Studies on Oxazaphospholidines with Pesticidal Activities : I. Synthesis and Insecticidal Activities of 2-Chloromethyl-1,3,2-oxazaphospholidine 2-Oxides

Tawata, Shinkichi
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Eto, Morifusa
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Ishiguro, Takeo
Aburabi Laboratories of Shionogi Seiyaku Co.

https://doi.org/10.5109/23663

出版情報：九州大学大学院農学研究院紀要. 22 (3), pp.169-177, 1978-07. Kyushu University
バージョン：
権利関係：

J. Fac. Agr., Kyushu Univ., 22, 169-177 (1978)

Studies on Oxazaphospholidines with Pesticidal Activities

I. Synthesis and Insecticidal Activities of 2-Chloromethyl-1,3,2-oxazaphospholidine 2-Oxides

Shinkichi Tawata, Morifusa Eto and Takeo Ishiguro*

Laboratory of Pesticide Chemistry, Faculty of Agriculture,
Kyushu University 46-02, Fukuoka 812

(Received November 30. 1977)

A number of 3, 5-disubstituted 2-chloromethyl-1, 3, 2-oxazaphospholidine Z-oxides were prepared by the reaction of 2-aminoalcohols with chloromethylphosphonic dichloride. Characteristic mass fragmentation pattern was observed with these cyclic phosphonamidates. The cyclic compounds were examined for anticholinesterase and insecticidal activities. Some of them showed considerable miticidal activity.

INTRODUCTION

We have interests in the biological activities of heterocyclic compounds derived from 2-aminoethanols (Tawata *et al.*, 1974) and of cyclic phosphorus compounds (Eto, 1976). Nakanishi and Inamasu (1969) prepared a series of 2-chloromethyl-3-(substituted)-1,3, 2-oxazaphospholidine Z-oxides from 2-alkylaminoethanols and examined their insecticidal activity. Some other physiological activities including herbicidal, hypertensive and carcinostatic activities have been asserted for some compounds of this series (Asta-Werke Akt. -Ges. Chemische Fabrike, 1960 ; Deutche Gold- und Silber-Scheidenstalt, 1966 ; Segre, 1966). We tried to synthesize new compounds of this ring system having a side chain at the 5-position.

This paper describes some chemical properties and insecticidal and anticholinesterase activities of the new five-membered cyclic phosphonamidates.

MATERIALS AND METHODS

Aminoalcohols

Aminoalcohols were prepared as described previously (Tawata *et al., 1974).* Thus, an epoxide (0.1 mole) was heated with an appropriate primary amine (0.1 mole) in an autoclave at 150°C for 6 hr. The resulting aminoalcohol was distilled in *vacuo* in order to remove by-products.

Chloromethylphosphonic dichloride

Paraformaldehyde 3 g was added to phosphonyl trichloride 20.7 g kept in an ice-bath. After the initial vigorous reaction subsided and evolution of hy-

* Aburabi Laboratories of Shionogi Seiyaku Co., Shiga-ken

drogen chloride gas ceased, the mixture was heated to 120–130°C in a sealed tube for 24 hr; after the reaction time all solid disappeared. Hydrogen chloride gas was removed from the reaction mixture and then the reaction product was distilled under reduced pressure. The fraction collected had b. p. 83–86°C at 10 mmHg; the reported b. p. is 87–88°C at 15mmHg (Kinnear and Perren, 1952). Yield, 8.3 g.

Preparation of 2-chloromethy-3-propyl-5-methyl-1,3,2-oxazaphospholidine 2-oxide (No. 1)

A mixture of 1-propylamino-2-propanol (0.02 mole) and triethylamine (0.04 mole) was added, drop by drop, into a solution of chloromethylphosphonic dichloride (0.02 mole) in 100 ml of dioxane at 0°C with stirring. The reaction mixture was stirred for 2 hr at room temperature, then the precipitate of triethylammonium chloride was filtered out and washed twice with ether. After the solvents were removed under reduced pressure, 2-chloromethyl-5-methyl-3-propyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 1) was obtained by distillation in *vacuo*.

