[Chem. Pharm. Bull. 12 (4) 398 ~ 403]

UDC 547.854.07

57. Akira Takamizawa and Yoshiro Sato: Studies on the Pyrimidine Derivatives. XXVIII.[*1] A New Method for Synthesis of Diethyl Ethoxycarbonylphosphite from Tris(ethoxythiocarbonyl) Phosphorotrithioite, and on the Reactions of these Organophosphorus Compounds with Thiamine Sodium Salt.

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Previous work in this series,[1] has reported a series of thiamine derivative, "O,S-bis(alkoxycarbonyl)thiamine," which showed excellent thiamine activity. During the course of an investigation of alkoxycarbonylating agents in relations to this, some organophosphorus compounds were examined.

In 1933, Noller and Dutton[2] reported that on the reaction of trialkyl phosphorites with phenol, ethyl phenyl ether was obtained. Recently, Walling, Basedow and Savas[3] described that by heating triethyl phosphorite and thiophenol together, ethyl phenyl sulfide and diethyl phosphite were obtained in good yield. In this paper, tris(alkoxycarbonyl) phosphorotrithioite (II), as the alkoxycarbonylating agent, and its related compounds has been studied.

The reaction of potassium O-ethyl thiocarbonate (Bender's salt[4]), prepared from the alcoholic potassium hydroxide with carbonyl sulfide, with phosphorus trichloride in carbon disulfide, gave an unstable colorless oil at room temperature, and the elementary analysis and molecular weight (depression of freezing point of benzene) of it coincided with $C_9H_{15}O_6S_3P$: tris(ethoxycarbonyl) phosphorotrithioite (IIa). The freshly prepared oil contains in its infrared spectrum (Fig. 1a) carbonyl modes at 1720 and 1133 cm^{-1}, but no bands at near 1250 (P=O) and 800~600 cm^{-1} (P=S). The nuclear magnetic resonance spectrum consists of only one three-four pattern (at 8.70 and 5.67 τ) (Fig.2 a) due to magnetical equivalence of the three ethyl groups.

Generally, trialkyl phosphorites form the corresponding phosphite when reacted with alkyl halides or with acyl halides respectively (Michaelis-Arbuzov reaction). But on the reaction of IIa with ethyl chloroformate, a colorless oil, b.p$_{2.0}$ 101~104°, contained no sulfur and gas was produced. The infrared spectrum of the oil (Fig. 1c) displays bands at 1713 and 1214 cm^{-1}, assignable to a carbonyl group, and at 1273 (P=O) and 1015 cm^{-1} (P-O-C). From elementary analysis this oil was expected to be diethyl ethoxycarbonylphosphite (IIIa), which was synthesized by Nylén[5] out of triethyl phosphorite and ethyl chloroformate. The boiling point and infrared spectrum of the oil produced from IIa agreed closely with IIIa prepared by a method similar to that described by Nylén. The gas chromatogram (Fig. 3) showed that the gas contains two species, a carbonyl sulfide and an ethyl chloride. Further, when this gas was absorbed in ethanol solution of potassium hydroxide, it gave I. This reaction gave a 97% yield, either at room temperature or on rised temperature.

From the reaction of potassium O-ethyl dithiocarbonate (potassium xanthogenate) with phosphorus trichloride, similarly, a yellow plate crystal, m.p. 68~70°, was obtained.

[*1] Part XXVII. A. Takamizawa, K. Hirai: This Bulletin, **12**, 393 (1964).

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1) A. Takamizawa, K. Hirai: Vitamins (Kyoto), **23**, 425 (1961); This Bulletin, **10**, 1102 (1962).

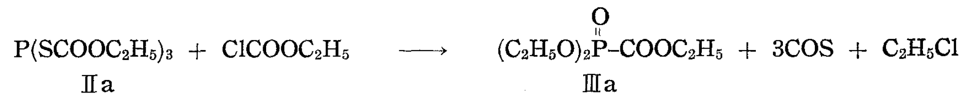
2) C.R. Noller, G.R. Dutton: J. Am. Chem. Soc., **55**, 424 (1933).

