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Heterocyclic Compounds Containing Phosphorus. II

On the Formation and Cleavage of Cyclic Thiophosphates

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Synopsis

Ethane-1,2-bis-(dichlorothiophosphate) was prepared by the action of phosphorus sulfochloride on sodium ethylene diglycolate. Cyclic chlorothiophosphates reported in previous manuscript were synthesised by the reaction between phosphorus sulfochloride and sodium monoglycolates derived from the corresponding glycohols. Attempts to lead the chlorothiophosphates to tertiary thiophosphates with sodium ethoxide resulted in failure because of the formation of ring cleaved products. The products may have a structure of $\text{OH}-\underset{\text{R}}{\text{CH}_2}-\text{CH}-\text{OP}(\text{S})(\text{OR})_2$ or $\text{OH}-\underset{\text{R}}{\text{CH}}-\text{CH}_2-\text{OP}(\text{S})(\text{OR})_2$, where R represents alkyl radical and

R do alkyl or hydrogen. The rates of esterification showed that the products had the structure of the latter except where R was hydrogen.

In continuing the study on the preparation of cyclic chlorothiophosphates⁽¹⁾ by the action of phosphorus sulfochloride on α, β -glycohols in solvent (chloroform was used) near its boiling point or in presence of pyridine, sodium glycolates has been treated with phosphorus sulfochloride with the view of obtaining the same cyclic chlorothiophosphates presented in the previous report. Other intension has also been to prepare the tertiary thiophosphates by the reaction between sodium ethoxide and cyclic chlorothiophosphates.

As were presented in the previous manuscript, ethylene and propylene glycohols and glycerine- α -monoethyl ether were employed in the reaction. Although a number of methods have been devised for converting ethyleneglycol to its mono- or di-sodium glycolates⁽²⁾ using metallic sodium or sodium ethoxide, none have been reported on the methods to derive other glycohols to sodium glycolates. Therefore, other glycohols than ethyleneglycol have been treated in accordance with the methods employed for ethyleneglycol. The glycolates thus obtained were subjected to reaction with phosphorus sulfochloride. A compound containing phosphorus, sulfur and chlorine was isolated from the reaction with di-sodium ethyleneglycolate, but the compound differed greatly from the expecting one in its physical constants, and melting point of phenylhydrazide derived from it was 130~131°C and mixed melting point with a desired sample (m. p. 185°C) proved it to be different compound. Analytical data showed that the compound was ethane-1,2-bis-(dichlorothiophosphate) (II). This represents that two functional groups

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(1) T. Yamasaki and T. Sato, Sci. Rep. RITU, A 6 (1954), 384.

(2) Schmid, Waschkau, Ludwig, M. 49, 109; Beil., 2te Erg. Bd. 1. 518.

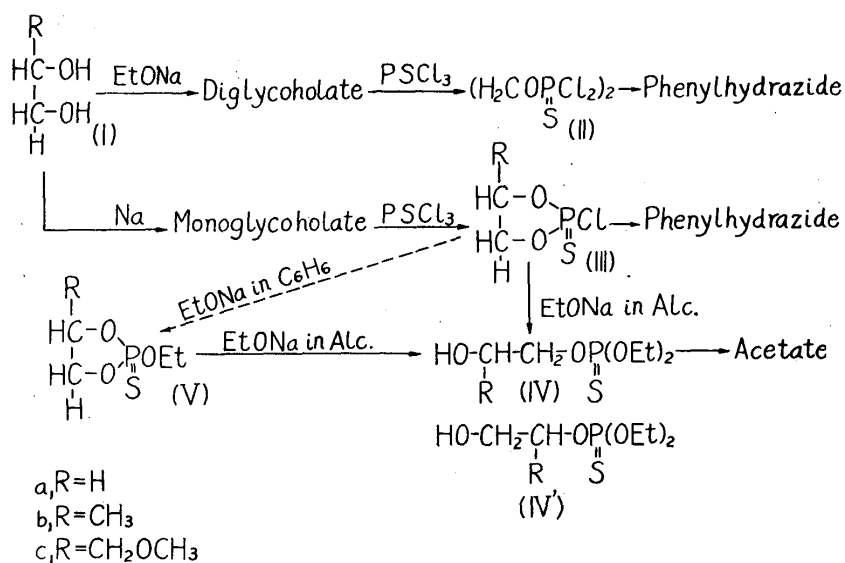
R. De Forcrand, Ann. ch. [6] 20 (1890) 439.