All compounds listed in Table 1 were prepared by the same method.

Assay of enzyme activity

Pig erythrocytes suspended in phosphate buffer solution (M/15, pH 7.3) were used as a crude acetylcholinesterase solution. The Hestrin's photometric method (Hestrin, 1949) was slightly modified for the assay of acetylcholinesterase activity. The residual activity of cholinesterase was assayed after incubation with an inhibitor at 37°C for 20 min. The inhibitory activity was expressed as the molar concentration of the inhibitor for 50 % inhibition (I_{50}).

Assay of insecticidal activity

Insecticidal activity was determined on A) houseflies *Musca domestica*, B) American cookroaches *Periplaneta americana*, C) green rice leafhoppers *Nephotettix cincticeps*, D) tobacco cutworm larvae *Plodenia litura*, E) pea aphids *Aphis craccivora*, F) citrus red mites *Panonychus citri*, G) carmine mites *Tetranychus cinabarinus*, and H) carmine mite eggs according to the procedures reported previously (Tawata *et al., 1974).*

The samples were dissolved in a small amount of dimethylformamide and diluted with distilled water or acetone to make 2000, 500 and 200 ppm solutions. The test solutions were applied to the host plants, insects or filter paper on which insects were placed. Mortality was determined at 24 or 48 hr after the treatment. Ovicidal activity was determined by counting the number of hatching larvae after 7 days.

Other methods

Infrared absorption spectra (ir) were recorded from 10 % chloroform solutions with a Shimazu IR-27G spectrophotometer with a grating. Mass specta were obtained with a Nippon-Denshi mass spectrometer JMS-01 SG at 75 eV. Proton nuclear magnetic resonance spectra (pmr) were determined in deuteriochloroform using tetramethylsilane as an internal standard on a Nippon-Denshi MH 100 spectrometer (100 MHz).

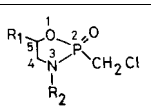
RESULTS

Spectrometric identification of synthesized compounds

Sixteen five-membered cyclic chloromethylphosphonamidates were synthesized from chloromethylphosphonic dichloride and a series of 2-aminoalcohols. All preparations are the mixtures of cis- and *trans*-isomers. The isolation of each isomer was not attempted. Table 1 shows the yields, boiling points and analytical data of the obtained cyclic phosphonamidates.

Their structures were confirmed spectrometrically. Fig. 1 shows the ir spectrum of 2-chloromethyl-3-isobutyl-5-methyl-1, 3, 2-oxazapholidine 2-oxide (No. 4). It exhibits a characteristic absorption in the region of stretching vibration for the phosphoryl group (1250 cm-'). A number of strong bands are observed in the 800-1050 cm^{-1} region (C-O-P group). Carbon-hydrogen stretching absorption occurs at 2900 cm^{-1}.

Table 1. Physical and analytical data of Z-chloromethyl-3, 5-disubstituted-1, 3, 2-oxazaphospholidine 2-oxides.