3) C. Walling, O.H. Basedow, E.S. Savas: *Ibid.*, **82**, 2181 (1960).

4) C. Bender: Ann., **148**, 137 (1868).

5) P. Nylén: Ber., **57**, 1023 (1924).

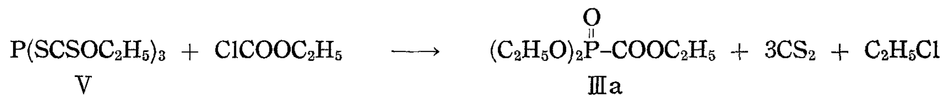
$$\underset{\text{I}}{3\text{KSCOOC}_2\text{H}_5} + \text{PCl}_3 \longrightarrow \underset{\text{IIa}}{\text{P(SCOOC}_2\text{H}_5)_3} + 3\text{KCl}$$



$$\underset{\text{IIa}}{\text{P(SCOOC}_2\text{H}_5)_3} + \text{ClCOOC}_2\text{H}_5 \longrightarrow \underset{\text{IIIa}}{(\text{C}_2\text{H}_5\text{O})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{-COOC}_2\text{H}_5} + 3\text{COS} + \text{C}_2\text{H}_5\text{Cl}$$

The elementary analysis, infrared spectrum (Fig. 1b), and nuclear magnetic resonance spectrum (Fig. 2b) were in good agreement with $C_9H_{15}O_3S_6P$: tris(ethoxythiocarbonyl) phosphorotrithioite (V). This compound (V) was reacted with ethyl chloroformate to give a colorless oil b.p$_{10}$ 125~128°, containing no sulfur, and a low boiling point oil and gas. In this case also, the produced oil was identified as diethyl ethoxycarbonylphosphite (IIIa), the low boiling point oil as carbon disulfide and the gas as ethyl chloride.

$$3\text{KSCSOC}_2\text{H}_5 + \text{PCl}_3 \longrightarrow \underset{\text{V}}{\text{P(SCSOC}_2\text{H}_5)_3} + 3\text{KCl}$$



$$\underset{\text{V}}{\text{P(SCSOC}_2\text{H}_5)_3} + \text{ClCOOC}_2\text{H}_5 \longrightarrow \underset{\text{IIIa}}{(\text{C}_2\text{H}_5\text{O})_2\overset{\overset{\text{O}}{\|}}{\text{P}}\text{-COOC}_2\text{H}_5} + 3\text{CS}_2 + \text{C}_2\text{H}_5\text{Cl}$$

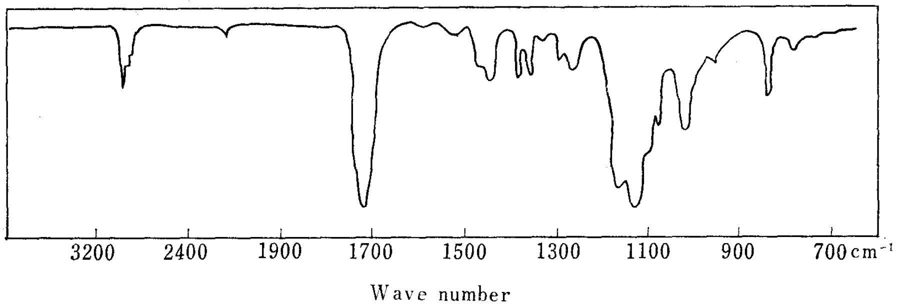


Fig. 1a. Infrared Spectrum of Tris(ethoxycarbonyl) Phosphorotrithioite (IIa) (film)

