

Synthesis and Insecticidal Activity of Some O,O-Dialkyl O-3,5,6-Trihalo-2-pyridyl Phosphate and Phosphorothioates

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The synthesis, physical properties, and insect toxicities of a series of O,O-dialkyl O-3,5,6-trihalo-2-pyridyl phosphates and phosphorothioates are described. These materials were prepared by the reaction of a 3,5,6-trihalo-2-pyridinol with a substituted phosphorus halide in an inert solvent in the presence of a hydrogen chloride acceptor. The results of the insecticide tests show that these compounds have a wide spectrum of insect toxicity and are effective in several different solvent systems.

WHILE a large amount of effort has been directed to a study of organophosphate insecticides prepared from substituted phenols, little attention has been given to organophosphate esters of pyridinols. Andrews *et al.* reported on the preparation and anticholinesterase activity of dialkyl phosphate esters of 3-pyridinol (1). Phosphorothionate esters have also been prepared from unsubstituted pyridinols (2). Ring substitution appears to have been restricted to nitro and to methyl groups (7, 8, 11), for the only examples noted in the patent literature were phosphate and phosphorothionate esters of 4,6-dimethyl-2-pyridinol, 2,6-dimethyl-4-pyridinol, and 2,6-dimethyl-3-nitro-4-pyridinol (8, 11). We have recently synthesized a large number of organophosphate esters of halogenated pyridinols and have noted unusual insecticidal activity (10). This paper deals with the synthesis, physical properties, and insecticidal activity of a series of 3,5,6-trihalo-2-pyridyl phosphates and phosphorothionates. Certain biological and chemical properties of one of the compounds, O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate (trademark Dursban), have been noted in detail (5, 9). Mammalian toxicity data on Dursban have been published (6) but are not yet available on the other compounds discussed here.

Chemical Studies

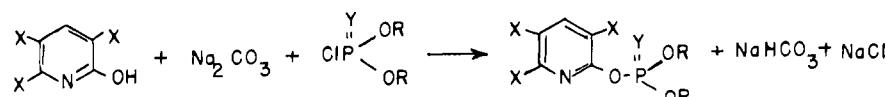
6-Chloro-2-pyridinol exists as these tautomers shown below. The predominant tautomer depends on the pH. 6-Chloro-2-pyridinol shows some of



the properties of a phenol and can be readily halogenated in the 3- and 5-positions.

The reaction of a 3,5,6-trihalo-2-pyridinol with either O,O-dialkyl phosphorochloridothioate or dialkyl phosphorochloridate in an inert solvent such

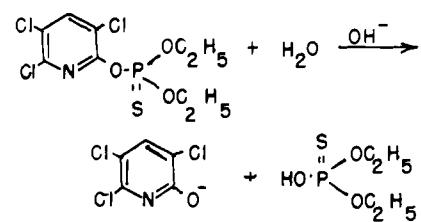
as dimethylformamide in the presence of a hydrogen chloride acceptor such as sodium carbonate gave the desired O,O-dialkyl O-3,5,6-trihalo-2-pyridyl phosphorothioates and phosphates in good yields.



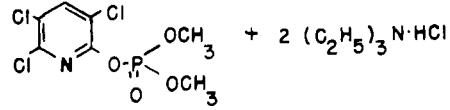
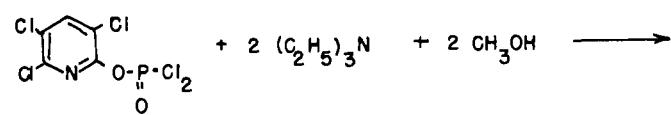
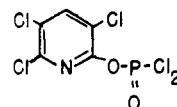
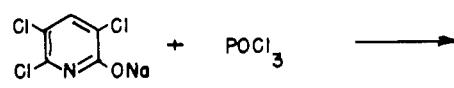
Because of the unavailability of dimethyl phosphorochloridate, dimethyl 3,5,6-trichloro-2-pyridyl phosphate was prepared by the reaction of phosphoryl chloride with one equivalent of the anhydrous sodium salt of 3,5,6-trichloro-2-pyridinol in isobutyl methyl ketone at -40° to -10° F. The intermediate, O-3,5,6-trichloro-2-pyridyl phosphorodichloridate, was then made to react without isolation or purification with 2 equivalents of methanol using triethylamine as a hydrogen chloride acceptor at -10° to 25° F.