No.	R_1	R_2	Yield (%)	B. p. °C/mmHg	Elemental Analysis (Found/Calcd.) C	H	N
1	Me	n-Pr	33	104-7 /0. 1	(39.29 (39.80	7. 20 7. 10	6. 43 6. 66)
2	Me	*i-Pr*	33	104–5 /0. 1	'39. 56 (39.80	7. 06	6. 66)
3	Me	*n*–Bu	35	112–5 /0. 09	42.45 (42.22	7. 56	6. 03
4	Me	i-Bu	37	113–6 /0. 2	42.21 (42.22	7. 56	6. 03
5	Me	s-Bu	22	108–10 /0. 05	42.57 (42.22	7. 56	6. 03
6	Me	t-Bu	35	104-5 /0. 05	42.20 42.22	7. 56	6. 02
7	Et	n-Pr	39	115–8 /0. 07	(42. 54 (42. 22	7. 56	6. 22)
a	Et	i-Pr	46	115–6 /0. 04	'42. 63 (42.22	7. 56	6. 22)
9	Et	n-Bu	48	128–30 /0.06	45. 03 (45.19	7. 95	5. 81)
10	Et	i-Bu	52	125–30 /0.07	45.77 45.19	7. 95	5. 81)
11	Et	*s*–Bu	42	70-5 /0.06	(44.91 (45. 19	7. 58	5. 79
12	Et	*t*–Bu	40	114–8 /0. 04	45.35 45.19	a. 06	5. 81)
13	Ph	n-Pr	45	162-8 /0. 1	('52. 29 (52.74	7.95 6.22	5. 21) 5: 12)
14	Ph	i-Pr	46	156-60 /0. 1	'52. a7 (52.74	6.29	5. 12)
15	Ph	*n*-Bu	21	155-6 /0. a	54.70 54.35	6. 67	4.80)
16	Ph	i-Bu	52	160-5 /0. 1	(54.40 54.35	6.82	4.80)

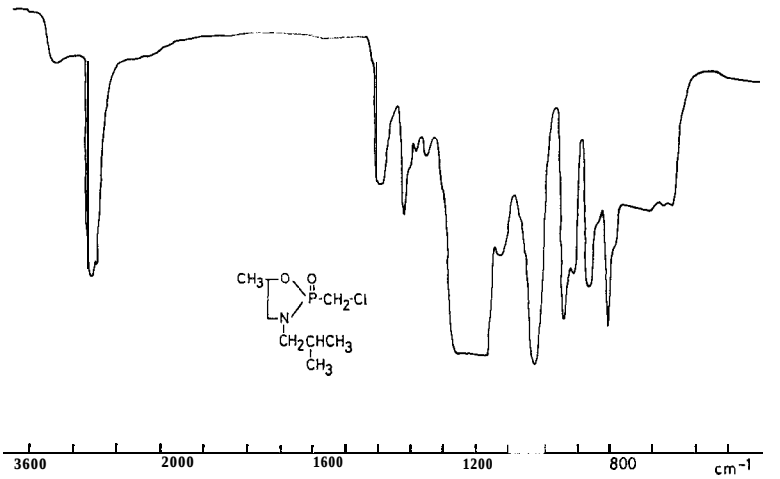


Fig. 1. Infrared spectrum of 2-chloromethyl-3-isobutyl-5-methyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 4).

Fig. 2 shows the pmr spectra of 2-chloromethyl-3-*sec*-butyl-5-methyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 5) (Spectrum C) and the starting aminoalcohol (Spectrum B). It includes also the spectrum in the region of δ 2-3 ppm of the aminoalcohol after the D_2O exchange (Spectrum A). The protons of hydroxyl and amino groups are represented by signals around δ 2.6 ppm. This is confirmed by the comparison of spectrum A with B ; the proton integration value was decreased from 5H to 3H by the D_2O exchange.

The signals split by spin -spin coupling with phosphorus ($J_{PCH}=10$ Hz) in a region between δ 3.8 and 4. Oppm are assigned to the exocyclic methylene protones (7) on the phosphorus atom; the two doublets indicate the existence of cis- and trans-isomers. The triplet around 1. 5 ppm assignable to the methyl protons (4) at the 5-position may be due to overlapping of two doublets of the cis- and trans-isomers. The pmr data obtained from the spectrum C are tabulated in Table 2. The convention is used in the present paper that cis and *trans* refer to the relation between the C_5-methyl group and the phosphoryl oxygen atom. The methyl protons of the *cis* compound may shift to lower magnetic field in comparison with those of the *trans* compound, owing to the anisotropic effect of the phosphoryl group.

Table 2. Pmr spectrum of 2-chloromethyl-3-*sec*-butyl-5-methyl-1, 3. 2-oxazaphospholidine 2-oxide (No. 5).

