

# Synthesis and biological activity of *O,O*-dialkyl *S*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) thio- and dithiophosphates

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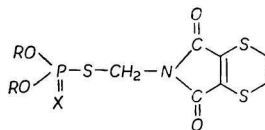
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*Dedicated to Professor E. Krasnec on his 60th birthday*

*N*-Hydroxymethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (*II*) and *N*-chloromethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (*III*) have been prepared. Starting from *III*, *O,O*-dialkyl *S*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) thiophosphates (*IV*–*VIII*) and *O,O*-dialkyl *S*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) dithiophosphates (*IX*–*XIII*) have been synthesized using potassium *O,O*-dialkyl thio- and dithiophosphates, respectively as reagents. Compounds *IV*–*XIII* showed insecticidal and acaricidal effects.

*O,O*-Dimethyl *S*-(phthalimidomethyl) dithiophosphate, known under the trade name "Imidan", has been used successfully in the place of preparations based on DDT in the fight against potato beetle. The synthesis and biological activity of *O,O*-dialkyl *S*-(phthalimidomethyl) thio- and dithiophosphates was first described by *Faucher* [1]. In search for similar biologically active substances we synthesized *O,O*-dialkyl *S*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) thio- (*IV*–*VIII*) and dithiophosphates (*IX*–*XIII*) (Scheme 1).



X = O      *IV*–*VIII*  
X = S      *VIII*–*XIII*

The synthesis of *IV*–*XIII* was carried out in a manner similar to that used for the preparation of *O,O*-dialkyl *S*-(phthalimidomethyl) dithiophosphates [2, 3]. A useful starting material for the synthesis of *IV*–*XIII* was 3,6-dithia-3,4,5,6-tetrahydrophthalimide (*I*), the preparation of which was described by *Schweizer* [4]. Reaction

of *I* with formaldehyde in water with or without a catalytic amount of triethylamine afforded *N*-hydroxymethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (*II*). It was found that the presence of triethylamine did not substantially affect the yields which were in the range of 85–90% of the theoretical. Although the chromatography showed that the crude reaction product *II* contained some of the unconsumed imide *I*, attempts to improve the yield of the desired products by the use of twofold excess of formaldehyde and/or by prolongation of the reaction period were unsuccessful.

*N*-Chloromethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (*III*), one of the starting materials for the preparation of *IV–XIII*, was prepared by chlorination of *II* with thionyl chloride in chloroform or without using the extraneous solvent.

As the second reagent in the presented syntheses potassium salts of *O,O*-dialkyl thiophosphoric and dithiophosphoric acids were used. These were made by a common procedure using as reagents either dialkyl phosphites, sulfur and the corresponding potassium alkoxides or sulfur pentasulfide, the corresponding alcohol and the product of a reaction of the latter two was then allowed to react with potassium alkoxide in benzene. The obtained yields compared well with those reported [5–9].

The reaction of *III* with potassium *O,O*-dialkyl dithiophosphate and with potassium *O,O*-dialkyl thiophosphate under the same conditions gave equal yields of the product showing in both instances comparable nucleophilicity of the sulfur atom.

It is noteworthy that, due to poor nucleophilicity of the anion of *O,O*-dialkyl phosphoric acid, no reaction was observed when *III* was allowed to react with phosphates. Thus, attempts to prepare *O,O*-dialkyl *O*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) phosphates were unsuccessful though the reaction was conducted at higher temperature and the reaction period was doubled. (Similarly, no reaction took place between *N*-chloromethylphthalimide and the anion of *O,O*-dialkyl phosphoric acid.)

“Imidan”, which according to its chemical structure most resembles the synthesized substances, was used as standard for testing the biological activity of the new compounds. Their fungicidal and herbicidal activity was very low not only in comparison to “Imidan”, which is inactive in this respect, but also to other known standards.

Measurable insecticidal activity towards *Musca domestica* was observed. The activity, however, was by orders lower than that of “Imidan”. Acaricidal activity of the synthesized compounds was comparable with that of “Imidan”. Acaricido-ovicidal activity was not observed.

## Experimental

Melting points were determined on a Kofler hot stage. The i.r. spectra were measured in *nujol* using a UR-20 Zeiss spectrometer. Thin-layer chromatography was carried out on Silufol (Lachema, Brno) using ethyl acetate–benzene–cyclohexane 2 : 1 : 1 as irrigant. The compounds were located directly by the colour of the spots produced. The analytical data and physicochemical constants are summarized in Table 1. The starting 3,6-dithia-3,4,5,6-tetrahydrophthalimide (*I*) was prepared as described by *Schweizer* [4] except that after alkaline hydrolysis of 3,6-dithia-3,4,5,6-tetrahydrophthalonitrile the acidity of the reaction mixture was adjusted to pH 1, instead of pH 2–3 as described.