lization from either petroleum ether or methanol. These materials are soluble in most organic solvents and insoluble in water. O,O-Diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate hydrolyzes in

basic and acid media to form O,O-diethyl phosphorothioic acid:



The estimated half life of this reaction in 50 volume % aqueous methanol solution



at 23° in buffered solution at pH 6 was determined to be 1930 days, while at pH 9.96 it was 7.2 days. The pyridyl phosphates and phosphorothioates used for insecticidal evaluation were found to be pure by vapor phase chromatography, and infrared and nuclear magnetic resonance spectroscopy. The physical properties and analytical data are listed in Table I.

Synthesis

The *O,O*-dialkyl phosphorochloridothioates and dialkyl phosphorochloridates were freshly redistilled commercial products. The 6-chloro-2-pyridinol was obtained from the Aldrich Chemical Co., Inc. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The synthetic procedures for the preparation of the various halogenated pyridinols and pyridyl phosphates and phosphorothioates are illustrated by the following examples.

3,5,6 - Trichloro - 2 - pyridinol. 6-Chloro-2-pyridinol (13.0 grams, 0.1 mole) was dissolved in 100 ml. of acetic acid and 50 ml. of concentrated hydrochloric acid was added. To this cloudy mixture, 22.7 grams (0.2 mole) of 30% hydrogen peroxide was added with stirring at 25° to 30° in about 5 minutes. This mixture was heated slowly with stirring, resulting in an exothermic reaction. The reaction mixture was heated at 90° to 100° with stirring for 0.5 hour. After addition of 100 ml. of water, the clear solution was cooled with an ice water bath. The precipitated product was filtered and dried to give 15.8 grams of product [m.p. 172-74° (lit. 174-75°) (4) yield 79.6%].

3,5 - Dibromo - 6 - chloro - 2 - pyridinol. 6-Chloro-2-pyridinol (129.5

grams, 1.0 mole) was dissolved in 1000 grams of 33% sulfuric acid. Bromine (320 grams, 2.0 moles) was added dropwise with stirring and cooling at 25° to 30° in about 2 hours. Stirring was continued for 0.5 hour longer at room temperature. After cooling in an ice water bath, the product was filtered, washed with water, and dried (m.p. 189-92°, yield 93%). Analysis: Calculated for $C_6H_2BrCl_2NO$: N, 4.87. Found: N, 4.98.

***O,O*-Diethyl 3,5,6-Trichloro-2-pyridyl Phosphorothioate.** To 200 ml. of dimethylformamide were added 43.5 grams (0.405 mole) of anhydrous sodium carbonate and 79.2 (0.40 mole) of 3,5,6-trichloro-2-pyridinol. To this stirred mixture was added 75.4 grams (0.40 mole) of *O,O*-diethyl phosphorochloridothioate at 22-25° over a period of 1 hour. This reaction mixture was stirred for an additional 3 hours at about 25°. Reaction mixture was diluted with 525 ml. of water and the crystallized product removed by filtration and dried (m.p. 40-42°, yield 93%). Recrystallization from methanol gave a colorless solid (m.p. 42-43°).

