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ORGANOPHOSPHORUS INSECTICIDES

Dimethyl 2,2-Dichlorovinyl Phosphate (DDVP), an Organic Phosphorus Compound Highly Toxic to Insects

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The presence of traces of a highly toxic impurity in a technical grade of the new insecticide O,O-dimethyl 2,2,2-dichloro-1-hydroxyethyl phosphonate was observed. Determination of chlorine and phosphorus in isolated material indicated the impurity was a dehydrohalogenation product. It was found that O,O-dimethyl 2,2,2-dichloro-1-hydroxyethyl phosphonate could readily be dehydrohalogenated with alkali to a product having insecticidal properties equivalent to the impurity originally observed. Subsequent work has shown that dehydrohalogenation is accompanied by rearrangement to dimethyl 2,2-dichlorovinyl phosphate. The toxicity of the compound is about equivalent to parathion against houseflies but significantly less against rats.

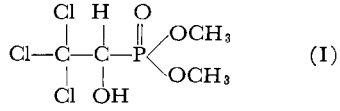
EXPERIMENTS on the toxicity of vapors of insecticidal compounds were conducted by passing air over the materials and exposing flies to the treated air. It was noticed that one of the organic phosphorus compounds under test gave unusually high fly mortality initially, but continued aeration of the sample produced no highly toxic vapors. This suggested that the initial effectiveness was due not to the compound itself but to a highly volatile impurity. These initial observations were made by W. F. Buren, V. A. Sedlak, and G. W. Pearce of this laboratory.

Analysis by a molybdenum blue colorimetric method showed a relatively high phosphorus content in the air initially, which decreased on continued aeration. The correlation between fly kill and phosphorus content, shown in Table I, indicates that the fly mortality rapidly becomes insignificant as the phosphorus concentration drops to 0.32 γ per liter of air and levels off. This behavior provided experimental evidence that a toxic impurity was present in the compound under test. The total amount of impurity present was calculated to be 0.1 to 0.2% based on the weight of material aerated and the total material in the air during the period of high mortality.

Table I. Correlation of Phosphorus Concentration in Air with Fly Mortality

Phosphorus, γ/Liter Air	Female Housefly Mortality, %
1.8	100
0.94	100
0.32	4
0.18	1.3
0.14	1.3

The material in which the highly toxic impurity was found, Bayer L 13/59 (Dipterex), is a commercial preparation of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate (I), whose structural formula is:



(I)

Isolation

On the basis of the foregoing evidence, efforts were made to isolate the toxic impurity in amounts large enough to identify. As no chemical method of analysis was available for tracing the impurity, bioassay techniques using houseflies were used throughout this work.

Because the unknown impurity was volatile, its recovery from air passed over relatively large quantities of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate appeared feasible. Accordingly, adsorption on Celite-545 and condensing in dry ice traps and solvent traps were attempted. Generally, the results were disappointing, in that the recoveries were low and the product recovered was still highly impure. However, microanalysis indicated that the material being sought probably had an atomic ratio of chlorine to phosphorus of less than 3 (*O,O*-dimethyl-2,2,2-trichloro-1-hydroxyethyl phosphonate has a theoretical ratio of 3).

Concentration of the active impurity by fractional crystallization was attempted; but although the impurity was concentrated, it could not be isolated in a sufficiently pure state.

The most successful concentration of the desired compound was accomplished by repeated washing of an ether solution with water, which removed most of the *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate, leaving the highly

toxic impurity in the ether phase. Products obtained by this procedure were subjected to countercurrent distribution studies, using an ether-acetone-water mixture and also a Skellysolve A–water mixture. Using these solvent pairs, a highly potent fraction which exhibited constant distribution characteristics was isolated. The amount of potent material obtained amounted to approximately 0.03% of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate. Microanalyses again indicated a chlorine-to-phosphorus ratio of less than 3.

As the material in question seemed to be a degradation product containing less than 3 atoms of chlorine, the possibility of synthesizing the unknown material by partially dechlorinating *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate was considered. Upon the slow addition of 1 mole of sodium hydroxide to 1 mole of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate in aqueous solution an oily material separated out. This product proved to have a biological activity against houseflies comparable to that of the material isolated directly from *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate. It contained 32.5% chlorine and on the basis of 2 atoms of chlorine per molecule had a molecular weight of 218. As this alkaline degradation product appeared to have toxic properties equal to the impurity native to it, further attempts to isolate and identify the impurity were abandoned. All subsequent effort was devoted to chemical identification of the alkaline degradation product.

Alkaline Degradation Product

Molar quantities of the alkaline degradation product were prepared by slow addition of 1 liter of 5*M* sodium hydroxide to a vigorously stirred solution of 5 moles of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate dissolved in 15 liters of water at room temperature. After the product had settled out, most of the clear water layer was siphoned off. The remaining water and product were separated in a separatory funnel and the product was taken up in ether. The ether solution was washed several times with equal volumes of water, dried over anhydrous sodium sulfate, and filtered, and the ether was distilled, the last traces being removed under vacuum. Fifty per cent yields of a good grade of technical material were obtained by this technique. Because the reaction is a dehydrohalogenation, it is possible that yields approaching stoichiometric proportions could be realized under the proper conditions.

