Studies on the Organophosphorus Insecticides

Part II. Synthesis and Toxicity of Phosphoroates and Phosphorothioates Containing Phenylacrylate or Phenylacrylonitrile Radicals.

By Yoshihiko NISHIZAWA

Laboratory of Sumitomo Chem. Co., Ltd., Osaka

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During an investigation of organophosphorus insecticide, the present author found that the reactions of O,O-dialkyl phosphorochloridate*¹⁾ or O,O-dialkyl phosphorochloridothioates with sodium salts of β -keto-esters or nitriles give new phosphoroates or phosphorothioates containing phenylacrylate or phenylacrylonitrile radicals, but do not give phosphonates.

The reactions of trialkylphosphites with α -halo- or α,α -dihalo-phenyl- β -keto-esters or nitrils also gave phosphoroates. Some phosphoroates prepared by this methods have high insecticidal activity.

In a previous paper¹⁾, the correlations between the oral toxicity of mice and the structures of many phosphoroates containing vinyl radical have been reported. Some of these phosphoroates had also high activity against some insects, namely, O,O-dimethyl-O-(1-phenyl-2-carboethoxy-vinyl)-phosphoroate (VG) and O,O-dimethyl-O-(1-methyl-2-phenyl-2-carboethoxy) phosphoroate (VM) had the most interesting activity as insecticides.

In the present paper, the syntheses, the confirmations of the structures and the activi-

ties of these derivatives are reported.

All of the compounds were prepared by two methods²⁾, one of them was the reaction of O,O-dialkyl phosphorochloridates (I, Y=O) or phosphorochloridothioates (I, Y=S) with sodium salts of β -keto-esters or nitrils containing phenyl radical in benzene solution (method-A). The other method was the reaction of trialkylphosphites (III) with α -chloro-, α,α -dichloro- β -keto-esters or nitriles containing phenyl radical (method-B) according to the following scheme.

*1) The names of the phosphorus compounds in this paper were named according to the Drake Committee's Report (*Chem. Eng. News*, **30**, 4515 (1952)).

1) Y. Nishizawa, *Bull. Agr. Chem. Soc. Japan*, **24**, 261 (1960).

2) These methods were applied for Japanese patent at 1957 and announced at 1960. See Japanese patent announced number Showa 35-1531, 1532, 2926, 3883.

(VA)	$R_1 = \text{CH}_3$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{H}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{S}$
(VB)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{H}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{S}$
(VC)	$R_1 = \text{CH}_3$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{H}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$
(VD)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{H}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$
(VE)	$R_1 = \text{CH}_3$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{Cl}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$
(VF)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{C}_6\text{H}_5$	$R_3 = \text{Cl}$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$
(VG)	$R_1 = R_2 = \text{CH}_3$		$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{CN}$	$Y = \text{S}$
(VH)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{CH}_3$	$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{CN}$	$Y = \text{S}$
(VI)	$R_1 = R_2 = \text{CH}_3$		$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{CN}$	$Y = \text{O}$
(VJ)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{CH}_3$	$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{CN}$	$Y = \text{O}$
(VK)	$R_1 = R_2 = \text{CH}_3$		$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{S}$
(VL)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{CH}_3$	$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{S}$
(VM)	$R_1 = R_2 = \text{CH}_3$		$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$
(VN)	$R_1 = \text{C}_2\text{H}_5$	$R_2 = \text{CH}_3$	$R_3 = \text{C}_6\text{H}_5$	$R_4 = \text{COOC}_2\text{H}_5$	$Y = \text{O}$

All of the synthesized compounds were liquid and purified by distillation under reduced pressure, but phosphorothioates could not be purified by distillation. The infrared absorption spectra of the distilled phosphorothioates show that they contained still a small oxo-thiol-form, because $\text{P}=\text{O}$ stretching vibration appears at $1350\sim 1200\text{ cm}^{-1}$.

So, the distilled phosphorothioates were purified again by silicagel column chromatography.

It was determined by following experiments that all of the synthesized compounds have phosphoroate- or phosphorothioate- form and not phosphonate.

1) The infrared absorption spectra of the synthesized phosphorus compounds showed that these compounds have $\text{C}=\text{C}$ ethylenic

double bond, because the characteristic absorption band of $\text{C}=\text{C}$ bond is shown at 1650 cm^{-1} and that of the carbonyl radical shift to 1700 cm^{-1} . It is considered that shift occurred by carbonyl radical conjugated with some unsaturated radical (see Fig. 1).

2) Chlorination of the synthesized phosphorus compounds in chloroform gave dichloro-derivatives which did not show the absorption band of $\text{C}=\text{C}$ bond.