Dimethyl 3,5,6-Trichloro-2-pyridyl Phosphate. To 250 ml. of isobutyl methyl ketone were added 0.1 mole (19.9 grams) of 3,5,6-trichloro-2-pyridinol and 0.1 mole of 50% sodium hydroxide with stirring, giving a very

thick mixture. Water was removed by distillation. This solution was cooled to about -40° and 0.1 mole (15.3 grams) of phosphoryl chloride was added all at once with stirring. Stirring was continued for 0.5 hour longer, while the temperature was allowed to rise to -10°. A solution of 0.2 mole (20.2 grams) of triethylamine in 0.22 mole (7.0 grams) of methanol was added dropwise with stirring and cooling at -10° to 0° in about 10 minutes. Stirring was continued for 1.25 hours longer, while the temperature was allowed to rise to 25°. Water (100 ml.) was added with stirring. The two layers were separated and the organic layer was washed with 100 ml. of 2% sodium carbonate solution and finally with 100 ml. of water. The solvent was removed by vacuum distillation. The residue was extracted with 100 ml. of boiling petroleum ether (b.p. 60-70°) and then with a 50-ml. portion of boiling petroleum ether. The combined extracts were cooled in an ice water bath. The crystallized product was removed by filtration, washed, and dried. Repeated recrystallization from petroleum ether gave a product melting at 86.5-88°.

Analysis: Calcd. for $C_7H_7Cl_3NO_4P$: N, 4.57; P, 10.11; Cl, 34.70. Found: N, 4.55; P, 9.77; Cl, 35.06.

Insecticide Tests. Insecticide screening test methods and insect species used

Table I. Physical and Analytical Data of *O,O*-Dialkyl 3,5,6-Trihalo-2-pyridyl Phosphates and Phosphorothioates

X_n	Y	R	Yield, % ^a	M.P., °C. ^b	Nitrogen		Sulfur		Chlorine		Phosphorus	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3,5,6-Trichloro	Sulfur	Methyl	62.0	43-44 ^c	4.34	4.32	9.94	9.96	32.98	33.54		
3,5,6-Trichloro	Sulfur	Ethyl	93.0	42-43 ^d	4.00	4.05	9.15	8.92	30.34	29.93		
3,5,6-Trichloro	Oxygen	Methyl	45.7	86.5-88 ^c	4.57	4.55	0.00	...	34.70	35.06	10.11	9.77
3,5,6-Trichloro	Oxygen	Ethyl	80.0	43-44 ^c	4.19	4.32	0.00	...	31.79	31.73	9.05	9.44
3,5-Dibromo-6-chloro	Sulfur	Ethyl	47.5	60-61 ^c	3.19	3.27	7.30	7.37				

^a Yield of technical grade material. ^b Melting point of purified material. ^c Recrystallized from petroleum ether (b.p. 60-70°). ^d Vapor pressure. 1.87×10^{-5} mm. Hg at 25°.

Table II. Toxicity to Insects and Associated Organisms of Some *O,O*-Dialkyl 3,5,6-Trihalo-2-pyridyl Phosphates and Phosphorothioates in Screening Tests

X	Y	R	LD	Species, ^a P.P.M.								
				2SSM	PC	BA	AR	HF	CFB	GF	RHS	D
3,5,6-Cl ₃	S	CH ₃	50	32	9.4	10.5	54	4.4	36	0.20	>2	0.016
			95	50	12.8	14.0	110	6.6	56	0.27	>2	0.025
3,5,6-Cl ₃	S	C ₂ H ₅	50	1.6	3.5	>500	16	4.0	20	0.18	>2	0.016
			95	2.7	6.0	>500	26	6.6	35	0.32	>2	0.025
3,5-Br ₂ , 6-Cl	S	C ₂ H ₅	50	1.5	2.5	220	1.7	3.0	3.5	>1	>1	0.078
			95	3.0	4.0	310	10.0	5.4	6.0	>1	>1	0.095
3,5,6-Cl ₃	O	CH ₃	50	5.8	4.5	>500	38	34	60	>2	>2	0.9
			95	8.0	13.4	>500	60	56	74	>2	>2	1.3
3,5,6-Cl ₃	O	C ₂ H ₅	50	1.7	10	130	7.2	23	56	0.25	>1	0.0010
			95	3.5	18	500	12.0	43	80	0.33	>1	0.0015
Ronnel			50	230	35	2.5	100	3	140	22	>2	0.025
			50	150	70	380	110	4	500	2	>2	1

^a 2SSM = two spotted spider mite; PC = plum curculio; BA = bean aphid; AR = American cockroach; HF = housefly; CFB = confused flour beetle; GF = goldfish; RHS = ram's horn snail; D = *Daphnia* spp.

