

Literature Cited

- (1) Arthur, B. W., Casida, J. E., *J. Econ. Entomol.* **51**, 49 (1958).
- (2) Dauterman, W. C., O'Brien, R. D., *J. Agr. Food Chem.* **12**, 318 (1964).
- (3) DuBois, K. P., Coon, M. J., *Arch. Ind. Hyg. Occupational Med.* **6**, 9 (1955).
- (4) Farbenfabriken Bayer A-G., Brit. Patent **786,013** (1957); *C. A.* **52**, 5450g (1958).
- (5) Holmstedt, Bo, *Pharmacol. Rev.* **11**, 567 (1959).
- (6) Jones, G. D. G., Connell, J. U., *Ann. Appl. Biol.* **41**, 271 (1954).
- (7) Krueger, H. R., Casida, J. E., *J. Econ. Entomol.* **50**, 356 (1957).
- (8) Maarsen, J. W., Smit, M. C., Matze, J., *Rec. Trav. Chim.* **76**, 713 (1957).
- (9) Metcalf, R. L., "Organic Insecticides," Interscience, New York, 1955.
- (10) Mounter, L. A., "Cholinesterases and Anticholinesterase Agents," Chap. 10, "Handbuch der Experimentellen Pharmakologie," Springer-Verlag, Berlin, 1963.
- (11) Negherbon, W. O., "Handbook of Toxicology," Vol. 3, Saunders, Philadelphia, 1959.
- (12) O'Brien, R. D., *Advan. Pest Control Res.* **4**, 75 (1961).
- (13) O'Brien, R. D., *Ann. N. Y. Acad. Sci.* **123**, 156 (1965).
- (14) O'Brien, R. D., *Can. J. Biochem. Physiol.* **37**, 1113 (1959).
- (15) Okinaka, A. J., Doull, J., Coon, J. M., DuBois, K. P., *J. Pharmacol. Exptl. Therap.* **112**, 231 (1954).
- (16) Oláh, G., Oswald, A., *Ann.* **602**, 118 (1957).
- (17) Oláh, G., Oswald, A., Mlinko, A., *Ibid.*, **602**, 123 (1957).
- (18) Olson, W. P., O'Brien, R. D., *J. Insect. Physiol.* **9**, 777 (1963).
- (19) Spencer, E. Y., *Can. J. Biochem.* **39**, 1790 (1961).

Received for review February 15, 1965.
Accepted May 25, 1965. Investigation supported in part by Public Health Service Research Grant GM 07804 from the National Institutes of Health.

INSECTICIDE SCREENING

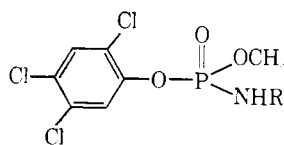
Synthesis and Insecticide Activity of Methyl 2,4,5-Trichlorophenyl Phosphoramidates

E. H. BLAIR and J. L. WASCO
Edgar C. Britton Research
Laboratory, The Dow
Chemical Co., Midland, Mich.

E. E. KENAGA
Biproducts Center,
The Dow Chemical Co.,
Midland, Mich.

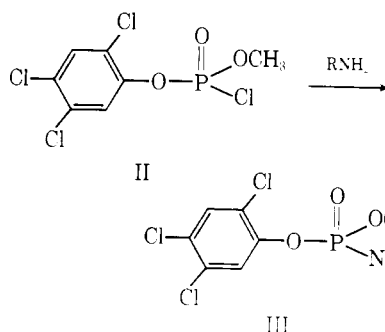
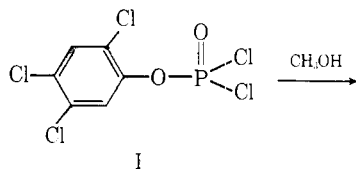
The synthesis, physical properties, and insect toxicities of a series of methyl 2,4,5-trichlorophenyl phosphoramidates are described. The amidophosphates were prepared by the controlled methanolysis and aminolysis of 2,4,5-trichlorophenyl phosphorodichloridate. While the amidophosphates show a wide spectrum of insecticidal activity, practical use against agricultural pests is limited by phytotoxicity to host plants and short residual toxicities to insects on treated foliage, soil, or aqueous habitats.