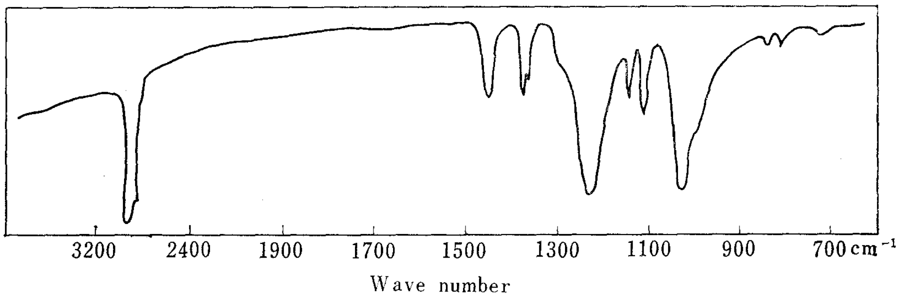


Fig. 1b. Infrared Spectrum of Tris(ethoxythiocarbonyl) Phosphorotrithioite (V) (Nujol)

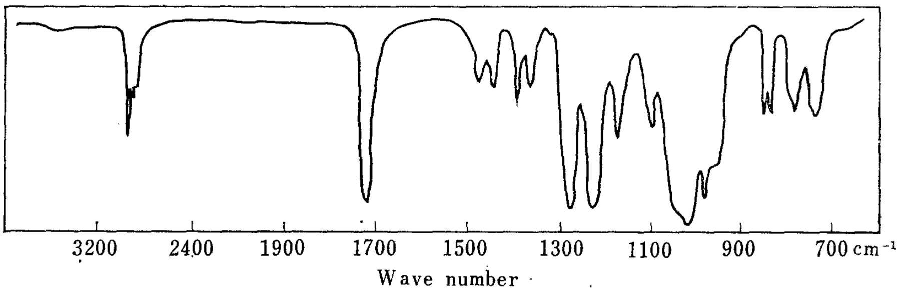


Fig. 1c. Infrared Spectrum of Diethyl Ethoxycarbonylphosphonate (IIIa) (film)

Thus tris(ethoxythiocarbonyl) phosphorotrithioite does not undergo the Michaelis-Arbuzov reaction, it undergoes an unusual reaction. Divinskii, Kabachnik, and Sidorenko[6] reported that the reaction of triethyl phosphorotrithioite with alkyl or acyl chloride gave diethyl phosphorochloridodithioite. But this was not developed subsequent.

$$(C_2H_5S)_3P + RCl \longrightarrow (C_2H_5S)_2P\text{-}Cl + R\text{-}S\text{-}C_2H_5$$

$$R{=}\text{alkyl or acyl}$$

Generally, trivalent phosphorus has a high affinity for free and bound sulfur, presumable because its size and high polarisability enables it to utilise the empty orbital of sulfur more effectively than is the case for oxygen or nitrogen.[7] Nevertheless, it is of interest to note in this case that from IIa or V, the phosphonate which does not contain sulfur was obtained.

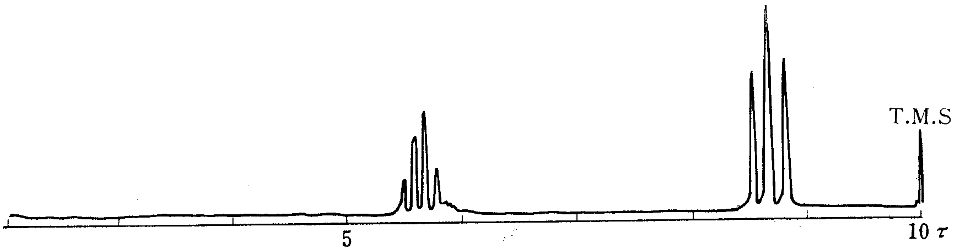


Fig. 2a. Nuclear Magnetic Resonance Spectrum of Tris(ethoxycarbonyl) Phosphorotrithioite (IIa) at 60 Mc.p.s., in Carbon Tetrachloride