3) Alcoholysis of the synthesized phosphorus compounds by sodium alcoholate in alcoholic solutions gave trialkyl phosphorates or phosphorothioates and β -keto-esters.

The melting points of the copper salts of these β -keto-esters coincided with those of starting β -keto-esters and mixed melting points did not depress respectively. It is considered

FIG. 1. Infrared spectrum of O, O-Dimethyl-O-(1-phenyl-2-carboethoxy-2-chlorovinyl) phosphoroate (VE)

EXPERIMENTAL

$$\text{(C}_2\text{H}_5\text{O)}_2\text{P(O)OC}(\underset{\text{(V'D)}}{\text{C}_6\text{H}_5\text{)}}\text{:CHCOOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{ONa} \longrightarrow (\text{C}_2\text{H}_5\text{O)}_3\text{P=O} + \underset{\text{I}}{\text{C}_6\text{H}_5\text{C=CHCOOC}_2\text{H}_5}$$

To a suspension of 6.8 g. of sodium ethoxide in 50 ml. of anhydrous benzene, there was added gradually 19.2 g. of ethyl benzoylacetate.⁴ The solution be-

4) The phosphorus compounds which had high toxicity towards the mice, also showed high activity as insecticide.

5) Ethyl α,α -dichlorobenzoylacetate was prepared by the chlorination of ethyl benzoylacetate with sulfuryl chloride in ether. B.p. 115~118°C./1mm. n_D^{25} 1.5303. Yield 67.0 %.

3) A.N. Pudovikl, *J. Gen. Chem. USSR*, **26**, 1606 (1956).

TABLE I. THE YIELD AND THE PHYSICAL AND THE MICROANALYTICAL DATA OF PHOSPHORUS COMPOUNDS*2)

No.	Formula	Yield %	B.P. °C	mmHg	n_D^{20}	Phosphorus %		Sulphur %		Chlorine %	
						Calcd.	Found.	Calcd.	Found.	Calcd.	Found.
VA	$(CH_3O)_2P(S)OC(C_6H_5):CHCOOC_2H_5$	34.8*3)	156~159	0.3	1.5488/25	9.8	9.2	10.1	10.3	—	—
VB	$(C_2H_5O)_2P(S)OC(C_6H_5):CHCOOC_2H_5$	34.9*3)	161	0.5	1.5348/23.5	9.0	8.9	9.3	9.6	—	—
VE	$(CH_3O)_2P(O)OC(C_6H_5):CClCOOC_2H_5$	59.0*4)	150~153	0.8	1.5188/25.5	10.6	10.2	—	—	9.26	9.61
VF	$(C_2H_5O)_2P(O)OC(C_6H_5):CClCOOC_2H_5$	64.3*4)	153~158	0.8	1.5068/25.5	8.6	8.9	—	—	9.51	9.65
VG	$(CH_3O)_2P(S)OC(CH_3):C(C_6H_5)CN$	37.1*3)	143~147	1.0	1.5447/26	10.9	10.8	11.3	10.8	—	—
VH	$(C_2H_5O)_2P(S)OC(CH_3):C(C_6H_5)CN$	40.6*3)	150~155	0.6	1.5334/26.5	10.0	9.8	10.2	10.5	—	—
VI	$(CH_3O)_2P(O)OC(CH_3):C(C_6H_5)CN$	40.0*4)	153~160	0.3	1.5165/26.5	11.6	11.3	—	—	—	—
VJ	$(C_2H_5O)_2P(O)OC(CH_3):C(C_6H_5)CN$	10.3*4)	143~145	0.7	1.5048/26	10.5	10.1	—	—	—	—
VK	$(CH_3O)_2P(S)OC(CH_3):C(C_6H_5)COOC_2H_5$	21.3*3)	150~154	0.8	1.5211/29	9.4	9.8	9.7	9.3	—	—
VL	$(C_2H_5O)_2P(S)OC(CH_3):C(C_6H_5)COOC_2H_5$	20.0*3)	145~150	0.8	1.4993/23	8.7	9.0	8.9	8.6	—	—
VN	$(C_2H_5O)_2P(O)OC(CH_3):C(C_6H_5)COOC_2H_5$	31.0*4)	152~156	0.3	1.4963/24	9.1	9.0	—	—	—	—

*2) Caution; Many phosphorates are powerful cholinesterase inhibitors and therefore highly toxic.