THE synthesis, physical properties, and insect toxicities of a series of *O*-methyl *O*-(2,4,5-trichlorophenyl) phosphoramidates were recently reported (2). As a continuing part of this study we have prepared the corresponding phosphoramidates in high purity for comparative insecticidal evaluation,



Chemical Studies

2,4,5-Trichlorophenyl phosphorodichloridate appeared to be an ideal starting material, since many phosphorus acid chlorides of this type are readily prepared by heating a phenol with excess phosphoryl chloride in the presence of a metal halide catalyst (8, 10). The stepwise esterification and amidation of this dichloridate under controlled conditions would be expected to give the desired methyl 2,4,5-trichlorophenyl phosphoramidates.



We had difficulty, however, in preparing the 2,4,5-trichlorophenyl phosphorodichloridate using magnesium chloride or magnesium metal as a catalyst. Yields ranged from 0 to 45%. These results are in agreement with those of Orloff, Worrel, and Markley (8), who found that the yield of dichloridate was decreased by the presence of electron-withdrawing substituents in the aryl group. We have noted that traces of catalyst in the crude product appear to promote disproportionation at distillation temperatures.

An improved method for the preparation of 2,4,5-trichlorophenyl phosphorodichloridate was to add molten 2,4,5-trichlorophenol to an excess of phosphoryl chloride containing pyridine equimolar to the amount of phenol. The pyridine hydrochloride was filtered

and the product distilled under reduced pressure.

Very little information outside the patent literature (7, 5, 9) is available on the esterification and amidation of aryl phosphorodichloridates. Orloff, Worrel, and Markley (8) prepared triesters by the solvolytic reaction of aryl phosphorodichloridates with alcohols.

We have prepared triesters in a similar manner. Dimethyl 2,4,5-trichlorophenyl phosphate (IV) was prepared in high yields by treating I with excess methanol.

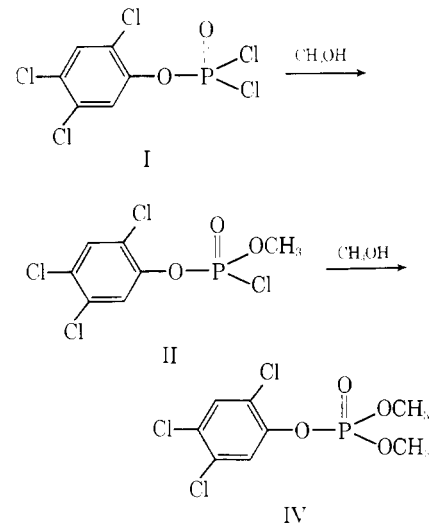
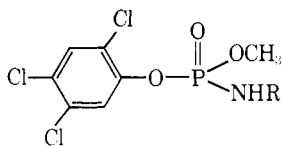


Table I. Physical and Analytical Data on Methyl 2,4,5-Trichlorophenyl Phosphoramidates



R	Yield, ^a %	M.P., °C.	Analysis, %					
			Nitrogen		Chlorine		Phosphorus	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
—H	75	123–124 ^b	4.82	4.96	36.70	36.80		
—CH ₃	68	99.5–100.5 ^b	4.60	4.52	35.00	35.00	10.17	10.15
—C ₂ H ₅	77	67–68 ^c	4.40	4.62	33.40	33.40		
—C ₃ H ₇	25	52–53 ^c	4.21	4.28	32.00	32.04	9.32	9.18
—CH(CH ₃) ₂	62	83–84 ^c	4.21	4.19	32.00	32.00		
—C ₄ H ₉	43.5	31–32 ^c	4.04	4.07	30.69	30.56	8.94	8.90
—CH(CH ₃)C ₂ H ₅	69	64–65.5 ^c	4.04	3.87	30.69	30.98	8.94	8.97
—CH ₂ CH(CH ₃) ₂	62	58–59 ^c	4.04	3.93	30.69	30.70	8.94	8.90
—C(CH ₃) ₃	59	91–92 ^c	4.04	4.15	30.69	30.70		

^a Yield of purified material.

