Evaluation of O,O-Dialkyl S-Alkylthiomethyl Phosphorodithioates

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This paper reports results obtained in a study of phosphorodithioates as systemic insecticides. The objective was to find a compound with long residual activity which would be effective against both sucking and chewing insects. Compounds of the structure $(RO)_2P(=S)-CH_2-S-R'$ were found to be highly effective. They are prepared by reaction of an O,O-dialkyl hydrogen phosphorodithioate, formalin, and a mercaptan. Systemic activity was evaluated against the two-spotted spider mite using excised bean plants. The most promising have R and R′ = ethyl and R = ethyl, R′ = isopropyl. As seed treatments using a 50% activated carbon formulation they are effective against early season cotton pests and show promise against a wide variety of insects on other crops.

THE TERM "SYSTEMIC INSECTICIDE" is now well established in the agricultural chemical vocabulary. By systemic is meant that the compound is absorbed by the plant, is translocated and exerts its action at a point distant from the site of entry. Work with compounds able to do this was first conducted by Hurd-Karrer and Poos (*5*) in 1936 using salts of selenium. The high toxicity of selenium compounds to mammals prevented their use on food crops. They were used extensively against insects on florist crops in the greenhouse.

The next major development in the field of systemics was not reported until 1947, when the results of Schrader's work were published (*10*, *12*). The most recent review of his work was by Geary in 1953 (*1*). The literature on systemics has become voluminous, as indicated by the bibliography in 1954 by Giang (*2*), which contains 455 titles.

Of the many compounds which have been tested as systemics, three have reached commercial usage. The first was schradan (octamethyl pyrophosphoramide). It has been sold in Great Britain and the United States, mostly for use on ornamental plants and is also registered for use on cotton.

Hanane (a mixture of tetramethyl phosphorodiamidic fluoride and octamethylpyrophosphoramide) has been used for control of swollen shoot disease of cocoa in West Africa (*11*). Demeton (a mixture of *O,O*-diethyl *S*-ethylthioethyl phosphorothioate and *O,O*-diethyl *O*-ethylthioethyl phosphorothioate) is the most widely used systemic today. It is registered for use on several crops including cotton, apples, and walnuts.

Although rapidly becoming an established part of our pest-control arsenal, all current systemics have certain shortcomings. They have been ineffective against chewing insects and are phytotoxic in certain types of applications. In common with most other phosphate insecticides, they possess a high level of mammalian toxicity. The effort to find new compounds which will overcome one or more of these disadvantages continues on many fronts.

Various phosphate structures which have shown systemic activity have been discussed by Ivy (*6*). Recently it has been found that the *O,O*-dialkyl *S*-alkylthiomethyl phosphorodithioates, $(RO)_2P(=S)-SCH_2SR'$, also possess outstanding systemic activity. This paper describes the chemical and biological properties of this new series of phosphorodithioates.

Chemical Tests

The *O,O*-dialkyl hydrogen phosphorodithioate intermediates were made by the method of Hoegberg and Cassaday (*3*).

Preparation of *O,O*-Dialkyl *S*-Alkylthiomethyl Phosphorodithioates. The appropriate *O,O*-dialkyl hydrogen phosphorodithioate (1 mole) was permitted to react with 37% formalin (1 mole). This reaction was rapid and slightly exothermic and formed $(RO)_2P(=S)-SCH_2OH$. After addition of the desired mercaptan (1 mole), the reaction mixture was stirred at less than 50° C. for 4 to 16 hours. The product, $(RO)_2P(=S)-SCH_2SR'$, was obtained by washing the reaction mixture with a sodium carbonate solution and stripping under reduced pressure to remove the volatile impurities. The procedure has been reported (*4*).

When the equation

$$(RO)_2P(=S)-SH + CH_2O\ (aq.) + R'SH \rightarrow (RO)_2P(=S)-SCH_2S-R$$

is examined, several products appear theoretically possible. Some of these are: $(RO)_2P(=S)-SCH_2S-P(=S)(OR)_2$, $(RO)_2P(=S)-SCH_2OR'$, $(RO)_2P(=S)-SCH_2OC(=S)-H$, $H_2SP(=S)(OR)_2$, $R'SCH_2SR'$, and $(RO)_2P(=S)-SCH_2OCH_2SR'$

Considering these, it became imperative that the structure of the principal product be determined. It was thought that the unambiguous synthesis of one of the homologs would be sufficient. The compound *S-tert* butylthiomethyl *O,O*-di-*n*-propyl phosphorodithioate was chosen because it was at that time the least toxic to mammals.