Table III. Insecticidal Activity of Some O,O-Dialkyl O-3,5,6-Trihalo-2-pyridyl Phosphates and Phosphorothioates Using Topical Tests

X	Y	R	$\mu\text{G. per Insect}$					
			Housefly		American Cockroach		Plum Curculio	
			Adult	Female	Nymph	LD ₅₀	LD ₉₅	Adult
3,5,6-Cl ₃	S	CH ₃	0.038	0.075	0.78	2.03	0.08	0.12
3,5,6-Cl ₃	S	C ₂ H ₅	0.045	0.075	0.67	1.1	0.1	0.7
3,5-Br ₂ , 6-Cl	S	C ₂ H ₅	0.046	0.138	1.00	1.5	0.37	0.92
3,5,6-Cl ₃	O	CH ₃	0.102	0.24	0.20	0.62	0.04	0.10
3,5,6-Cl ₃	O	C ₂ H ₅	0.055	0.182	0.17	0.38	0.11	0.35
Ronnel			0.065	0.108	5.20	10.40	4.50	13.30
Malathion			0.56	0.95	6.40	20.40	0.27	1.92
DDT			0.088	0.176	120.0	400.0	6.0	6.0
Diazinon			0.082	0.152	1.54	4.90	0.90	4.70

Table IV. Toxicity of Some O,O-Dialkyl O-3,5,6-Trihalo-2-pyridyl Phosphates and Phosphorothioates to the German Cockroach

(CSMA oil spray method)

X	Y	R	G. Tox./100 MI. Oil	
			LD ₅₀	LD ₉₅
3,5,6-Cl ₃	S	CH ₃	0.032	0.046
3,5,6-Cl ₃	S	C ₂ H ₅	0.046	0.085
3,5-Br ₂ , 6-Cl	S	C ₂ H ₅	0.053	0.080
3,5,6-Cl ₃	O	CH ₃	0.020	0.041
3,5,6-Cl ₃	O	C ₂ H ₅	0.012	0.026
Ronnel			0.38	0.54
Malathion			0.28	1.55
Diazinon			0.028	0.10

have been described (2). Insects were immersed in aqueous acetone emulsion compositions. In addition to six insect species, information on aquatic organisms is also given in this paper. The aquatic tests were conducted on a water flea, *Daphnia spp.*; a ram's horn snail, *Helisoma trivolvis* (Say); and the goldfish, *Carassius auratus* (L.). These organisms were held in 500-cc. containers of water at 65° F. Mortality readings were taken after 24 hours' exposure with *Daphnia* and fish and after 72 hours with snails. Results shown in Table II indicate that the *O,O*-dialkyl trihalo-2-

pyridyl phosphates and phosphorothioates are wide-spectrum insecticides of a high order of toxicity.

Topical insecticide test methods as previously described (2) are nonaqueous, acetone applications of single droplets to each individual insect, thus minimizing possible hydrolysis effects on the less stable compounds. These results (Table III) again illustrate the potential usefulness of this new group of pyridyl phosphorus-containing insecticides.

The official cockroach spray test method (3) of the Chemical Specialties Manufacturers Association (CSMA) was

used for evaluating toxicity to the German cockroach. A specific refined oil was sprayed on the male cockroach, which after 30 seconds was transferred from contact with the sprayed container to an unsprayed container. The treated cockroaches were held without food or water at 80° F. for 48 hours before mortality counts were made. Results shown in Table IV indicate that Dursban and chemical relatives are effective insecticides in oil compositions.

Acknowledgment

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