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REACTION OF ALKYLTHIOLCHLOROPHOSPHONITES AND DIALKYLCHLORODI-THIOPHOSPHITES WITH CARBONYL COMPOUNDS

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Thiol esters of α -hydroxyalkylthiophosphinic acids (I), which have not yet been described, hold interest as potentially physiologically active compounds. A possible pathway for the synthesis of (I) may be the addition of acid S-alkylthiophosphonites (II) to carbonyl compounds



However, we were unable to find information indicating the existence of (II) as a free compound. On the other hand, several reactions of S-alkylchlorothiophosphonites (III) which yield the products of the addition of thiolphosphonites (II) to unsaturated ketones indicate that thiophosphonites (II) are formed as intermediates from acid chlorides (III) by hydrol-ysis [1, 2].

Hence, as continuation of work on the synthesis of α -hydroxyalkylphosphoryl compounds [3-5], we studied the reaction of S-alkylchlorothiophosphonites (III) for R = Et and Ph and S,S-dialkylchlorodithiophosphites (IV) with aldehydes and ketones in the presence of hydroxyl-containing compounds.

The reaction of acid chlorides (III) with aldehydes or ketones and water in equimolar amounts at 10-15°C in ether yields S-alkyl esters of alkyl- and aryl- α -hydroxyalkylthio-phosphinic acids (I) in 60-90% yield



The reaction of diethylchlorodithiophosphite (IV) (R = Et) with carbonyl compounds and water proceeds analogously to give S,S-diethyl- α -hydroxyalkyldithiophosphonates (I) with R = EtS

$$\begin{array}{c} O\\ (EtS)_2PCl + R^3CHO + H_2O \rightarrow R^3CHP(SEt)_2 + HCl\\ i\\ OH \quad (I)\end{array}$$

 $R^3=Cl_3C,\ \text{o-}O_2NC_6H_4.$

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2114-2121. September, 1983. Original article submitted December 15, 1982. TABLE 1. Properties of Thioesters (I) with the General Formula

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R ³ OH	IR spectrum, cm ⁻¹	HOv	3150 3270	3100	2000	3110	3210	3210	3200	3260	3100	3170
		vP=0	1180	1180 1180 1180	1100	1160	1190	$1190 \\ 1180$	1160	1170	1170	H70
	Calculated, ϕ_{0}	G	11	33,2 32,0 22,0	0,00	11	1		I	1	33,5	1
		ø	11,2	10,0 9,4 0,3	7.6	10,4 10,4	13,1	11.4 10.4	11,8	11.8	20,2	19,9
		Ъ	10,8 13.1	16.40	л Х	10,1	12'.7	12,0	11.5	11.5	9.7	9.6
		H	4,2	, , , , , , , , , , , , , , , , , , ,	4	6,2 6,2	7,1	4,0	1.		4.00	5,0
		ç	25,2 50,8	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	38,U	62,812 62,812	54,1	56,2	57,8	57.8	22,7	41,1
	Chemical formula		C ₆ H ₁₂ Cl ₃ O ₂ PS	$C_{10}H_{12}CI_{3}O_{2}PS$ $C_{10}H_{12}CI_{3}O_{2}PS$ $C_{10}H_{12}CI_{3}O_{2}PS$	Cutha GlaO2PS	C ₁₂ H ₁₀ O ₂ PS C ₁₆ H ₁₀ O ₂ PS	C11H17O2PS	C12H1002PS C14H002PS	CisHisO2PS	C13H19O2PS	CaH1.2Cl3O.PS	CitH10NO2PS2
	Found, $\gamma_{\!$	ت 		33,2 32,1	31,1	11	I	11	1	1	33.9	1
		s	11,6	10.0 9.5	A'I	11.2	13,4	11,7 10.4	11,6	11.3	20.3	19,6
		đ	10,7 13.9	1445 1445	8,1	12,0 9,9	12,6	11,8	11,6	11,3	0.00	9,4
		H	3,9	0 0 0 0 0 0 0	4,2	10 10 10	0,7	7 9 10 0	50	1.1	~ e.	0 0
		J	25,5 50,8	30,83 30,83 30,83 1,12 8,02 1,12 1,12 1,12 1,12 1,12 1,12 1,12 1	31,1	55.9 62.9 62.9	53,6	56,7 62,8	57.7	58.3 28,3 2,5	22,0 22,0	41,6
	MP, ° C		97-98 88-90	158 130	130	116 121	106	8384 102	95-96	127	113	109
	Yield.		70 65	22 6 5	22	605	14	71 62	90	64 64	80 80	73
	britoqmoo R R R		ccl ³		ccl3	Pr Pr	Me	Me	(CH ₂)	(CH2) 5	(CH ₂)5	o-NO2C6H4
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			E C	1 M M M M M	7	- - - - - - - - - - - - - - - - - - -	E.	Pr	ц Ц	Me	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Ē
			톂	544	r n	d d d	Ч	d L L L	Ph	44	EtS	EtS
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In the case of chloral which forms a stable hydrate with water, the hydrate reacts directly without the addition of water