S-tert-Butylthiomethyl *O,O*-di-*n*-propyl phosphorodithioate was prepared by a well recognized method, as indicated by the equation

$$(n\text{-}C_3H_7O)_2P(=S)-SK + ClCH_2S-C(CH_3)_3 \rightarrow (n\text{-}C_3H_7O)_2P(=S)-SCH_2SC(CH_3)_3$$

The potassium *O,O*-di-*n*-propyl phosphorodithioate was prepared by the method of Hoegberg and Cassaday (*3*).

The *tert*-butyl chloromethyl sulfide was prepared by the method of Walter, Goodson, and Fosbinder (*13*).

***S-tert*-Butylthiomethyl *O,O*-Di-*n*-propyl Phosphorodithioate.** A solution of potassium *O,O*-di-*n*-propyl phosphorodithioate (75.7 grams, 0.3 mole) in 200 ml. of acetone was added over an 11-minute period to *tert*-butyl chloromethyl sulfide (41.6 grams, 0.3 mole) contained in a 500-ml. three-necked, round-bottomed flask fitted with a stirrer, reflux condenser, addition funnel, and thermometer (immersed in reaction medium). During the addition, the temperature rose from 27° to 35° C., where it was maintained by means of an ice bath. After 20 minutes at 35° C. the cloudy reaction mixture was stirred overnight at room temperature. After filtration through a Hyflo mat to remove the precipitated potassium chloride, the filtrate was stripped (final conditions 100° C. at 0.3 mm.) to leave a clear pale yellow liquid weighing 85.6 grams (90.2% yield); n_D^{25} 1.5171.

Analysis Calculated for $C_{11}H_{25}O_2PS_3$. %P, 9.79; %S, 30.40. Found. %P, 9.60; %S, 30.20.

The product prepared by the general method previously described had a refractive index of n_D^{25} 1.5172.

Calculated for $C_{11}H_{25}O_2PS_3$. %P, 9.79; %S, 30.40. Found. %P, 9.81; %S, 31.0.

Infrared curves of the two products were identical.

Most tests were conducted with compounds of technical grade having a purity of 90 to 95%. However, when compounds VIII, IX, and X (Table I) were purified by low temperature crystallization or distillation, there was no significant change in systemic activity. Studies are in progress to determine physical constants of purified compounds.

Biological Tests

The following procedure was used for evaluating systemic activity.

The two-spotted spider mite (*Tetranychus bimaculatus* Harvey) was used as the test animal. The mites were cultured on bean plants in the greenhouse. Test plants were infested by pinning a leaf section heavily infested with adult mites to each test leaf and allowing the mites to migrate to the fresh tissue. Efforts were made to have approximately 100 mites per leaf. Plants were selected for testing when the first true leaves were fully expanded, but before the first trifoliate developed. Each stem was cut at ground level and inserted in a narrow-mouthed, 2-ounce bottle containing the test solution. The stem was wrapped at the bottle mouth in nonabsorbent cotton to retard evaporation. The bottle was placed in a box provided with a series of slots in the top, through which the stem projected. A constant flow of clean air was drawn past the infested leaves and through the slots by means of a blower connected to an exhaust system. This prevented any vapors of the test compounds from reaching the mites on the leaves.

The test compounds were formulated in water using a complex polyethylene glycol–fatty acid ester emulsifier (Alrodyne 315). One part of the test compound was mixed with two parts of emulsifier; 300 mg. of this mixture and 99.7 ml. of water were shaken together to give complete emulsification. A 1 to 10 dilution of this solution gave the test concentration of 100 p.p.m. Compounds which showed activity at this level were tested at lower concentrations.

Those compounds active at 1 p.p.m. in this test were further evaluated using seed, soil, and foliage applications.