Proton No.	1	2	3	4		5	6	7	
				cis	*trans*			*cis* or	*trans*
Chemical shift (δ)	4.84	3.44	3.11	1.52	1.44	1.26	1.00	3.86	3.84

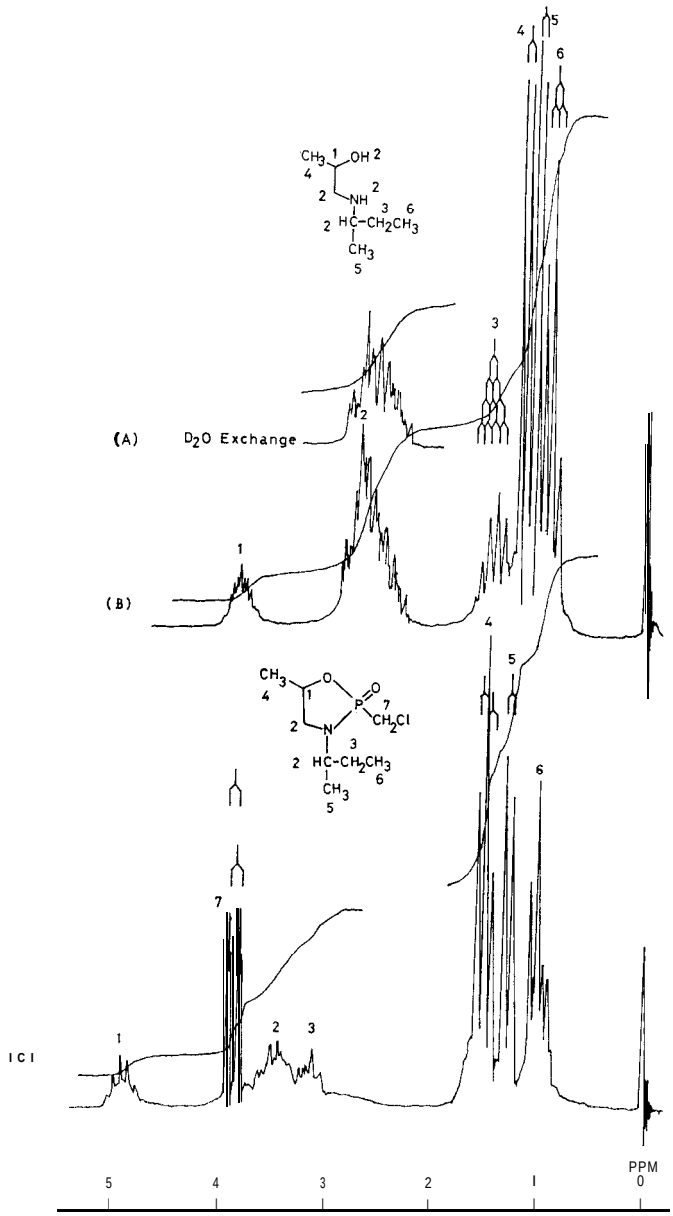


Fig. 2. Pmr spectra of 2-chloromethyl-3-*sec*-butyl-5-methyl-1,3, 2-oxazaphospholidine 2-oxide (No. 5) (spectrum C) and 1-methyl-2-*sec*-butylaminoalcohol (spectra A and B).

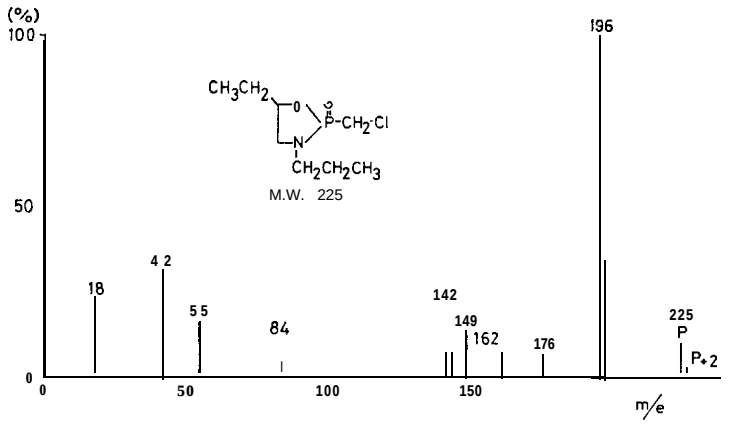


Fig. 3. Mass spectrum of 2-chloromethyl-3-propyl-5-ethyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 7).