The physical constants, yields, and analytical data for (I) are given in Table 1. The product structures are supported by IR and ³¹P NMR spectroscopy. The IR spectra of thioesters (I) in the 3270-3080 cm⁻¹ region have intense bands for OH groups involved in hydrogen bonding. The band at 1190-1160 cm⁻¹ corresponds to the phosphoryl group, while the band at 1110-1100 cm⁻¹ corresponds to the Ph-P group. The bands in the vicinity of 700 cm⁻¹ are related to P-C vibrations [7].

The ${}^{31}P-{}^{1}H$ NMR spectra of thioesters (I) obtained from symmetric ketones (see Table 1, Ib,h,i,k-m) have unitary signals with δP 49.5-65.5 ppm, which is in the δP range for $R_2P(0)SR^1$ thiophosphinates [8]. The ${}^{31}P-{}^{1}H$ NMR spectra of thioesters (I) with asymmetrical phosphorus and carbon atoms have two ${}^{31}P$ signals for diastereomers (see Table 1, Ie,g).

In considering the mechanism for the formation of α -hydroxyalkylphosphoryl compounds (I), we must take account of the following findings. ³¹P NMR monitoring of the reaction between acid chloride (III) with R = Ph and water in 1:1 ratio in ether at -70°C indicated the formation of a small amount of phenylphosphonic acid PhPH(0)OH (δ P 26.5 ppm, J_{PH} = 585.9 Hz) and showed a doublet with δ P 37.0 ppm and J_{PH} = 580 Hz whose intensity gradually diminishes upon warming to 5°C until it disappears completely. Phenylphosphonic acid is apparently formed as a result of the complete hydrolysis of PhP(C1)SEt

$$PhP(Cl)SEt + 2H_2O \rightarrow PhPH(O)OH + HCl + EtSH$$

The doublet with δP 37.0 ppm and JpH = 580 Hz was assigned to intermediate S-ethylphenylthiophosphonite (II) with R = Ph for the following reasons: 1) the coupling constant JpH = 580 Hz indicates the presence of a P-H bond [8] and, 2) the nature of the variation in ³¹P chemical shifts in the series



is in qualitative accord with the nature of the variation in δP in going from oxygen esters to isostructural thiolic and thionic esters of different phosphorus acids such as phosphinic and phosphonic acids



Finally, the formation of S-ethylphenyl- α -hydroxyalkylthiophosphinates (I) which are thiolic analogs of the standard products of the addition of hydrophosphoryl compounds to aldehydes and ketones in the reaction of acid chloride (III) (R = Ph) with carbonyl compounds in the presence of water indicates the intermediate formation of (II).