The objectives of a primary evaluation test for any type of biological activity are that it be simple and rapid, so that large numbers of compounds can be tested with as little expenditure of time and effort as possible. It is also important that the compounds be given every possible opportunity to exert any biological activity of which they are capable. These objectives appeared to be satisfactorily accomplished by this procedure which exposed conducting tissues for initial uptake of the candidate systemic. This technique is designed to detect all compounds of possible systemic value but avoids the factor of initial penetration of foliage or root system required for practical use. Several compounds which are lethal to mites in the primary test give no kill when tested by a technique where they are required to penetrate intact tissues.

Alrodyne 315 was selected from a large number of emulsifiers investigated as solubilizers of organic phosphates. It gave a clear homogeneous solution of the short-chain members of this series, but the longer chained compounds produced slightly bluish or cloudy solutions, indicating that probably fine emulsions were formed.

The data presented here are from the primary evaluation test described above.

Structure-Toxicity Relationships

It is apparent from Table I that when R is constant, systemic activity decreases rapidly as the length of R′ increases. When R′ is ethyl or isopropyl, the activity appears to be about the same, but larger groups are less effective, with R′ = dodecyl showing no activity. This relationship of the R′ group appears to hold when R is methyl, ethyl, or isopropyl. When R is propyl, there is so little activity that no comparisons are possible.

Considering the homologs where R is either methyl or ethyl (I *vs.* VIII, II *vs.* IX, etc.), the ethyl compound in most

Table I. Systemic Test Results against Two-Spotted Mite

$$(RO)_2P(S)SCH_2SR'$$

Compound No.	R	R′	LD_{50} Range, Mg./Kg., Mice[a]	% Kill of Mites 100 p.p.m.	10 p.p.m.	5 p.p.m.	1 p.p.m.
I	CH_3—	C_2H_5—	4–16	100	92	91	82
II	CH_3—	Iso-C_3H_7—	4–16	100	94	85	67
III	CH_3—	C_3H_7—	8–32	100	100	81	0
IV	CH_3—	CH_2=CH—CH_2—	16–64	100	100	95	0
V	CH_3—	$(CH_3)_3C$—	16–64	85	0	0	0
VI	CH_3—	$(CH_3)_2CHCH_2$— $(CH_3)_2C$—	...	99	19	0	0
VII	CH_3—	$C_{12}H_{15}$—	...	0	0	0	0
VIII	C_2H_5—	C_2H_5—	1–4	100	100	100	100
IX	C_2H_5—	Iso-C_3H_7—	4–16	100	100	100	98
X	C_2H_5—	C_3H_7—	16–32	100	100	100	55
XI	C_2H_5—	CH_2=CH—CH_2—	4–16	100	100	69	30
XII	C_2H_5—	$(CH_3)_3C$—	1–4	97	63	0	0
XIII	C_2H_5—	C_5H_7—	...	100	90	..	..
XIV	C_2H_5—	*tert*-C_7H_{15}—	16–32	93	0	..	..
XV	C_2H_5—	C_8H_{17}—	...	30	0	..	..
XVI	C_2H_5—	$C_{12}H_{25}$—	...	0	..	..	..
XVII	Iso-C_3H_7—	C_2H_5	64–256	100	93	33	0
XVIII	Iso-C_3H_7—	Iso-C_3H_7—	64–256	100	100	80	13
XIX	Iso-C_3H_7—	C_3H_7	128–256	100	83	..	31
XX	Iso-C_3H_7—	CH_2=CH—CH_2—	16–64	100	100	28	0
XXI	Iso-C_3H_7—	*tert*-C_4H_9	64–256	100	0	..	..
XXII	C_3H_7—	C_2H_5—	64–256	100	0	0	0
XXIII	C_3H_7—	Iso-C_3H_7—	128–512	98	0	0	0
XXIV	C_3H_7—	C_3H_7—	128–256	99	0	0	0
XXV	C_3H_7—	CH_2=CH—CH_2—	64–128	100	0	0	0
XXVI	C_3H_7—	*tert*-C_4H_9—	64–256	3	0	..	..
XXVII	C_4H_9—	*tert*-C_4H_9—	...	0	..	..	..