R. De Forcrand, Bl. [3] 7 (1892), 123.

of hydroxyl of the ethyleneglycohol reacted with phosphorus sulfochloride respectively. Ib and Ic were treated with sodium ethoxide in accordance with the method employed for ethyleneglycohol to obtain di-sodium glycolates and resulting products were subjected to action with phosphorus sulfochloride, but compounds gained were not the ones assumed as the condensation products between glycolols and phosphorus sulfochloride.

Reaction of monoglycolates with phosphorus sulfochloride gave the cyclic thiophosphates expected. Phenylhydrazides led from Ia, Ib and Ic had the same melting points as the ones reported in the previous paper respectively, and mixed melting point on each samples with authentic samples showed no depression. But the yields were so poor that the method could not be recommended for the preparation of cyclic chlorothiophosphates.

The actions of cyclic chlorothiophosphates and sodium alcoholate lead to none of the desired tertiary thiophosphates. In all cases neither the quantities of the reactants nor the solvents did not effect on the products. The products were isolated as neutral and in liquid state and qualitative analysis showed that sulfur and phosphorus were contained in the compounds. They had physical constants different from the tertiary thiophosphates expected. The products reacted with Grignard reagent to give gaseous material and neither sodium nitroprusside nor iodine solution yielded a color reaction. It was felt, from the observation before mentioned, that the compounds might be a esters of thiophosphoric acid bearing at least one hydroxyl group. Attempts to led to crystalline derivatives resulted in failure. Analysis were made on the esters and the acetates led from before and it was proved that the one from ethyleneglyhole was O- β -hydroxyethyl O,O-diethylthiophosphates (IVa) and its acetate and other ones from propylene glycolate and glycerine- α -monoethyl ether were the homologues of (IVa)



Reaction Charts

and their acetates. This means that the cyclic thiophosphates suffered from ring cleavage during reaction process. The physical properties were indicated in Table 2 and 3.

Table 1. The cyclic secondary chloro thiophosphates

Products	b. p. (°C/mm)	n_D (/°C)	Yield (%)	Phenylhydrazids (°C)
IIIa	78-83/2	1.5219/16	19	185
IIIb	99.5/4	1.4995/18	23	137
IIIc	108-111/3	1.5078/11.5	23	104

Table 2. The products by ring cleavages (IV)

Products	Yields (%)	b. p. (°C/mm)	n_D (/°C)	d_4 (°C)	MR	Formula	P (%)		S (%)	
							Calc.	Found	Calc.	Found
IVa	25	108-109/2	1.4695/18	1.1767/18	50.8	C ₆ H ₁₅ O ₄ PS	14.46	14.62	14.97	14.51
IVb	52	119-121/4	1.4659/20	1.1361/20	55.5	C ₇ H ₁₇ O ₄ PS	13.57	13.39	14.05	13.91
IVc	53	130-132/1	1.4658/23	1.1557/23	61.9	C ₈ H ₁₉ O ₅ PS	11.99	12.12	12.42	12.16

Table 3. The acetates of (IV)

The acetates of	b. p. (°C)	n_D (/°C)	d_4 (/°C)	MR	Formula	P (%)	
						Calc.	Found
IVa	117/2.5	1.4622/20	1.1585/20	60.8	C ₈ H ₁₇ O ₅ PS	12.09	11.59
IVb	133/8	1.4600/23	1.1262/23	65.7	C ₉ H ₁₉ O ₅ PS	11.46	11.65
IVc	129/2.5	1.4638/17	1.1536/17	71.8	C ₁₀ H ₂₁ O ₅ PS	10.31	10.17

The construction of (IVa) was capable of being proved by analytical result, while on the other products, it might be postulated two isomers exist respectively. The isomerism in each of these two is due to the location of hydroxy grouping on either C_α or C_β position. In other word, the hydroxyl of the former was secondary while the one of the latter was primary. Menschutkin⁽³⁾ had reported that when alcohols esterified with phenylacetic acid, the rate of esterification (he represented as "Anfangsgeschwindigkeit") showed whether alcohols were primary, secondary or tertiary. When Anfangsgeschwindigkeit was over 50, the alcohol was primary and from 20 to 30, it indicated secondary. As was obvious from the analytical data, the product from ethylene glycohol had a primary alcohol and the

Table 4. "Anfangsgeschwindigkeit" of the compounds produced by the ring cleavages of (III).

Compounds	A. G. Value No. of the experiments		Classification of the alcohol
	1	2	
IVa	51.3	50.9	Primary
IVb	20.4	20.2	Secondary
IVc	26.7	27.1	Secondary

(3) E. Funakubo, "Yukikagobutsu-Kakuninho" I, p. 11 (1953).

result obtained in accordance with the method of Menshutkin gave the value over 50. Thus, it was considered that the method might be capable to apply to our study. The results were shown in Table 4 and it was proved that the hydroxyl groups of the compounds (IVb) and (IVc) were secondary ones. Researches by infra-red spectrum will be discussed in near future.