Thus, we may assume that this reaction proceeds through the hydrolysis of the acid chloride RP(C1)SR¹ with the formation of S-alkylthiophosphonites and the addition of these intermediates to aldehydes or ketones, i.e., by a scheme analogous to that given by Akamsin et al. [2]



However, the replacement of water in this reaction by acetic acid leads to the formation of a product lacking sulfur, such as the acid chloride of phenyl- α -hydroxycyclohexyl-phosphonic acid (V) in 50% yield



Product (V) is identical in its IR spectrum to the acid chloride obtained by the reaction of PhPCl₂ with cyclohexanone in the presence of acetic acid [4] whose structure was proven by x-ray diffraction structural analysis [10]. ³¹P NMR spectroscopy indicates that the reaction of the acid chloride PhP(Cl)SEt with cyclohexanone in the presence of propionic acid leads to analogous results.

Thus, the direction of the reaction of S-alkylchlorothiophosphonites (III) with carbonyl compounds depends on the nature of the hydroxyl-containing compound. Hence, we carried out a more detailed study of the reaction of acid chloride (III) (R = Ph) with other hydroxyl-containing compounds, namely, aliphatic alcohols and carboxylic acids.

A ³¹P NMR study of the reaction of acid chloride (III) (R = Ph) with ethanol showed that the reaction has a complex course. At 0°C, the spectrum has a signal at δ P 147 ppm which is naturally assigned to the mixed 0,S-ester of phenylthiophosphonic acid PhP(SEt)OEt (a value of δ P 145 ppm was obtained for an authentic sample obtained according to Steiniger [11]). Then a doublet appears with δ P 23.9 ppm and JpH = 566.4 Hz which is clearly related to O-ethylphenylphosphonite Ph(EtO)P(O)H. The ³¹P NMR spectrum of the reaction mixture of acid chloride (III) (R = Ph) and methanol at -10°C shows a signal with δ P 149 ppm which should be assigned to O-methyl-S-ethylthiophosphonite PhP(SEt)OMe and a doublet for acid O-methylphenylphosphonite Ph(MeO)P(O)H with δ P 28.0 ppm and JpH = 566.0 Hz. The ³¹P NMR spectral parameters for the O-alkylphenylphosphonites are in accord with the data given by Mark, et al. [8]. Distillation of the reaction mixtures gives O-methylphenylphosphonite in 63% yield and O-ethylphenylphosphonite in 56% yield, which were identified by their physical constants which are in accord with those given by Pudovik and Yarmukhametova [12] (see Experimental).

The finding that O-alkylphenylphosphonites which are compounds lacking sulfur are formed in the reaction of the starting acid chloride (III) (R = Ph) with alcohols may be attributed to subsequent transformation of mixed O,S-esters PhP(OR)SEt whose formation was confirmed spectroscopically (see above).



In a model experiment, O-ethylphenylphosphonite was isolated by distillation as the major product after passing dry HCl through a solution of authentic O,S-diethylphenylthio-phosphonite in excess ethanol. This reaction is most readily understood as a phosphoryla-tion of ethanol by a thiophosphonite with SEt as the leaving group



Acidolysis of acid chloride (III, R = Ph) by acetic acid at 0°C proceeds by a complex course and leads to unexpected results. In addition to the signal for the starting acid

chloride PhP(Cl)SR (δ P 141.8 ppm), the ³¹P NMR spectrum shows signals for phenyldichlorophosphine (δ P 161 ppm) and the products of its stepwise acidolysis: the acid chloride of phenylphosphonic acid PhPH(0)Cl with δ P 19.9 ppm and Jp_H = 610 Hz and phenylphosphonic acid PhPH(0)OH with δ P 25.3 ppm and Jp_H = 590 Hz [13]. The addition of cyclohexanone to the reaction mixture leads to the formation of the acid chloride of phenyl- α -hydroxycyclohexylphosphonic acid with δ P 64.5 ppm. The ³¹P NMR spectral parameters of all these compounds are in accord with those given in our previous work [5, 13].