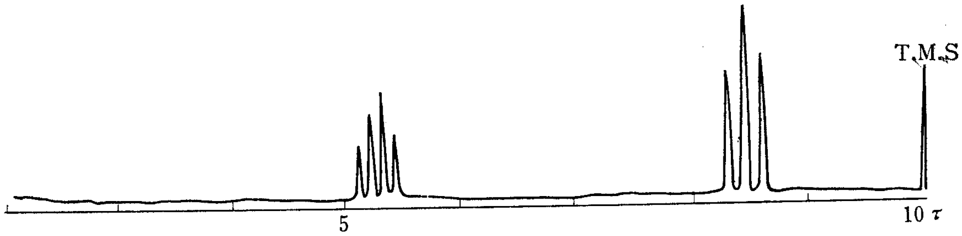


Fig. 2b. Nuclear Magnetic Resonance Spectrum of Tris(ethoxythiocarbonyl) Phosphorotrithioite (V) at 60 Mc.p.s., in Carbon Tetrachloride

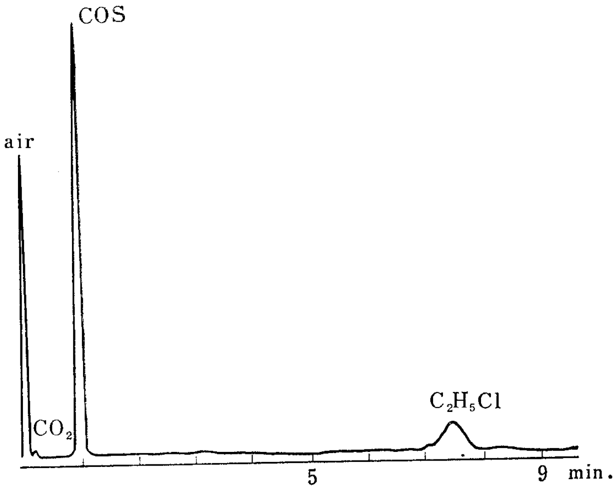


Fig. 3. Gas Chromatogram of a Mixture generated from the Reaction of Tris(ethoxycarbonyl) Phosphorotrithioite (IIa) with Ethyl Chloroformate, using Dioctyl Phthalate Column (3 m.) at 35°, H_2, 100 ml./min.

When IIa was treated with thiamine sodium salt (VII) in dry benzene, there were obtained O,S-bis(ethoxycarbonyl)thiamine (IXa), which was found to be identical with the product derived from VII and ethyl chloroformate,[1] and thiamine anhydride (X) as by-product. At lower temperature S-ethoxycarbonylthiamine (VIIIa) was obtained. Tris(butoxycarbonyl) phosphorotrithioite (IIb), prepared in a similar manner from potassium O-butylthiocarbonate and phosphorus trichloride, gave O,S-bis(butoxycarbonyl)-thiamine (IXb) and (X) as by-product