Reaction processes to give (IV) were studied. (Vb) was refluxed in ethanol for 2 hour and was recovered unreacted (Vb) quantitatively. (Vb) was converted easily into (IVb) if the solvent contained small amount of sodium ethoxide. Rueggeber⁽⁴⁾ had declared that O,O,O-triethylphosphate reacted with butanol to give O,O-diethyl O-butyl phosphate and O,O-dibutyl O-ethyl phosphate in the presence of sodium butylate. The present result might be capable to consider as one of the example of the Rueggeberg's researches. The process of ring cleavage of (V) to (IV) was proved as mentioned above but the formation of (V) by the action of sodium ethoxide on (III) was not clear. All attempts to prepare (V) by route of (III) to (V) resulted in the formation of a product assumed as the mixture of (V) and unreacted (III), but the separation of these two compounds were unsuccessful.

Experimental Part

Reaction between ethylene diglycolate and phosphorus sulfochloride

To a solution of sodium ethoxide prepared from 4.8 g (0.2 mole) of sodium and 50 ml of absolute ethanol was added 6.2 g (0.1 mole) of ethyleneglycole and resulting solution was refluxed for 1 hour and cooled. In a four necked flask equipped with a mercury sealed stirrer, a thermometer and calcium chloride tube to protect from moisture was placed a solution consisting of 45 cc of anhydrous benzene and 17 g (0.1 mole) of phosphorus sulfochloride. To the solution was added the solution of disodium ethylene diglycolate through dropping funnel with stirring while maintaining the temperature at 10°C by means of ice bath. Stirring continued after completion of the addition for 10 minutes then allow to stand overnight. Sodium chloride obtained was filtered and the filtrate was condensed under reduced pressure, washed with water and extracted with benzene. Organic layer was washed with water and dried over calcium chloride. After removal of the solvent, the residue was subjected to distillation under reduced pressure to give a fraction boiling at 78°C at 4 mm, n_D 1.4938. The yield was 5.5 g. Analysis of its phenylhydrazide (m. p. 130~131°C) showed it to be ethane-1,2-bis-(dichlorothio-phosphate).

Anal. Calcd. for $(C_{13}H_{16}N_4OPS)_2$: N, 18.24; P, 9.92; S, 10.42

Found: N, 18.19; P, 9.65; S, 10.31

Reaction between monoglycolates and phosphorus sulfochloride

Monoglycolates were prepared by the action of 0.2 mole of glycohols and 0.1 mole of metallic sodium in accordance with the method described by De Forcrand. The monoglycolates were dissolved in 30 cc of absolute ethanol respectively and the solution was added to the mixture of 0.1 mole of phosphorus sulfochloride

(4) W. H. C. Reuggeberg, J. Chernach, J. Amer. Chem. Soc., **70** (1948), 1802.

in 50 cc of dry benzene placed in a four necked flask fitted with a mechanical stirrer, a dropping funnel. The temperature of the reactants were kept at 10°C by ice bath. After the completion of the addition, the products were treated by the procedure described before. The products and phenylhydrazides led from the products are shown in Table I. and mixed m. ps. of the phenylhydrazides with authentic samples showed no depression.

Reaction between cyclic secondary thiophosphates and alcoholate

A mixture of 0.1 mole of III (prepared as described in above section) and 40 cc of dry benzene was placed in a four necked flask attached to a mechanical stirrer, a thermometer, a dropping funnel and a calcium chloride tube, and 60 cc of ethanol solution of sodium ethoxide derived from 0.15 mole of metallic sodium was added slowly with stirring while the temperature maintaining at 20~25°C. After the reaction subsided, the flask was allowed to stand overnight and followed by the removal of solvent under reduced pressure. The residue was washed with water and was extracted with benzene, organic layer was dried over sodium sulfate and distilled in vacuo. The physical constants of the products are represented in Table 2. In Table 3, the acetates derived from (IV) are shown. Unsuccessful attempts were made to prepare derivatives in crystalline state. They were *p*-nitrobenzoation, 3,5-dinitrobenzoation, tosylation and trisylations. α -Naphthylamine gave a red coloration when mixed with 3,5-dinitrobenzoates. Acetates were made by reacting (IV) with acetylchloride in the presence of pyridine.