The material was purified by distillation. In general, the product appeared to be heat-sensitive, so that short distillation times at low pressures were required. What appeared to be the purest fractions obtained were prepared by fractionation in an unpacked vacuum-jacketed (silvered) column 6 mm. in inside diameter and 30 cm. long. The distillation was carried out at a nominal pressure of about 1 mm. and the head temperature stayed fairly constant at 84° C. A summary of analyses of middle fractions from this distillation is presented in Table II.

Table II. Analysis of Distilled Fractions

Refr. Index 25°	Found, % Cl	Found, % P	% of Theoretical[a] Cl	% of Theoretical[a] P	Molar Cl/P
1.4519	31.0	13.9	96.6	99.2	1.95
1.4519	31.5	14.2	98.2	101.4	1.94

[a] Molecular weight of 221 assumed on basis of loss of 1 mole of HCl from parent compound (I).

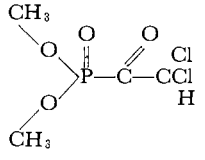
Table III. Comparative Toxicity of Dimethyl 2,2-Dichlorovinyl Phosphate to Houseflies[a]

	Approx. LD_{50}[b], γ/Fly
I (tech.)	0.2
DDVP (tech.)	0.03
DDVP (purified)	0.022
Parathion (tech.)	0.023

[a] Data given and all bioassay work supplied by D. A. Lindquist, formerly of this laboratory, now at Iowa State College, Ames, Iowa.
[b] Topical applications.

These data confirmed the preliminary observation that the atomic ratio of chlorine to phosphorus was less than 3 to 1. Molecular weights calculated from the chlorine and phosphorus analyses given in Table II on the assumption that no major change in molecular size occurred vary from 218 to 229. The vapor pressure characteristics indicated that no great change in molecular size was involved. This assumption proved correct, as found by a direct determination of molecular weight. Using a modified Signer method (*4*) with azobenzene as a reference and ether as solvent, a value of 227 was obtained, which agrees very well with the values calculated from the chlorine and phosphorus determinations. On the basis of the foregoing it was evident that the alkaline degradation of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate consisted in the loss of one atom of chlorine and probably one atom of hydrogen. Therefore, a dehydrohalogenation was considered to be the major change in the empirical composition of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate when treated with one mole of alkali. Other changes such as hydrolysis of the ester linkages or loss of oxygen would have been detected by salt formation or greater change in molecular size than that observed. Dehydrohalogenation gives a product having an empirical composition of $C_4H_7O_4PCl_2$ (II).

Several structural formulas were possible on the basis of this information. Initially it was assumed that the hydroxyl group was intact, but later considerations showed that this was not the case. Final confirmation of this decision was obtained later by infrared spectra. A rearrangement therefore accompanied or followed the dehydrohalogenation reaction. The most logical rearrangement appeared to be formation of the α-keto phosphonate:

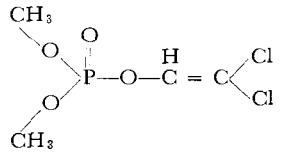


O,O-Dimethyl dichloroacetyl phosphonate (III)

Kabachnik and Rossiĭskaya (*7*) state that α-keto phosphonic acid esters readily form *p*-nitrophenylhydrazones, which are usually more soluble in ethyl alcohol than the hydrazine reagent. An orange red precipitate was obtained on heating II with 2,4-dinitrophenylhydrazine, followed by acidification with hydrochloric or sulfuric acids. This derivative was found to be the dinitrophenyl osazone of glyoxal. It contained no chlorine or phosphorus, melted with decomposition at 322° C. (*6*, *10*, *11*), and gave a blue color with sodium hydroxide in the presence of ethyl alcohol (*2*). Although the hydrazone was not obtained, this did not appear to eliminate the presence of the carbonyl group, as a reaction had taken place which could be interpreted as indicative of the carbonyl group at the alpha-carbon. The phosphorus-carbon bond of α-keto phosphonic acids has been found to be extremely heat-sensitive (*8*) and more unstable than other phosphorus-carbon linkages. Rupture of the phosphorus-carbon bond to form a glyoxal did not therefore seem to be unlikely. Furthermore, heating II, especially in the presence of acids, gave as a decomposition product an aldehyde, which appeared to be dichloroacetaldehyde. The latter is known to give osazones of glyoxal (*3*). The aldehyde obtained from the thermal decomposition of II gave a 2,4-dinitrophenyl osazone identical with that obtained from II directly.

As the reaction with dinitrophenylhydrazine did not give conclusive evidence of the carbonyl group, recourse was made to ultraviolet absorption spectra. No peaks were found at the wave lengths associated with carbonyl absorption in the usual solvents. The evidence for III was therefore not very conclusive.

