хлорокисью фосфора. Моно-*O*-алкилгидроксилами́ды были приготовлены также реакцией свободного основания *O*-алкилгидроксилами́нов с диэтил- или дифенилфосфитом в присутствии четыреххлористого углерода. В кислой среде *O*-алкилгидроксилами́ды подвергаются гидролизу с образованием солей *O*-алкилгидроксиламмония. В щелочной среде происходит омыление эфирных групп, а в случае бис- и трис(*O*-алкилгидроксилами́дов) также частичный разрыв связей P—N.

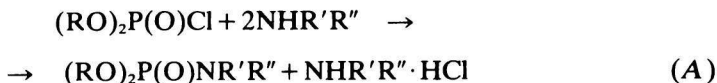
While the amides and hydrazides of phosphoric acid were widely dealt with in the literature, we possess but scanty pieces of knowledge on phosphorylated hydroxylamines. *Kreutzkamp* and *Schindler* [1] prepared hydroxylamide of the diphenylphosphinic acid $(C_6H_5)_2P(O)NHOH$ by condensation of hydroxylamine with the chloride of this acid. *Cates* [2] prepared esters of hydroxylamido- and *O*-methylhydroxylamidophosphoric acids and studied their physiological effect. However, detailed chemical characteristics of the above substances were not given.

Theoretically, the phosphorylation of hydroxylamines may take place on both, the nitrogen or oxygen atom. Formation of *O*-phosphorylated hydroxylamines was observed in the course of enzymatic processes [3] and in the course of the reaction

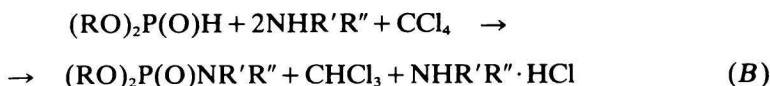
of hydroxylamine with amidophosphate [4] or with *p*-nitrophenylmethylphosphate, respectively [5]. Since *O*-phosphorylated hydroxylamine hydrolyzes readily, it was not possible to isolate it.

In order to prevent a possible formation of *O*-phosphorylated derivatives of hydroxylamine, *O*-methyl- and *O*-benzylhydroxylamines were used for syntheses.

For preparation of the amides of phosphoric acid most frequently the reactions between amines and chlorides of this acid are used; e.g.



Monoamides may be also conveniently prepared by a reaction of amine with dialkyl or diaryl ester of the hydridophosphoric (phosphonic) acid $(\text{RO})_2\text{P}(\text{O})\text{H}$ in the carbon tetrachloride medium [6]



Both above methods were also used with success for the synthesis of *O*-alkylhydroxylamides of phosphoric acid.

Experimental

Literature sources according to which the following substances were prepared are referred to in parentheses: *O*-methylhydroxylamine [7]; *O*-benzylhydroxylamine [8]; chloride of the diphenyl ester of phosphoric acid [9]; dichloride of the phenyl ester of phosphoric acid [10]; diethyl ester of hydridophosphoric acid [11]; diphenyl ester of hydridophosphoric acid [12]; diphenyl ester of phosphoric acid [9]. All remaining chemicals were of anal. grade, supplied by Lachema, Brno.

The purity of the reagents, as well as the course and results of hydrolytic processes were checked and followed by chromatographic method. The esters and the products of the acid hydrolysis were chromatographed on a layer of SiO_2 (Silikagel L 40/100 μ , Lachema, Brno) by elution with a mixture of ether—benzene (2:1). The base hydrolysis was followed by paper chromatography on Whatman No. 4, elution was performed with a mixture of isopropyl alcohol—*isobutyl* alcohol—water—concentrated ammonia (20:60:19:1). After the product has been hydrolyzed using the mixture concentrated hydrochloric acid—alcohol (1:3), the detection was performed by spraying the chromatographic paper with 1% alcoholic solution of picryl chloride and by exposing it to ammonia vapours. The R_f values, the results of analyses, and the melting points of the synthesized substances are listed in Table 1.

$^1\text{H-N.m.r.}$ spectra were recorded with a Varian T-60 spectrometer in the solutions of deuterated dimethyl sulfoxide; tetramethylsilane was the internal standard.