^b Recrystallized from methanol.

^c Recrystallized from petroleum ether (30–60°).

While Orloff *et al.* reported that the methanolysis of an aryl phosphorodichloride proceeded in two stages, they made no attempt to limit the reaction to the first stage.

Mathieson and Russel (4) reported the stepwise alkoxylation of phenyl phosphorodichloridate with butanol and undecanol in the presence of pyridine. This method, however, was not suitable for the preparation of the monochloride (II) because of the rapid dealkylation of the methyl ester by the tertiary base.

Our studies of the solvolysis of aryl phosphorodichloridates have shown that equimolar amounts of methanol and dichloridates react to give a mixture containing variable amounts of unreacted dichloridate (I) and dimethyl ester in addition to the desired monomethyl phosphorochloridate (II). This mixture on treatment with an aliphatic amine gave the desired phosphoramidate (III) contaminated with appreciable amounts of dimethyl ester (IV) and aryl *N,N'*-dialkyl phosphorodiamidate, the latter resulting from amidation of dichloridate (I).

Since the insecticidal properties of the methyl 2,4,5-trichlorophenyl phosphoramidates were to be determined, it was necessary that the dimethyl ester and the diamide be absent, for these impurities would also be expected to have biological properties.

The synthesis procedure recently described for the preparation of certain aryl methyl methylphosphoramidates (6) was found suitable for the preparation of methyl 2,4,5-trichlorophenyl phosphoramidates.

This method uses excess methanol (about 125% of theory) to convert all the 2,4,5-trichlorophenol phosphorodichloridate to the desired monochloride (II) and dimethyl ester. On treatment with excess aliphatic amine, II is

amidated to III and the dimethyl ester (IV) is dealkylated to a water-soluble salt (6).

The rate of amide formation was considerably more rapid than that previously noted with the thio analogs (2), indicating the high electrophilic character of the phosphoryl group.

While the amidation reaction was rapid, the dealkylation of the dimethyl ester required 2 to 6 hours, depending on the concentration and structure of the amine. The rate of dealkylation appeared to decrease with large bulkier amines, undoubtedly because of steric effects. The methyl 2,4,5-trichlorophenyl phosphoramidates were resistant to dealkylation.

All the methyl 2,4,5-trichlorophenyl phosphoramidates were crystalline solids with well defined melting points. Crystallization of the butylamide, however, was difficult. This amide was distilled under high vacuum and kept at 25–28° C. for 2 months, during which time it slowly crystallized (m.p. 30–32°). On recrystallization from petroleum ether it melted at 31–32°. Using this product as a source of seed material, other preparations of the butylphosphoramidate could be crystallized without distillation.

The methyl 2,4,5-trichlorophenyl phosphoramidates used for insecticidal evaluation were found to be pure by vapor phase chromatography, infrared, and nuclear magnetic resonance spectroscopy. The correlations between infrared spectra and the structure of these phosphoramidates have been reported by Nyquist (7). The physical properties and analytical data are listed in Table I.

Synthesis Procedures

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are corrected. Vapor

phase chromatographic analyses were performed with a 2-foot × 0.25-inch column of 20% silicone gum rubber on Chromosorb P (60- to 80-mesh) in an F&M Model 500 programmed temperature gas chromatographic apparatus. All phosphorus compounds except the methyl 2,4,5-trichlorophenyl phosphorochloridate were analyzed by vapor phase chromatography. The latter decomposed on the heated column but did not interfere with the determination of the other compounds.