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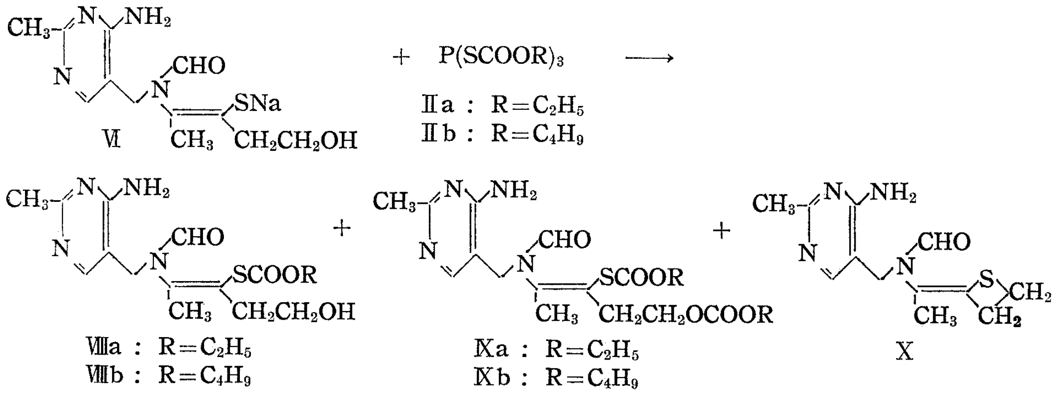
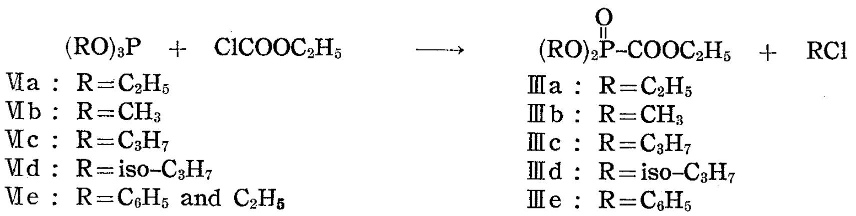
[6] A.F. Divinskii, M.I. Kabachnik, V.V. Sidorenko: Doklady Akad. Nauk. S.S.S.R., **60**, 999 (1948).
[7] J.I.G. Cadogan: Quart. Revs., **16**, 208 (1962).

when reacted with Ⅶ. Thus it was found that the reaction of tris(alkoxycarbonyl) phosphorotrithioite (Ⅱ) with the -SNa group of thiamine gave S-alkoxycarbonyl or O,S-dialkoxycarbonyl derivatives.

It is expected that diethyl ethoxycarbonylphosphite (Ⅲa) has an ethylating ability. Indeed, when Ⅲa and Ⅶ were treated together in dry benzene, S-ethylthiamine was obtained, but also in this case Ⅸa was given in poor yield. In connection with above facts, dimethyl, dipropyl, diisopropyl, and diphenyl ethoxycarbonylphosphite were synthesized from ethyl chloroformate and the appropriate trialkyl or ethyl diphenyl phosphorite. When they were treated with Ⅶ in a similar method, in each cases, Ⅸa and the respective corresponding S-methyl, S-propyl, and S-isopropyl thiamine were obtained, except the phenyl analogue. When diphenyl ethoxycarbonylphosphite (Ⅲe) was treated with Ⅶ, only X was obtained.

From the reaction of Ⅴ with Ⅶ in dry benzene, the corresponding ethoxythiocarbonyl derivative was not obtained, but an unknown thiamine derivative contained phosphorus was obtained.

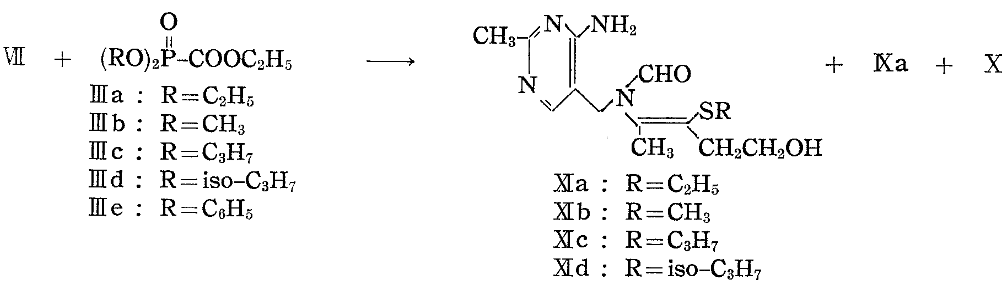




$$(RO)_3P + ClCOOC_2H_5 \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\text{-}COOC_2H_5 + RCl$$

Ⅵa : R=C_2H_5
Ⅵb : R=CH_3
Ⅵc : R=C_3H_7
Ⅵd : R=iso-C_3H_7
Ⅵe : R=C_6H_5 and C_2H_5