### *N*-Hydroxymethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (*II*)

A stirred 15% water solution of *I* (0.2 mole) and formaldehyde (0.53 mole) was heated within 20 minutes to 93–95°C. The stirring was continued for additional 2 hours and

Table 1

Survey of the prepared organophosphoric compounds

No.	R	X	Formula	<i>M</i>	Calculated/found		Yield [%]	M.p. [°C] Solvent	$\bar{\nu}(\text{CO})$ [cm <sup>-1</sup> ]	<i>R<sub>F</sub></i>
					% P	% S				
<i>IV</i>	CH <sub>3</sub>	O	C <sub>9</sub> H <sub>12</sub> NO <sub>5</sub> PS <sub>3</sub>	341.33	9.08	28.16	98	129—130	1720	0.20
<i>V</i>	C <sub>2</sub> H <sub>5</sub>	O	C <sub>11</sub> H <sub>16</sub> NO <sub>5</sub> PS <sub>3</sub>	369.37	9.24	28.10	94	ethanol	1778	0.27
					8.39	26.03		98—99	1721	
<i>VI</i>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	O	C <sub>13</sub> H <sub>20</sub> NO <sub>5</sub> PS <sub>3</sub>	397.41	8.21	26.12	96	methanol	1779	0.41
					7.80	24.21		84—85	1720	
<i>VII</i>	<i>iso</i> -C <sub>3</sub> H <sub>7</sub>	O	C <sub>13</sub> H <sub>20</sub> NO <sub>5</sub> PS <sub>3</sub>	397.41	7.60	24.21	77	diethyl ether	1778	0.35
					7.80	24.20		107—108	1718	
<i>VIII</i>	<i>iso</i> -C <sub>4</sub> H <sub>9</sub>	O	C <sub>15</sub> H <sub>24</sub> NO <sub>5</sub> PS <sub>3</sub>	425.45	7.55	24.42	73	methanol	1779	0.55
					7.27	22.55		52—54	1720	
<i>IX</i>	CH <sub>3</sub>	S	C <sub>9</sub> H <sub>12</sub> NO <sub>4</sub> PS <sub>4</sub>	357.39	7.13	22.21	92	diethyl ether	1778	0.69
					8.66	35.90		84—85	1720	
<i>X</i>	C <sub>2</sub> H <sub>5</sub>	S	C <sub>11</sub> H <sub>16</sub> NO <sub>4</sub> PS <sub>4</sub>	385.45	8.45	36.13	78	ethyl acetate	1778	0.75
					8.03	33.30		119—120	1718	
<i>XI</i>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	S	C <sub>13</sub> H <sub>20</sub> NO <sub>4</sub> PS <sub>4</sub>	413.47	8.45	33.72	81	ethyl acetate	1778	0.79
					7.48	31.02		71—73	1720	
<i>XII</i>	<i>iso</i> -C <sub>3</sub> H <sub>7</sub>	S	C <sub>13</sub> H <sub>20</sub> NO <sub>4</sub> PS <sub>4</sub>	413.47	7.76	31.40	84	methanol	1778	0.78
					7.48	31.02		121—123	1719	
<i>XIII</i>	<i>iso</i> -C <sub>4</sub> H <sub>9</sub>	S	C <sub>15</sub> H <sub>24</sub> NO <sub>4</sub> PS <sub>4</sub>	441.51	7.56	31.27	90	methanol	1778	0.82
					7.02	29.06		78—79	1720	
					6.97	29.43		methanol	1778	

allowed to cool to 18°C. The separated yellow product was dried and recrystallized from methanol. Yield 37.5 g (86.3%), m.p. 136–138°C.

For  $C_7H_7NO_3S_2$  (217.26) calculated: 29.41% S, 6.44% N; found: 29.72% S, 6.20% N.

### *N*-Chloromethyl-3,6-dithia-3,4,5,6-tetrahydrophthalimide (III)

#### *Procedure A*

Into a three-necked 500-ml flask containing *II* (33 g; 0.15 mole) and chloroform (200 ml) thionyl chloride (37 g; 0.31 mole) was added dropwise with mechanical stirring. The temperature of the reaction mixture was kept at 35°C for two hours, the solution was filtered while warm and the unchanged thionyl chloride and chloroform was evaporated. The crude product was recrystallized from toluene or ethyl acetate to give *III* (51.6%), m.p. 146–148°C.

For  $C_7H_6ClNO_2S_2$  (235.69) calculated: 27.20% S, 15.05% Cl, 5.94% N; found: 26.98% S, 14.96% Cl, 5.56% N.

#### *Procedure B*

A mixture of *II* (21.7 g; 0.1 mole) and thionyl chloride (119 g; 1 mole) in a 250-ml flask was refluxed with stirring for two hours. After having been cooled to room temperature the mixture was poured onto ice (600 g) and the separated product was crystallized from ethyl acetate to give *III* in 76.3% yield, m.p. 146–148°C.

### *O,O*-Dialkyl *S*-(3,6-dithia-3,4,5,6-tetrahydrophthalimidomethyl) thio- (*IV*–*VIII*) and dithiophosphates (*IX*–*XIII*)

A mixture of *III* (0.08 mole), potassium *O,O*-dialkyl thio- or dithiophosphate (0.1 mole) and ethyl methyl ketone or acetonitrile (110 ml) was heated with stirring at 80°C for 6 hours. The mixture was cooled to 15°C and poured into water (500 ml). The separated yellow product was recrystallized from ethanol or ether.

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