Fig. 3 shows the mass spectrum of 2-chloromethyl-3-propyl-5-ethyl-1, 3,2-oxazaphospholidine 2-oxide (No. 7). It reveals a molecular ion peak at m/e 225 and prominent peaks at m/e 227 (P+2), m/e 196 (base peak), m/e 176, m/e 149, m/e 142, m/e 84, m/e 55 and m/e 42. The presumed fragmentation processes are given in Fig. 4. It is interesting to note that a simultaneous rearrangement of two hydrogen atoms to the phosphorus-connected oxygen and nitrogen with the elimination of an alkyne occurs significantly at the second step of the fragmentation of this phosphonamidate as illustrated in Fig. 5.

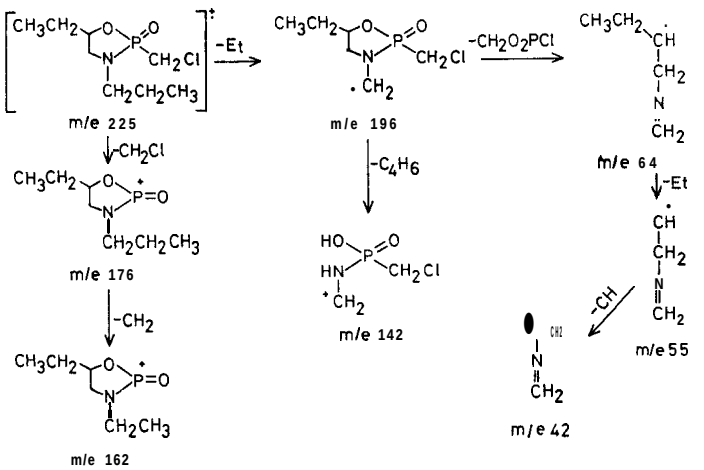


Fig. 4. Proposed fragmentation processes of 2-chloromethyl-5-ethyl-3-propyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 7).

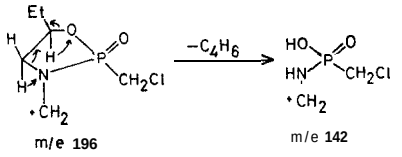


Fig. 5. Double hydrogen rearrangement of m/e 196.

Anticholinesterase activity

I_{50} values of 1, 3, 2-oxazapholidine 2-oxide derivatives toward pig erythrocyte acetylcholinesterase are shown in Table 3. The compounds which have methyl or ethyl group at the 5-position (No. 1-12) show only a poor anticholinesterase activity. However, the 5-phenyl derivatives (No. 13-16) exhibits relatively strong activity. The branched alkyl substituent on the 3-position nitrogen atom appears to be a little more effective than corresponding straight chain alkyl group for acetylcholinesterase inhibition. Thus, 5-phenyl-4-isobutyl-2-chloromethyl-1, 3, 2-oxazaphospholidine 2-oxide (No. 16) shows the highest activity among the examined compounds.

Table 3. Anticholinesterase activity of 2-chloromethyl-3, 5-disubstituted-1, 3, 2-oxazaphospholidine 2-oxides.