Ⅲa : R=C_2H_5
Ⅲb : R=CH_3
Ⅲc : R=C_3H_7
Ⅲd : R=iso-C_3H_7
Ⅲe : R=C_6H_5



Experimental

Potassium O-Ethyl Thiocarbonate (I)——Since I was obtained by means of passage of COS through a solution of KOH in EtOH,[4] in this paper I was synthesized by the following method: To a solution of 84.2 g. of KOH in 99% EtOH, H_2S was saturated in one half volume of the solution under cooling with ice, and then the two halves of the solution were combined. To this cold solution. 80 g. of ethyl chloroformate was added dropwise. A mixture of I and KCl was precipitated. This mixture was collected on a Büchner funnel, and dried in a vacuum desiccator. Yield, 112 g.

Tris(ethoxycarbonyl) Phosphorotrithioite (IIa)——To a suspension of 60 g. of I in 200 ml. of dry CS_2, 7.5 g. of PCl_3 was added dropwise below 10°. Then, with stirring, the temperature was maintained at

40~45° for 1 hr. The precipitate was removed with suction, and filtrate was concentrated under reduced pressure. The residue was a colorless unstable oil. Yield, 12.2 g. *Anal.* Calcd. for $C_9H_{15}O_6S_3P$: C, 31.20; H, 4.37; P, 8.94; mol. wt., 346.4. Found : C, 31.95; H, 4.83; P, 9.47; mol. wt., 269 (depression of freezing point of benzene).

Tris(ethoxythiocarbonyl) Phosphorotrithioite (V)——To a suspension of 64.0 g. of potassium O-ethyl dithiocarbonate (potassium xanthogenate) (Ⅳ) in 200 ml. of dry CS_2, with stirring, 13.7 g. of PCl_3 was added dropwise at a temperature of under 10°. Then the temperature was maintained 40~45° for 1 hr. The precipitate was filtered off with suction, and the solvent was removed under reduced pressure. A yellow plate crystal was obtained, m.p. 68~70°. Yield, 37.4 g. *Anal.* Calcd. for $C_9H_{15}O_3S_6P$: C, 27.39; H, 3.83; P, 7.86. Found : C, 27.70; H, 3.99; P, 7.97.

Potassium O-Butyl Thiocarbonate——This compound was prepared from a solution of K_2S in EtOH and 100 g. of butyl chloroformate by the same method as with which I was prepared. Yield, 165 g. ($KSCOOC_4H_9 + KCl$).

Tris(butoxycarbonyl) Phosphorotrithioite (IIb)——To a suspension of 59 g. of $KSCOOC_4H_9 + KCl$ in 200 ml. of dry CS_2, 5.5 g. of PCl_3 was added dropwise with stirring below 10°, then at 40~45° for 1 hr. The filtrate was concentrated under vacuum. The residue was a pale yellow oil. Yield, 12.2 g. *Anal.* Calcd. for $C_{15}H_{27}O_6S_3P$: P, 7.20. Found : P, 8.02.

Reaction of IIa with Ethyl Chloroformate——Ⅱa (10.0 g.) and 20 g. of ethyl chloroformate were mixed together at room temperature, and then heated at 50°. After 30 min., gas was generated and continued for 10 hr. This gas was collected in an injector through a rubber stopper fitted on the top of condencer. The mixture was distilled to give an oil of b.p_{10} 120~125°. Yield, 5.9 g. The IR spectrum and boiling point of the product were identical to those of diethyl ethoxycarbonylphosphite (Ⅲa). When the gas was absorbed into KOH in EtOH, a colorless crystal, m.p. 183° (decomp.), precipitated. This was found to be identical with I. The retention times of the gas chromatogram were in good agreement with that of authentic COS and C_2H_5Cl, respectively.

When above reaction mixture allowed to stand for 5 days, the same result was obtained.