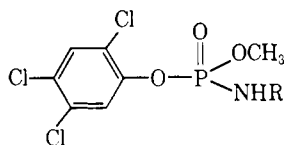
2,4,5-Trichlorophenyl Phosphorodichloridate. Two moles (395 grams) of molten 2,4,5-trichlorophenol was added over a period of 1 hour to a well stirred solution of phosphoryl chloride (1 liter) containing 158.2 grams (2 moles) of pyridine. External cooling was necessary to keep the temperature below 28° during the addition. After standing overnight, the pyridine hydrochloride was filtered and the excess phosphoryl chloride distilled from the product. Final traces were removed by reduced pressure. Pyridine hydrochloride was slightly soluble in the phosphorus acid chloride mixture and volatilized into the condenser, where it solidified. At times it was necessary to shut down the distillation in order to remove the solids. The 2,4,5-trichlorophenyl phosphorodichloridate was distilled through a short-path column at reduced pressure [b.p. 113.5–15° (0.25 mm.), *n*_D²⁰ 1.5674, *d*₄²⁵ 1.6538 (yield 68.5%)].

Analysis. Calculated for C₆H₂Cl₃O₂P: Cl, 56.00; P, 9.85. Found; Cl, 56.43; P, 9.78.

Methyl 2,4,5-Trichlorophenyl Isobutylphosphoramidate. Four grams (0.125 mole) of methanol dissolved in 30 ml. of carbon tetrachloride was added in 15 minutes to a stirred solution of 31.4 grams (0.1 mole) of 2,4,5-trichlorophenyl phosphorodichloridate in 200 ml. of carbon tetrachloride at 25°. After 30-minute stirring at room temperature the methanolysis product was purged with nitrogen to remove hydrogen chloride. An analysis of this product by gas chromatography showed the absence of unreacted dichloridate and the presence of dimethyl 2,4,5-trichlorophenyl phosphate. Twenty grams (0.272 mole) of isobutylamine was added to the methanolysis product in 15 minutes. The reaction was exothermic and it was necessary to use an ice bath to keep the temperature below 30°. An analysis of products via vapor phase chromatography 1.5 hours after the amine addition indicated the absence of the dimethyl ester. The amidation product was washed four times with water to remove the amine hydrochloride and the amine salt of the dealkylated dimethyl ester and dried. The solvent was removed at reduced pressure, leaving 31 grams of oil which solidified on standing. Recrystallization of the solids from 50 ml. of hexane yielded 23 grams (66.5%) of crystals (m.p. 54–55°). One more recrystallization gave an analytical sample (m.p. 58–59°).

Methyl 2,4,5-Trichlorophenyl Butylphosphoramidate. To a stirred solution of 62.8 grams (0.2 mole) of 2,4,5-trichlorophenyl phosphorodichloridate in

Table II. Insecticidal Activity of Methyl 2,4,5-Trichlorophenyl Phosphoramidates



R	LD	Screening Tests (Insect Species ^a , P.P.M.)								Topical Tests, µg. per Female Housefly
		2SSM	MBB	PC	SAW	BA	AR	HF	CFB	
H	50	P	220	70	P	P	100	70	P	0.084
	95	P	320	120	P	P	200	170	P	0.20
Methyl	50	9	7	65	300	220	90	50	300	0.076
	95	20	13	100	P	320	120	70	P	0.12
Ethyl	50	6	70	50	400	35	125	17	400	0.05
	95	9	85	65	P	50	190	28	P	0.076
<i>n</i> -Propyl	50	18	35	35	P	220	110	20	P	0.067
	95	28	55	45	P	320	160	30	P	0.104
Isopropyl	50	6	40	12	450	220	12	12	330	0.036
	95	9	60	17	P	320	18	18	500	0.094
<i>n</i> -Butyl	50	P	52	70	P	P	P	45	P	0.166
	95	P	68	170	P	P	P	110	P	0.27
<i>tert</i> -Butyl	50	11	65	6	170	P	11	17	14	0.35
	95	15	110	8	500	P	15	20	18	0.86
<i>s</i> -Butyl	50	40	50	45	70	250	7	10	35	0.152
	95	130	140	60	170	P	12	15	46	0.230
Isobutyl	50	P	26	20	P	70	38	7	70	0.18
	95	P	40	30	P	80	50	10	80	0.29

^a 2SSM. Two-spotted spider mite
 MBB. Mexican bean beetle
 PC. Plum curculio
 SAW. Southern armyworm
 BA. Bean aphid
 AR. American cockroach
 HF. Housefly
 CFB. Confused flour beetle
 P. >500 p.p.m.