Table 1

Physical constants and results of analyses on the derivatives of *O*-alkylhydroxylamides of phosphoric acid

No.	Compound	Formula	M	Calculated/found				Yield %	M.p., °C Solvent	R _f
				% C	% H	% N	% P			
I	(C ₂ H ₅ O) ₂ PO(NHOCH ₃)	C ₅ H ₁₄ NO ₄ P	183.12	32.80	7.71	7.65	16.91	80	—	0.05
				32.51	7.93	7.68	16.76			
II	(C ₂ H ₅ O) ₂ PO(NHOCH ₂ C ₆ H ₅)	C ₁₁ H ₁₈ NO ₄ P	259.22	50.97	7.00	5.40	11.95	60	—	0.11
				50.32	6.82	4.92	11.47			
III	(C ₆ H ₅ O) ₂ PO(NHOCH ₃)	C ₁₃ H ₁₄ NO ₄ P	279.21	55.92	5.05	5.02	11.09	52	59—60	0.55
				56.11	5.19	5.14	11.13			
IV	(C ₆ H ₅ O) ₂ PO(NHOCH ₂ C ₆ H ₅)	C ₁₉ H ₁₈ NO ₄ P	355.33	64.22	5.11	3.94	8.72	68	Ether—pentane 70	0.60
				64.45	5.40	3.87	8.63			
V	(C ₆ H ₅ O)PO(NHOCH ₃) ₂	C ₈ H ₁₃ N ₂ O ₄ P	232.16	41.39	5.64	12.07	13.34	60	62—63	0.30
				40.94	5.75	12.15	13.67			
VI	(C ₆ H ₅ O)PO(NHOCH ₂ C ₆ H ₅) ₂	C ₂₀ H ₂₁ N ₂ O ₄ P	384.36	62.50	5.51	7.29	8.06	75	Ether—pentane 78	0.38
				62.62	5.78	7.19	8.11			
VII	PO(NHOCH ₂ C ₆ H ₅) ₃	C ₂₁ H ₂₄ N ₃ O ₄ P	413.40	61.01	5.85	10.16	7.49	55	Water—alcohol 94	0.10
				60.37	5.99	10.33	7.42			
VIII	NH ₂ OCH ₂ C ₆ H ₅ · (HO)(C ₆ H ₅ O) ₂ PO	C ₁₉ H ₂₀ NO ₅ P	373.34	61.13	5.40	3.75	8.30	92	Carbon tetrachloride 110—111	0.00
				60.86	5.80	3.71	8.76			
IX	(NaO)(C ₆ H ₅ O)PO(NHOCH ₃)	C ₇ H ₉ NNaO ₄ P	225.09			6.22	13.76	70	—	0.28 ^a
						5.93	13.79			
X	(NaO)(C ₆ H ₅ O)PO(NHOCH ₂ C ₆ H ₅)	C ₁₃ H ₁₃ NNaO ₄ P	301.21			4.65	10.28	63	—	0.59 ^a
						4.46	10.27			
XI	(NaO)PO(NHOCH ₃) ₂	C ₂ H ₈ N ₂ NaO ₄ P	178.04	13.49	4.53	15.73	17.40	75	—	0.06 ^a
				12.98	4.71	15.58	17.68			
XII	(NaO)PO(NHOCH ₂ C ₆ H ₅) ₂	C ₁₄ H ₁₆ N ₂ NaO ₄ P	330.26	50.92	4.88	8.48	9.38	40	—	0.58 ^a
				50.48	4.67	8.35	9.49			

^aR_f values for paper chromatography.