Reaction of V with Ethyl Chloroformate——A mixture of 11.9 g. of V and 20 g. of ethyl chloroformate was heated slowly. At 90°, it started to boil and gas and oil, b.p. 45°, were distilled. The residue was distilled at reduced pressure, b.p_{10} 125~128°. Yield, 5.13 g. This oil was identical with Ⅲa, the liberated oil and gas were proved to be identical with CS_2 and C_2H_5Cl, respectively, by means of IR spectrum and gas chromatography.

Diethyl Ethoxycarbonylphosphite (IIIa)——This compound was prepared by a method similar to that described by Nylèn,⁵⁾ from 16.6 g. of triethyl phosphorite (Ⅵa) and 10.8 g. of ethyl chloroformate, b.p_{10} 130~132°. Yield, 18.2 g. *Anal.* Calcd. for $C_7H_{15}O_5P$: P, 14.74. Found : P, 14.16.

Dimethyl Ethoxycarbonylphosphite (IIIb)——A mixture of 38.6 g. of trimethyl phosphorite (Ⅵb) and 50 g. of ethyl chloroformate was heated together at 30°. Distillation of the product gave Ⅲb, b.p_{12} 124~126°. Yield, 53.8 g. *Anal.* Calcd. for $C_5H_{11}O_5P$: C, 32.97; H, 6.09; P, 17.02. Found : C, 33.24; H, 6.16; P, 15.65.

Dipropyl Ethoxycarbonylphosphite (IIIc)——From the reaction of 20.8 g. of tripropyl phosphorite (Ⅵc) and 13.0 g. of ethyl chloroformate, a colorless oil, b.$p_{5.0}$ 127~130°, was obtained. Yield, 18.8 g. *Anal.* Calcd. for $C_9H_{19}O_5P$: P, 13.03. Found : P, 12.68.

Diisopropyl Ethoxycarbonylphosphite (IIId)——From the reaction of 56.3 g. of triisopropyl phosphorite (Ⅵd) with 35.0 g. of ethyl chloroformate, a colorless oil, b.$p_{5.0}$ 113~115°, was obtained. Yield, 46.6 g. *Anal.* Calcd. for $C_9H_{19}O_5P$: P, 13.03. Found : P, 12.85.

Diphenyl Ethoxycarbonylphosphite (IIIe)——A mixture of 15.6 g. of ethyl diphenyl phosphorite (Ⅵe) with 13.0 g. of ethyl chloroformate was refluxed for 8 hr., and then the reaction product was distilled, b.$p_{0.06}$ 146~148°. Yield, 16.2 g. *Anal.* Calcd. for $C_{15}H_{15}O_5P$: C, 58.81; H, 4.94; P, 10.11. Found : C, 48.38; H, 4.94; P, 9.98.

Reaction of IIa with Thiamine Sodium Salt (VII)——To a suspension of dry Ⅶ, prepared from 3.37 g. of thiamine hydrochloride, in 50 ml. of dry benzene, 7.0 g. freshly prepared Ⅱa was added at room temperature under stirring, and then heated to 75° for 2 hr. The reaction mixture was extracted with *N* HCl, HCl was washed with Et_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved in *N* HCl again, and washed with Et_2O and extracted with $CHCl_3$ after decoloring. From the $CHCl_3$ extract. Ⅸa-HCl, m.p. 120~121° (decomp.), was obtained. Yield, 1.47 g. The IR spectrum of the product was identical with the sample of O,S-bis(ethoxycarbonyl)thiamine hydrochloride reported before.²⁾ The HCl extract was neutralized and extracted with $CHCl_3$. Thiamine anhydride which was identified with the authentic sample was obtained from $CHCl_3$ layer. m.p. 137~140° (decomp.). Yield, 0.24 g.