A possible explanation for the experimental results obtained is based on the assumption that acid chloride PhP(Cl)SEt undergoes acidolysis in the first reaction step with the formation of S-ethylphenylthiophosphonite (II) which is unstable under the reaction conditions and reacts further with acetyl chloride which accumulates in the mixture to give the acid chloride of phenylphosphinic acid



Literature data indicate that acetyl chloride undergoes an exchange reaction with trialkyltrithiophosphates and thiophosphites [14] which lead to the corresponding acid chlorides with change in the valence of the phosphorus atom

> $(RS)_{3}PO + AcCl \rightarrow (RS)_{2}P(O)Cl + AcSRl$ $(RO)_{2}PSR + AcCl \rightarrow (RO)_{2}PCl + AcSR$

In earlier work [5, 13], we showed that the acid chloride of phenylphosphonic acid PhPH(0)Cl in systems containing acetyl chloride and acetic acid undergoes reversible exchange reactions with the formation of phenyldichlorophosphine and phenylphosphonic acid PhPH(0)OH. We also found that the acid chloride of phenylphosphonic acid readily adds to cyclohexanone with the formation of the acid chloride of phenyl- α -hydroxycyclohexylphosphinic acid, probably by the following scheme [5, 13]



Thus, the alcoholysis and acidolysis of acid chlorides (III) at temperatures down to -20°C do not lead to hydrophosphoryl compounds (II). The final products of these reactions are organophosphorus compounds not containing sulfur.

Hence, S-alkylthiophosphonites RPH(0)SR, in contrast to the extensively studied and stable thionic isomers RPH(S)OR [15] are unstable under normal conditions and cannot be obtained in the free state. However, they have high reactivity at the instant of formation in solution relative to addition to aldehydes and ketones as indicated by the high or, at least, satisfactory yields of the final products. At low temperature, their formation in solution upon the hydrolysis of acid chloride RP(C1)SR may be detected by ³¹P NMR spectroscopy (see above).

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets. The 31 P NMR spectra were taken on a Bruker HX-90 spectrometer at 36.43 MHz relative to 85% H₃PO₄.

<u>S-Ethylphenyl- α -hydroxyisopropylthiophosphinate.</u> A sample of 2.04 g (0.01 mole) Sethylphenylchlorothiophosphonite in 20 ml absolute ether was added to a flask equipped with a stirrer, thermometer, and reflux condenser and a solution of 0.18 g (0.01 mole) water in 0.58 g (0.01 mole) acetone was added with stirring and cooling to 10-15°C from a dropping funnel. The reaction was continued until the liberation of HCl ceased (3-4 h). The crystalline substance obtained was filtered off, washed with a small amount of cold absolute hexane and recrystallized from acetone to yield 1.8 g (74%) S-ethylphenyl- α -hydroxyisopropylthiophosphinate. Thioester (Io) was obtained by analogy (see Table 1).

<u>S-Propylphenyl- α -hydroxybenzylthiophosphinate.</u> A sample of 2.18 g (0.01 mole) S-propylphenylchlorothiophosphonite in 20 ml absolute ether was added to a flask equipped with a stirrer, thermometer, and reflux condenser. A solution of 0.18 g (0.01 mole) water and 1.06 g (0.01 mole) benzaldehyde in 5 ml tetrahydrofuran was added with stirring and cooling to 10-15°C. The crystalline product formed after 5 h was filtered off, washed with cold absolute hexane and recrystallized from acetone to yield 1.8 g (60%) S-propylphenyl- α -hydroxybenzylthiophosphinate. Thioesters (Ib), (If), (Ig), and (Ij)-(Im) were obtained by analogy (see Table 1).