[a] By intraperitoneal injection using 2 Carworth Farms albino mice (18 to 22 grams) per dose.

cases shows slightly more systemic activity than the methyl. This agrees with the work of Ivy, Rainwater, Scales, and Gorzycki (*7*), Magee and Gaines (*9*), and others, where contact insecticidal activity was considered.

Compounds where R = isopropyl and R = propyl present a contrast (XVII *vs.* XXII, XVIII *vs.* XXIII, etc.), with the isopropyl compounds showing much more activity. This is in contrast to the parathion series, where the propyl and isopropyl homologs are about equal in contact toxicity.

Previous work with many phosphate series has shown that when R contains more than three carbon atoms, the biological activity is lost. Therefore, only a single example where R was butyl was prepared. It was inactive in the systemic test.

It is apparent that in this series there is a direct correlation between mammalian toxicity and systemic activity. Increasing the length of R will give a safer compound, but only with considerable loss of systemic activity. Changes in R′ do not produce significant changes in mammalian toxicity until the chain length is too great for systemic activity.

The most active compounds of this series are VIII and IX. They have been identified in field tests as experimental insecticides 3911 and 12008, respectively. Compound X has also been field tested under the number 12009. It was selected on the basis of its spectrum of activity in contact toxicity tests.

One of the most interesting applications of these compounds is the treatment of cottonseed for protection of young plants against early season pests. A preliminary report of this work has been given by Ivy, Scales, and Gorzycki (*8*).

In field tests during 1954, compound 12008 applied to cottonseed as a 50% powder on activated carbon at the rate of 4 pounds of technical per 100 pounds of seed gave protection against thrips and aphids for 4 to 6 weeks. In greenhouse tests, 3911 has shown considerably longer residual effectiveness and also appears promising against the boll weevil. As foliage sprays and soil treatments, these compounds are effective against aphids, mites, certain scales, leaf hoppers, and flea beetles.

While the results given in this paper show compounds VIII (3911) and IX (12008) to be the most potent systemics, several others have a high enough level of activity to indicate that they may prove useful for specific applications.

Further extensive field testing will be required to determine the place of these compounds in the pest control picture.

Summary

A new series of phosphorodithioates has been prepared by treating an appropriate *O,O*-dialkyl hydrogen phosphorodithioate with formalin and a mercaptan to give $(RO)_2P(S)-CH_2-S-R'$. The systemic activity of these compounds was evaluated against the two-spotted spider mite using excised bean plants. Maximum activity is obtained when R is ethyl. In decreasing order of toxicity are: methyl, isopropyl, and *n*-propyl. Considering R′, highest activity is obtained when it is ethyl or isopropyl. Increasing the chain length decreases the activity, with R = dodecyl showing no toxicity.

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PESTICIDE SAFETY EVALUATION

Mammalian Investigations on *p*-Chlorophenyl Phenyl Sulfone (Sulphenone)

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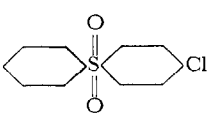
COMPREHENSIVE STUDIES were designed to evaluate the safety of Sulphenone residues which may occur following its use on raw agricultural commodities used for food. In the interest of brevity exploratory studies and those on other than commercial grade have been omitted or markedly condensed.

Materials

The material used in these studies was *p*-chlorophenyl phenyl sulfone, originally designated as Compound R-242 and later as Sulphenone. The samples were received from the Stauffer Chemical Co. at various times throughout the progress of the studies. The original investigations were conducted on a relatively less pure sample of the material than were the later experiments. The active ingredient in all the samples was *p*-monochlorophenyl phenyl sulfone.



The crude material, R-242A, contained approximately 45% of the active ingredient, the technical material, R-242-C and R-242-D, about 70%, and R-242-B was the pure material. The chief impurity is diphenyl sulfone with small quantities of bis(*p*-chlorophenyl) sulfone and of the other monochlorodiphenyl sulfone isomers.

The pure *p*-chlorophenyl phenyl sulfone is a white crystalline powder almost insoluble in water. It has no detectable odor or taste under the conditions of usage. *p*-Chlorophenyl phenyl sulfone