No.	R_1	R_2	I_{50}
1	Me	n-Pr	10^{-3}
2	Me	i-Pr	3×10^{-4}
3	Me	n-Bu	10^{-3}
4	Me	i-Bu	9×10^{-4}
5	Me	s-Bu	7×10^{-4}
6	Me	t-Bu	8×10^{-4}
7	Et	n-Pr	10^{-3}
8	Et	i-Pr	7×10^{-4}
9	Et	n-Bu	10^{-3}
10	Et	i-Bu	10^{-4}
11	Et	s-Bu	10^{-3}
12	Et	t-Bu	10^{-3}
13	Ph	n-Pr	6×10^{-5}
14	Ph	i-Pr	9×10^{-5}
15	Ph	n-Bu	10^{-6}
16	Ph	i-Bu	3×10^{-7}

Insecticidal activities

Experimental results on the pesticidal properties of the cyclic phosphonamidates against houseflies (A), American cockroaches (B), tobacco cutworm larvae (C), green rice leafhoppers (D), pea aphids (E), citrus red mites (F), carmine mite adults (G) and eggs (H) are presented in Table 4.

The cyclic phosphonamidates have no insecticidal activity except against green rice leafhoppers and aphids to which certain compounds, for example No. 13, show a relatively high insecticidal activity. Mites are much more susceptible to the phosphonamidates than insects. However, the eggs of mites are insensitive to the compounds.

Table 4. Insecticidal activities of 2-chloromethyl-3, 5-disubstituted-1, 3, 2-oxazaphospholidine 2-oxides.

No.	Insect*	A		B	C	D		E	F		G		H
	Conc. (ppm)	2000	500	2000	2000	500	200	2000	2000	200	500	200	2000
1			0	0				30	68			33	4
2		75 0	0	0	0	50	20	50	68	26	100 32	30	2
		0		0	0	0	0	‥	71	5			1
3		0	0	0	0	50	10	20	81	25	105	100	10
5				0	0		0	10	65	5			2
7		1 0	00	0	0	0	0	50	90	18	14	11 6	0
8		95	00	0	0	50	20	40	59	11	95	73	0
		0				0	0			13	22	4	1
9		22		0		36	8			30	100	24	0
10			0	0	0		0	20	71	8			
11		0	0	0	00	18 9	16	20 30	21 97	3	74	17	01
12		0	0	0	0	0	0	60	68	19	3	9	0
13		71	0	0	0	100	46	90	97	22	100	100	20
14					0	0	0	50	95		6	1	
15		20	0	0	0	80	20	90	76	8	22	13	66
16		100	0	0	0	0	0	50	100	13	7	1	23
Phosalone		100	100	0	0	100	100	100	91	0	100	0	98

* A) Houseflies, B) American cockroaches, C) Tobacco cutworms, D) Green rice leafhoppers, E) Pea aphids, F) Citrus red mites, G) Carmine mites. H) Carmine mite eggs.

The insecticidal and miticidal activities are influenced by the N-alkyl group rather than the substituent of 5-position. N-Normal alkyl derivatives are much more active than corresponding branched alkyl derivatives. Thus, 5-methyl-3-*n*-propyl (No. 1), 5-methyl-3-*n*-butyl (No. 3), 5-ethyl-3-*n*-propyl (No. 7), 5-ethyl-3-*n*-butyl (No. 9), 5-phenyl-3-*n*-propyl (No. 13) and 5-phenyl-*n*-butyl (No. 15) derivatives are relatively good miticides. This tendency in the structure-insecticidal or miticidal activity relationship contrasts with that in the structure-anticholinesterase activity relationship mentioned above.

DISCUSSION

The extremely high reactivity of five-membered cyclic phosphate and phosphonate esters are well known by the intensive researches of Westheimer and his coworkers (Covitz and Westheimer, 1963 ; Eberhard and Westheimer, 1965 ; Haake and Westheimer, 1961). However, they are only poor inhibitors of acetylcholinesterase with few exceptions (Fukuto and Metcalf, 1965). Any attempts to get insecticides in the series of five-membered cyclic phosphorus compounds were not successful (Edmundson and Lambie, 1966 ; Fukuto and Metcalf, 1965). This may be due to that the five-membered cyclic phosphorus esters are too labile to allow the reaction with the target enzyme to proceed.