*3) By the method-A

*4) By the method-B

TABLE II. THE ACTIVITY AND THE TOXICITY OF NEW PHOSPHORUS COMPOUNDS
Ephesia cautella WALKER
Topical Method

No.	Dose (τ /one)	Kill (%)	Dipping Method		Topical Method		Oral Toxicity towards Mice. L_{50} 50mg/kg	
			Dilution	Kill (%)	Dose (τ /larva)	Kill (%)		
VA	—	—	—	—	7.0	90	275.0	
VB	—	—	—	—	20.0	80	78.0	
VC*3)	0.67	90	—	—	—	—	11.7	
VD*3)	—	—	—	—	2.0	100	24.0	
VE	—	—	—	—	0.67	70	8.8	
VF	—	—	—	—	0.67	80	16.0	
VG	—	—	—	—	20.0	90	174.0	
VH	20.0	20	—	—	—	—	145.0	
VI	20.0	40	× 200	72.9	—	—	400.0	
VJ	6.7	40	—	—	—	—	220.0	
VK	20.0	20	× 800	100	6.7	90	225.0	
VL	20.0	10	× 200	83.2	—	—	230.0	
VM*3)	20.0	60	× 3200	72.0	0.67	100	32.0	
VN	20.0	20	× 200	77.5	2.0	10	120.0	

*3) The yield, the physical and the microanalytical data of these compounds were reported in previous paper.

Other many phosphoroates and phosphorothioates were also prepared by the above two methods. The yield, the physical and the microanalytical data were shown in Table I.

4) Alcoholysis of O,O-diethyl-O- (1-phenyl-2-carboalcohoxy-vinyl) phosphorothioate (VB).

To a solution of sodium alcoholate prepared from 1.2 g. of sodium and 100 ml. of absolute alcohol was added 17.2 g. of O,O-diethyl-O- (1-phenyl-2-carboethoxy-vinyl) phosphorothioate (VB) at room temperature. After refluxing for one hour, the reaction mixture was neutralized with 3 g. of acetic acid, and the alcohol was distilled off.

Ether and water were added to the residue, the ether layer was washed with water and dried over anhydrous sodium sulfate. After removal of the ether, the residual oil was distilled in vacuo, triethyl phosphorothioate was obtained at 93~95°C/15 mm. Yield 6.3 g. n_D^{23} 1.4475.

Anal. Calcd. for $C_{10}H_{15}O_3PS$; P, 16.0; S, 16.3%

Found; P, 15.7; S, 16.2%

The residual oil was dissolved again in ether and shaken with saturated aqueous solution of copper acetate, when the green crystals were obtained. Yield 5.9 g.

The crystals melted at 181~182°C (from benzene).

A mixture of the crystals and the authentic specimen prepared from ethyl benzoylacetate and aqueous solution of copper acetate melted at 181~182°C.

Anal. calcd. for $C_{22}H_{22}O_6Cu$ 59.26; H, 4.71%

Found; C, 59.31; H, 4.56%

The same alcoholysis of 16.4 g. of O,O-diethyl-O- (1-phenyl-2-carboethoxy-vinyl) phosphoroate (VD), gave 6.3 g. of triethyl phosphate, b.p. 100~103°C./25 mm. n_D^{21} 1.4055.

Anal. Calcd. for $C_6H_{15}O_4P$; P, 17.0%

Found; P, 16.6%

From the residual oil, 6.3 g. of copper salt of ethyl benzoylacetate could be obtained by the same manner as mentioned above.

5) Acid hydrolysis of O,O-diethyl-O- (1-methyl-2-cyano-vinyl) phosphorothioate (VH) and O,O-diethyl-

O- (1-methyl-2-phenyl-2-carboethoxy-vinyl) phosphoroate (VN).

To a mixture of 100 ml. of alcohol and 100 ml. of 15% sulfuric acid was added 17.5 g. of O,O-diethyl-O- (1-methyl-2-phenyl-2-cyanovinyl) phosphorothioate (VH) and the reaction mixture was refluxed for 8 hours. After cooling, the alcohol was removed and the aqueous layer was extracted with ether. The ether solution was washed with water and dilute aqueous solution of sodium carbonate and then dried over anhydrous sodium sulfate.

After evaporation of the ether, the residual oil was dissolved again in alcohol and led to the semicarbazone by treating with semicarbazide hydrochloride and sodium acetate according to the usual method. The semicarbazone melted at 194~196°C. and the yield was 3.4 g.

A mixture of the semicarbazone and that of authentic methylbenzylketone melted at 194~196°C.

Anal. Calcd. for $C_{10}H_{13}N_3O$; C, 62.80; H, 6.85;

N, 21.98%

Found; C, 62.71; H, 6.86; N, 21.77%

When 33.3 g. of O,O-diethyl-O- (1-methyl-2-phenyl-2'-carboethoxy-vinyl) phosphoroate (VN) was hydrolyzed in the same manner as above mentioned, 10.9 g. of the same semicarbazone of methyl-benzyl ketone was obtained.

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