Classification of hydroxy radical of the compound derived from the ring cleavage of cyclic thiophosphates

Hydroxy radical bearing in the ring cleaved products derived from cyclic chlorothiophosphates were made classified by the method described by Menschutkin-Murahashi. Apparatur, reagents and method of measurement were identical with these authors. In all runs, near 500 mg of samples were used.

Alcoholysis of 4-methyl-2-ethoxy-2-thiono-1,3-dioxo-2-phosphacyclopentane (Vb)

(Vb) which was prepared by the method described in the previous report was used. It had a physical properties of b. p. 94/3 mm., n_D^{12} 1.4758, n_D^{16} 1.4840. 14 g of the sample was refluxed in 30 cc of absolute ethanol for 2 hours, followed by removal of the solvent in vacuo, the residue was subjected distillation. A fraction boiling at 119~122°C at 6 mm, n 1.4800 was recovered quantitatively.

(Vb) was refluxed in 30 cc of ethanol containing 0.27 g of sodium for 5 minutes. Solvent was removed by distillation and followed by washing once with water and extracted with benzene. Organic layer dried over sodium sulfate and distilled in vacuo. Fractions boiling at 119~123°C/6 mm, $n_D^{21.5}$ 1.4722, 6 g and 124~126°C/6 mm, n_D^6 1.4698, 4 g were collected. Both the fractions reacted with Grignard reagent vigorously. Analytical data identified with that of IVb.

Anal. Calcd. P, 13.57; Found P, 13.21

Reaction of alcoholate with 4-methyl-2-chloro-2-thiono-1,3-dioxo-2-phosphapentane (IIIb)

A suspension of 15 g of sodium ethoxid in benzene was placed in a four necked flask provided with a mechanical stirrer, a thermometer and a reflux condenser with a calcium chloride tube. A solution of 27.5 g of (IIIb) in 30 cc of benzene was added dropwise through a dropping funnel while the temperature keeping at 20~25°C. Immediately after the reaction had subsided, the product was washed with water, dried over sodium sulfate and subjected to fractional distillation. A fraction boiling at 110~115°C/5 mm, $n_D^{17.5}$ 1.4737, 13.3 g and polymer-like residue was collected. The former was redistilled under reduced pressure and the first fraction boiling at 115~120°C/8 mm, n_D^{15} 1.4809, 1 g, the second fraction, b. p. 120~125°C/8 mm, $n_D^{17.5}$ 1.4729, 1 g and third fraction boiling at 125~130°C/8 mm, $n_D^{17.5}$ 1.4728, 11 g was obtained. The third fraction was subjected to redistillation and distillates boiling 124~130°C/9 mm, n_D^{15} 1.47771, 3 g and 130~132°C/9 mm, n_D^{15} 1.4735, 7 g was collected. All fractions contained hydroxyl bearing compounds, and analytical data for phosphorous on the fraction boiling at 124~130°C/9 mm showed that almost equally amount of (IVb) and (Vb) were containing in it. Chlorine bearing compounds was not identified in this fraction.

Analysis	Calc. for C ₅ H ₁₁ O ₃ PS	17.00 %
	for C ₇ H ₁₇ O ₄ PS	13.57 %
Found		15.6 %

Other attempts to separate (IV) from (V) by leading to esters of higher boiling points were resulted in failure.

Summary

(1) Ethane-1,2-bis-(dichlorothiophosphate) was prepared by the action of phosphorus sulfochloride on sodium ethylene diglycolate.

(2) Cyclic chlorothiophosphates were synthesised by the reaction between phosphorus sulfochloride and sodium monoglycolates derived from α,β -glycohols.

(3) Reactions of cyclic chlorothiophosphates with sodium alcoholate led to the formation of compounds bearing the general formula assumed as

$$\text{OH}-\underset{\text{R}}{\text{CH}}-\text{CH}_2-\text{OP}(\text{S})(\text{OR})_2 \text{ or } \text{OH}-\underset{\text{R}}{\text{CH}}-\text{CH}_2-\text{OP}(\text{S})(\text{OR})_2.$$

(4) The determination of the rate of esterification with phenylacetic acid showed that the hydroxyl groups were the secondary ones. This indicates that the products had the structures of

$$\text{OH}-\underset{\text{R}}{\text{CH}}-\text{CH}_2-\text{OP}(\text{S})(\text{OR})_2.$$

(5) 4-methyl-2-ethoxy-2-thiono-1,3-dioxo-2-phosphacyclopentane was subjected to alcoholysis in the presence of sodium alcoholate and O,O-diethyl O- β -methyl propyl thiophosphate was resulted.

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