<u>S-Propylphenyl(β , β , β -trichloro- α -hydroxyethyl)thiophosphinate. A sample of 2.18 g (0.01 mole) S-propylphenylchlorothiophosphonite in 20 ml absolute ether was added to a flask equipped with a stirrer, thermometer, and reflux condenser. A solution of 1.5 g (0.01 mole) chloral hydrate in 10 ml absolute ether was added from a dropping funnel with stirring and cooling to 10-15°C. After HCl was no longer liberated, the crystalline product formed was filtered off, washed with absolute hexane, and recrystallized from chloroform to yield 3 g (87%) S-propylphenyl(β , β , β -trichloro- α -hydroxyethyl)thiophosphinate. Thioesters (Ia), (Ic), and (Id) were obtained by analogy (see Table 1).</u>

<u>S,S-Diethyl(β , β , β -trichloro- α -hydroxyethyl)dithiophosphonate. A sample of 2.84 g (0.015 mole) S,S-diethylchlorodithiophosphite in 15 ml anhydrous ether was placed in a flask equipped with a stirrer, thermometer, and reflux condenser. A solution of 2.48 g (0.015 mole) chloral hydrate in 15 ml ether was added with stirring. A crystalline product precipitated after 0.5 h. The precipitate was filtered off and washed with ether. Recrystallization from chloroform gave 2.85 g (90%) S,S-diethyl(β , β , β -trichloro- α -hydroxyethyl)di-thiophosphonate.</u>

<u>S,S-Diethyl(o-nitro- α -hydroxybenzyl)dithiophosphonate.</u> A solution of 0.18 g (0.01 mole) water and 1.51 g (0.01 mole) o-nitrobenzaldehyde in 15 ml ether and 2 ml tetrahydro-furan was added to a solution of 1.83 g (0.01 mole) S,S-diethylchlorodithiophosphite in 15 ml anhydrous ether. The crystalline product was filtered off, washed with ether, and recrystallized from benzene to yield 2.3 g (73%) S,S-diethyl(o-nitro- α -hydroxybenzyl)dithiophosphonate.

Acid Chloride of Phenyl- α -hydroxycyclohexylphosphinic acid. A sample of 2.16 g (0.01 mole) S-ethylphenylchlorothiophosphonite was added to a pear-shaped flask and 5 ml acetic acid and 1.02 g (0.01 mole) cyclohexanone were added at 0°C and left to stand for 10 days in a refrigerator. The crystalline product formed was filtered off, washed with anhydrous hexane, and recrystallized from acetone to give the product with mp 123-124°C [4]. The IR spectrum of this product was identical to that of a sample of the acid chloride of phenyl- α -hydroxycyclohexylphosphinic acid obtained by the reaction of PhPCl₂, cyclohexanone, and acetic acid according to our previous work [4].

<u>O-Ethylphenylphosphonite</u>. a) A sample of 3 ml anhydrous ethanol was added to 1.51 g (0.0073 mole) S-ethylphenylchlorothiophosphonite at 0°C. After 2 h in vacuum, excess ethanol was removed. Distillation yielded 0.7 g (56%) O-ethylphenylphosphonite with bp 93°C (1 mm), np^{20} 1.5240 [12].

b) A weak stream of dry HCl gas was passed for 4 h through a solution of 2.3 g 0,S-diethylphenylthiophosphonite in 3 ml anhydrous ethanol. After removal of the volatile products and excess ethanol, distillation in vacuum gave 0.7 g (20%) O-diethylphenylphosphonite with bp 95°C (1 mm), n_D^{20} 1.5240.

<u>O-Methylphenylphosphonite</u> was obtained by analogy to O-ethylphenylphosphonite (method a) in 61% yield, bp 90-91°C (1 mm), n_D^{20} 1.5340 [12].

CONCLUSIONS

1. The reaction of alkylthiolchlorophosphonites and dialkyldithiochlorophosphite with aldehydes or ketones in the presence of water yields thiolic esters of α -hydroxyalkylthiophosphinic acids.

2. ³¹P NMR spectroscopy showed that phenylphosphonites not containing sulfur are formed in the reaction of the acid chloride PhP(C1)SEt with aliphatic alcohols and carb-oxylic acids.

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