It is, therefore, interesting to know that the five-membered cyclic phosphonamidates have a moderate anticholinesterase activity and insecticidal activity. The introduction of atnide group may stabilize the cyclic phosphorus compounds to certain extent by the electromeric donation of electrons on

nitrogen forming $p\pi$-$d\pi$ bonding between phosphorus and nitrogen atoms. We expect more potent insecticides could be obtained in the series of five-membered cyclic phosphonamidates and phosphoramidates by further modifications.

As known with the insecticide schradan, phosphoramides are generally hydrophilic in nature and no effective to many insects including Diptera, Lepidoptera and Orthoptera, but are very effective to kill Hemipterous insects and mites ; the ganglia of schradan-insensitive insects are covered with a thick sheath, whereas those of sensitive insects are surrounded by a thin membrane (Saito and Matsui, 1960). This is probably the case for the selective toxicity of the present cyclic phosphonamidates. Introduction of hydrophobic groups to the cyclic phosphonamidates (and phosphoramidates) appears to be of interest to examine.

REFERENCES

Asta-Werke Akt. -Ges. Chemische Fabrike 1960 Cyclic phosphorus acid ester amides. *Brit. Patent, 812, 651; Chem. Abstr., 54* : *5472* f

Covits, F. and F. H. Westheimer 1963 The hydrolysis of methyl ethylene phosphate : Steric hindrance in general base catalysis. *J. Am. Chem. Soc.*, 85 : 1773-1777

Deutsche Gold- und Silber-Scheideanstalt 1966 2-Chloro-4-ethylamino-6-{*N*-(2-thio-2-phospholan-2-yl)-*N*-ethylamino}-*s*-triazines as herbicides. *Berg. Patent, 665, 127; Chem. Abstr., 64* : 19681 f

Ederhard. A. and F. H. Westheimer 1965 Hydrolysis of phosphonates. *J. Am. Chem. Soc.*, 87 : 253-260

Edmundson, R. S. and A. J. Lambie 1966 Cyclic organophosphorus compounds as possible pesticides. I. 1, 3, 2-Dioxaphospholans. *J. Chem. Soc. (C),* 1997-2001

Eto, M. 1976 Chemistry and biochemistry of salithion and related compounds. *Rev. Plant Protec. Res.*, 9 : 1-20

Fukuto, T. R. and R. L. Metcalf 1965 Reactivity of some 2-*p*-nitrophenoxy-1,3, 2-dioxaphospholane 2-oxides and -dioxaphosphorinane 2-oxides. *J. Med. Chem.*, 8 : 759-764

Haake, P. and F. H. Westheimer 1961 Hydrolysis and exchange in esters of phosphoric acid. *J, Am. Chem. Soc., 83* : 1102-1109

Hestrin, S. 1949 The reaction of acetylcholine and other carboxylic acid derivatives with hydroxylnminr. and its analytical application. *J. Biol. Chem.*, 180 : 249-261

Kinnear, A. M. andE. A. Perren 1952 Formation of organophosphorus compounds by the reaction of alkyl chloride with phosphorus trichloridr in the presence of aluminum chloride. *J. Chem. Soc.*, 3437-3445

Nakanishi, M. and S. Inamasu 1969 Cyclic organophosphorus compounds. *Japan Patent, 68* 16, *142* ; *Chem. Abstr., 70* : 68509 y

Saito, T. and C. Matsui 1960 Electron microscopy of the ganglionic sheath of insect. *Botyu-Kagaku, 25* : *71-73*

Segre, A. 1966 L-, D- and DL-ephedrine phosphates. *J. Med. Chem., 9* : 966-967

Tawata, S., M. Eto and K. Maekawa 1974 Preparation of 2-morpholinones and their biological activities. *J. Fac. Agr., Kyushu Univ., 18* : *258-268*