*Preparation of diphenyl esters
of O-alkylhydroxylamidophosphoric acid*

a) To *O*-alkylhydroxylamine (0.1 mole) in dry benzene or ether (300 ml) the solution of chloride of diphenylphosphoric acid (0.05 mole) in the above solvent (100 ml) was added dropwise under constant stirring for 30 min. After the whole amount had been added the stirring was continued for another 60 min and the whole was then allowed to boil under reflux for 30 min, the separated *O*-alkylhydroxylammonium chloride was then filtered off and the filtrate was evaporated to dryness. The oil formed was allowed to recrystallize in a refrigerator. The recrystallization took place in a mixture of ether—pentane.

b) To the solution of *O*-alkylhydroxylamine (0.1 mole) in dry ether (200 ml) dry carbon tetrachloride (100 ml) and diphenyl or diethyl ester of hydridophosphoric acid $(\text{RO})_2\text{P}(\text{O})\text{H}$ (0.05 mole) were added. Then this was allowed to stand at room temperature for 3 days, the separated *O*-alkylhydroxylammonium chloride was filtered off and evaporated to dryness. The yield was about 60—80%. This method is not suitable for preparation of the diphenyl ester of *O*-benzylhydroxylamidophosphoric acid.

The phenyl ester of bis(*O*-alkylhydroxylamido)phosphoric acid and tris(*O*-benzylhydroxylamide) of phosphoric acid were prepared in a similar way by condensation of the respective chlorides of phosphoric acid with *O*-alkylhydroxylamine in benzene or ether, under the condition that the ratios of $\text{NH}_2\text{OR}:(\text{C}_6\text{H}_5\text{O})\text{POCl}_2$ and of $\text{NH}_2\text{OCH}_2\text{C}_6\text{H}_5:\text{POCl}_2$ are 4:1 and 6:1, respectively, and that the condensation is performed under external cooling.

*Preparation of O-benzylhydroxylammonium salt
of diphenyl ester of phosphoric acid*

Diphenyl ester of *O*-benzylhydroxylamidophosphoric acid (3.5 g) and diphenyl ester of phosphoric acid (0.5 g) were dissolved in 50% alcohol (200 ml) and the solution was boiled for 48 h under reflux. The solution was evaporated to the volume of 50 ml and cooled subsequently. The precipitated crystals were sucked off and recrystallized from benzene.

*Preparation of sodium salt of phenyl ester of O-alkylhydroxylamidophosphoric
acid and of sodium salt of bis(O-alkylhydroxylamido)phosphoric acid*

Phenyl ester of *O*-alkylhydroxylamidophosphoric acid (0.01 mole) and sodium hydroxide (0.01 mole) were dissolved in 50% alcohol (100 ml) and the solution was steam heated for 4 h. Then it was evaporated to dryness, the crystalline residue was extracted with 3×10 ml ether and 2×5 ml alcohol. The solid residue was then dissolved in the least possible amount of methanol and precipitated with ether.

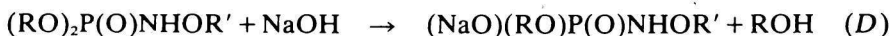
Results and discussion

As to their structure and properties, the *O*-alkylhydroxylamides of phosphoric acid resemble a great deal the corresponding amides. The diethyl esters of *O*-alkylhydroxylamidophosphoric acid are oily liquids, the phenyl esters of mono- and bis (*O*-alkylhydroxylamido)phosphoric acid and tris(*O*-benzylhydroxylamide) of phosphoric acid are white crystalline substances, which are easily soluble in alcohol, ether, benzene, and insoluble in water. From those only the diethyl ester of *O*-methylhydroxylamidophosphoric acid is miscible with water and partly soluble in ether. The melting points of the crystalline esters are lower by 30–40°C than those of the corresponding amides. Also the chemical properties are analogous to those of amides. The esters of *O*-alkylhydroxylamidophosphoric acids are submitted to hydrolytic cleavage of P—N bonds in acid medium, with the formation of the respective *O*-alkylhydroxylammonium salts



The ethyl esters hydrolyze more readily than the phenyl esters; the same observation was made with the esters of *N*-alkylamidophosphoric acids [13]. Bis(*O*-alkylhydroxylamides) and tris(*O*-benzylhydroxylamide), as well as the salts of *O*-alkylhydroxylamidophosphoric acids hydrolyze very easily.

In base medium the P—N bond is very stable. Only in the case of bis(*O*-alkylhydroxylamides) and tris(*O*-benzylhydroxylamide) the partial cleavage of the P—N bonds takes place, too. The saponification of the ester groups is, however, favoured. In the case of the diesters of mono-*O*-alkylhydroxylamidophosphoric acids, and in the case of their corresponding amides, only one ester group is saponified with the formation of an alkali salt of the monoester of *O*-alkylhydroxylamidophosphoric acid



There are just traces of a saponification of the second ester group if we use the alkali hydroxide in excess during a long boiling period in the presence of alcohol. The bis- and tris(*O*-alkylhydroxylamides) usually yield, under identical conditions, a diversified mixture of hydrolytic products.