Another possible configuration for II is:



Dimethyl 2,2-dichlorovinyl phosphate (IV) (DDVP)

The production of IV by alkaline dehydrohalogenation of I would involve a rearrangement from a phosphonate to a phosphate. Such a rearrangement seemed unlikely, as it involves formation of a tertiary phosphate ester under conditions that might normally be expected to favor hydrolysis of the ester. However, the extensive work of Barthel and coworkers (*1*) has clearly demonstrated by both chemical and physical methods that the dehydrohalogenation of I with alkali is accompanied by rearrangement to produce the vinyl phosphate, IV. They have also pointed out the significance of the rearrangement reaction and its potential use as a method of synthesizing other vinyl phosphates. Evidence obtained by the authors confirms the findings of Barthel and coworkers (*1*).

Among the early observations made on the compound under question was the fact that it readily absorbed bromine. Although attempts to isolate the bromine derivative were unsuccessful, the absorption of bromine can be considered as strong evidence of a double bond. The compound also reacted readily with potassium permanganate. The significance of the latter reaction as an indication of the double bond seemed questionable, since the compound appeared rather unstable and might be subject to attack by strong oxidizing agents at points other than a double bond. The negative evidence for a carbonyl group obtained from ultraviolet spectra can be considered as suggesting the alternative vinyl structure.

The strongest evidence of a vinyl structure is based on infrared absorption spectra. A comparison of spectra obtained on I and its dehydrohalogenation product clearly indicated that the hydroxy group was no longer present after dehydrohalogenation. At the same time strong bands at 1650 and 980 cm.$^{-1}$ appeared, both of which are strong evidence of the vinyl structure. Further evidence based on infrared spectra was obtained by a study of the spectra of the vinyl phosphate compound, *O,O*-diethyl 2-chlorovinyl phosphate, reported by Corey and coworkers (*5*). (A purified sample was supplied through the courtesy of the Shell Development Co., Denver, Colo.) This material exhibited a strong band at 1650 cm.$^{-1}$ corresponding closely to the dehydrohalogenation product of I. In addition, a strong but somewhat broader band was found around 980 cm.$^{-1}$. Thus, all infrared data would indicate the vinyl structure of IV.

Toxicological Aspects

Table III presents some typical data on the toxicity of dimethyl 2,2-dichlorovinyl phosphate toward houseflies, as compared to I and parathion. These data indicate that the compound is about equivalent to parathion and about ten times more toxic than its parent (I) against houseflies. It has shown particular promise in space spray and poison bait formulations for fly control.

The relative toxicity toward white rats is illustrated by Table IV, which indicates dimethyl 2,2-dichlorovinyl phosphate to be 5 to 10 times less toxic to rats than parathion but about 10 times more toxic than I.

The toxic properties of dimethyl 2,2-dichlorovinyl phosphate toward insects are of a high and potentially useful order. The compound is significantly less toxic to rats than parathion, although a still greater margin of safety toward higher animals is desirable.

Discussion

An organic phosphorus compound of remarkable insecticidal powers has been found and it is probable that its higher esters would also be toxic. The ethyl ester has been made in this laboratory by dehydrohalogenation of the corresponding ethyl ester of *O,O*-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate, and found to have an LD_{50} of about 0.1 γ per fly for topical application. The diethyl 2-chlorovinyl phosphate cited earlier (*5*) is insecticidally active. An LD_{50} of around 0.1 γ per fly for topical application was found for a technical grade sample of this compound supplied to this laboratory. It is possible the dimethyl 2-chlorovinyl phosphate would be more potent. The data on mammalian toxicity of diethyl 2-chlorovinyl phosphate given by Corey and coworkers indicate that it is considerably more toxic to rats than dimethyl 2,2-dichlorovinyl phosphate, but somewhat less effective insecticidally.

Table IV. Acute Toxicity to White Rats of Dimethyl 2,2-Dichlorovinyl Phosphate, Parathion, *O,O*-Dimethyl 2,2,2-Dichloro-1-hydroxyethyl Phosphonate[a]

		DDVP Purified, Mg./Kg.		Parathion (Tech.), Mg./Kg.		I (Tech.), Mg./Kg.	
Application	Sex	LD_{50}	Confidence[b] (19/20) limits	LD_{50}	Confidence (19/20) limits	LD_{50}	Confidence (19/20) limits
Dermal[c]	F	75	59–96	10.9	7.89–12.93	...	...
	M	107	84–137	21.0	14–34	...	...
Oral[d]	F	56	48–65	3.6	3.2–4.0	...	...
	M	80	62–104	13	10.2–16.5	630[e]	568–699

[a] Data supplied by Toxicology Section of this laboratory.
[b] Method of Litchfield and Wilcoxon (*9*).
[c] Xylene solution.
[d] In peanut oil by stomach pump.
[e] Water solution.

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