400 ml. of carbon tetrachloride, maintained at 25°, was added a solution of 8 grams (0.25 mole) of methanol in 50 ml. of carbon tetrachloride in 30 minutes. After additional 30-minute stirring at room temperature the methanolysis product was purged with nitrogen. Forty grams (0.545 mole) of *n*-butylamine was then added with cooling and the amidation product was stirred at room temperature for 3 hours. The reaction mixture was washed four times with water and dried, and solvent was removed. An analysis of this mixture showed the presence of dimethyl ester. The mixture was redissolved in 200 ml. of carbon tetrachloride and treated with 6 grams of butylamine for 5 hours. The solvent and excess amine were removed under reduced pressure. The mixture was then taken up in 400 ml. of hexane, and washed twice with 100 ml. of 0.5*N* NaOH and six times with water. Removal of solvent left 36 grams of light red oil which was distilled through a 1-foot Claisen head still at 0.3-micron pressure. Attempts to crystallize the colorless oil which distilled at 102–10° (43.5% of theory) by normal techniques were unsuccessful. When stored at 25–28° for 2 months the amide slowly crystallized to a single large white crystal, (m.p. 30–32°). On recrystallization from petroleum ether (30–60°) it melted at 31–32°.

Using this product as seed material, other preparations of the butylphosphoramidate were crystallized without distillation. ▮

Insecticide Testing Procedures and Results

The test methods used for screening and topical evaluation were as reported previously (2). The LD₅₀ and LD₉₅ for each compound on eight species are given in Table II. The methyl 2,4,5-trichlorophenyl phosphoramidates show a rather wide spectrum of insecticidal activity; however, practical use against agricultural pests is limited by phytotoxicity to the host plants and/or short residual toxicity to insects on treated foliage, soil, or aqueous habitats. Some members of this series, particularly the ethylamide derivative, are very effective, as shown by the housefly residual Panel Test (7). The ethyl derivative had a residual LD₉₅ of 189, 10, and 0 days at 40, 20, and 10 mg. per square foot, respectively.

The topical LD₅₀ ratings on the housefly adult are in fairly close agreement with those of Fukuto *et al.* (3), where the compounds tested are identical.

Literature Cited

- (1) Blair, E. H. (to Dow Chemical Co.), U. S. Patent 2,971,974 (Feb. 14, 1961).
- (2) Blair, E. H., Kauer, K. C., Kenaga, E. E., *J. Agr. Food Chem.* **11**, 237 (1963).
- (3) Fukuto, T. R., Metcalf, R. L., Winton, M. Y., March, R. B., *J. Econ. Entomol.* **56**, 808 (1963).
- (4) Mathieson, D. W., Russel, D. W., *J. Pharm. Pharmacol.* **9**, 612 (1957).
- (5) Moyle, C. L., Wade, L. L. (to Dow Chemical Co.), U. S. Patent 2,944,937 (July 12, 1960).
- (6) Neely, W. B., Unger, I., Blair, E. H., Nyquist, R. A., *Biochem.* **3**, 1477 (1964).
- (7) Nyquist, R. A., *Spectrochim. Acta* **19**, 713 (1963).
- (8) Orloff, H. D., Worrel, C. J., Marklev, F. X., *J. Am. Chem. Soc.* **80**, 734 (1958).
- (9) Wasco, J. L., Wade, L. L., Landram, J. F. (to Dow Chemical Co.), U. S. Patent 2,929,762 (March 22, 1960).
- (10) Zenftman, H., Preprint Division of Paint, Plastics, and Printing Ink Chemistry, Vol. 18, No. 2, 134th Meeting, ACS, Chicago, Ill., September, 1958, p. 361.

Received for review November 19, 1964.
 Accepted May 5, 1965.