The assumed structure of *O*-alkylhydroxylamidophosphoric esters was confirmed, apart from chemical evidence, by measurements of ¹H-n.m.r. spectra. In the spectra of phenyl esters (Table 2) the signals of the NH protons, of the aromatic groups, and of the —CH₂C₆H₅ and —OCH₃ groups could be observed. The signals of the protons were doublets and resulted from the spin-spin interaction between the proton of the NH group and the ³¹P nucleus. From the n.m.r. spectra of

Table 2

Values of chemical shifts of ^1H -n.m.r. spectra of phenyl esters of *O*-alkylhydroxylamides of phosphoric acid

No.	Compound	NH		Aromatic protons		Other		Assignment
		δ	Intensity	δ	Intensity	δ	Intensity	
I	$(\text{C}_6\text{H}_5\text{O})_2\text{PO}(\text{NHOCH}_3)$	9.70	1 H	7.10—7.65	10 H	3.58	3 H	O—CH ₃
II	$(\text{C}_6\text{H}_5\text{O})_2\text{PO}(\text{NHOCH}_2\text{C}_6\text{H}_5)$	9.66	1 H	7.15—7.60	15 H	4.77	2 H	O—CH ₂ —C ₆ H ₅
III	$(\text{C}_6\text{H}_5\text{O})\text{PO}(\text{NHOCH}_3)_2$	9.13	2 H	6.80—7.35	5 H	3.57	6 H	O—CH ₃
IV	$(\text{C}_6\text{H}_5\text{O})\text{PO}(\text{NHOCH}_2\text{C}_6\text{H}_5)_2$	9.11	2 H	7.15—7.60	15 H	4.77	4 H	O—CH ₂ —C ₆ H ₅
V	$\text{PO}(\text{NHOCH}_2\text{C}_6\text{H}_5)_3$	8.48	3 H	7.32	15 H	4.77	6 H	O—CH ₂ —C ₆ H ₅

substances containing a single NH group, *i.e.* of monohydroxylamides, the spin-spin interaction constant $J_{\text{H}-^{31}\text{P}} = 24$ Hz could be determined. All other substances showed broadened peaks of the doublet, while the distance between them was shorter. Even in the spectrum of bis(*O*-methylhydroxylamide) a broad singlet was observed. This broadening and approaching of both peaks of the doublet is presumably due to the intramolecular exchange of protons between the NH groups in the molecules of these substances.

References

1. Kreutzkamp, N. and Schindler, H., *Arch. Pharm.* **293**, 296 (1960).
2. Cates, L. A., *J. Med. Chem.* **11**, 382 (1968).
3. Cottam, G. L., Kupiecki, F. P., and Coon, M. J., *J. Biol. Chem.* **243**, 1630 (1968).
4. Jencks, W. P. and Gilchrist, M., *J. Amer. Chem. Soc.* **87**, 3199 (1965).
5. Brass, H. J., Edwards, J. O., and Fina, N. J., *J. Chem. Soc., Perkin Trans.* **1972**, 726.
6. Atherton, F. R., Openshaw, H. T., and Todd, A. R., *J. Chem. Soc.* **1945**, 660.
7. Ioffe, B. V. and Zelenin, K. N., *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* **1963**, 78.
8. Janny, A., *Ber.* **16**, 170 (1883).
9. Brigl, P. and Müller, H., *Ber.* **72**, 2121 (1939).
10. Katyshkina, V. V. and Kraft, M. Ya., *Zh. Obshch. Khim.* **26**, 3060 (1956).
11. McCombie, H., Saunders, B. C., and Stacey, G. J., *J. Chem. Soc.* **1945**, 380.
12. Walsh, E. N., *J. Amer. Chem. Soc.* **81**, 3023 (1959).
13. Stock, J. A., Hopwood, W. J., and Regan, P. D., *J. Chem. Soc (C)* **1966**, 637.

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