Reaction of VII with IIb——On the treatment of Ⅶ, prepared from 3.37 g. of thiamine hydrochloride, with freshly prepared Ⅱb in dry benzene, in a method similar to above, a colorless crystal, m.p. 86~88°, which was identified with the sample of O,S-bis(butoxycarbonyl)thiamine hydrochloride reported before was obtained. Yield, 1.89 g. From the HCl layer, m.p. 139~140° (decomp.) and m.p. 137~140°

(decomp.), which were identical to S-butoxycarbonylthiamine (VIIIb) and X respectively by IR spectra were obtained. Yield, VIIIb, 0.26 g., X, 0.35.

Reaction of VII with Dialkyl Ethoxycarbonylphosphite (III)——To a suspension of dry VII in dry benzene, 2 mol. equivalent of IIIa, b, c or d was added and heated for 2 hr. with stirring. The reaction mixture was extracted with *N* HCl and HCl was washed with Et_2O, and extracted with $CHCl_3$. The residue from the $CHCl_3$ layer was dissolved in *N* HCl and again extracted with $CHCl_3$ after decoloring. From the $CHCl_3$ layer dried over anhyd. Na_2SO_4, O,S-bis(ethoxycarbonyl)thiamine hydrochloride (IXa), m.p. 120~121° (decomp.) was obtained. Yield, 0.5~2.0%. The HCl extract was neutralized by K_2CO_3 and extracted with $CHCl_3$. From this $CHCl_3$ layer, S-alkylthiamine (XIa, b, c or d) corresponding to dialkyl ethoxycarbonylphosphite and X were obtained. These crystals were proved to be identical by IR spectra with authentic samples : S-ethylthiamine, S-methylthiamine, S-propylthiamine or S-isopropylthiamine, respectively.

Reaction of VII with Diphenyl Ethoxycarbonylphosphite (IIIe)——On the treatment of VII with IIIe by a similar method, X was given, but no further product was isolated.

Summary

On the reaction of potassium O-ethyl thiocarbonate (I) or potassium O-ethyl dithiocarbonate (IV) with phosphorus trichloride, tris(ethoxycarbonyl) phosphorotrithioite (IIa) or tris(ethoxythiocarbonyl) phosphorotrithioite (V) were synthesized, respectively. From the treatment of IIa or V with ethyl chloroformate, the same product, diethyl ethoxycarbonylphosphite (IIIa), accompanied by carbonyl sulfide and ethyl chloride from IIa, and carbon disulfide and ethyl chloride from V, were given in high yield.

When tris(alkoxycarbonyl) phosphorotrithioite (II) and thiamine sodium salt (VII) were reacted together, O,S-bis(alkoxycarbonyl)thiamine (IX) was produced. On the other hand, from the reaction of dialkyl ethoxycarbonylphosphite with VII, O,S-bis(ethoxycarbonyl)-thiamine (IXa) was also obtained, but in this cases S-alkylthiamines were main products.

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58. **Kunio Nakagawa, Ken-ichi Igano, and Jitsuo Sugita** : Oxidation with Nickel Peroxide. III.[*1] Oxidative Cleavage of α-Glycols, α-Hydroxy Acids, α-Keto Alcohols, and α-Keto Acids.

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In previous papers,[*1] it was shown that polyene alcohols, allylic alcohols, benzyl alcohols, and secondary aromatic alcohols were oxidized by nickel peroxide, readily obtainable by the treatment of nickel salts with sodium hypochlorite in alkaline solution, to give the corresponding carbonyl compounds in satisfactory yields. It seemed desirable to extend the investigation to other kinds of alcohols.

This paper reports the oxidative cleavage of α-glycols, α-hydroxy acids, α-keto alcohols, and α-keto acids by means of nickel peroxide. α-Hydroxy acids have analogous structure with glycols, namely, both of these compounds contains two hydroxyl groups attached to two neighbouring carbon atoms, and keto compounds might be able

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[*1] Part I : J. Org. Chem., **27**, 1597 (1962); Part II : This Bulletin, **11**, 296 (1963).

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