Two Fungicidally Active 5-Chloro-4-aryl-1, 2-dithiol-3-ones Derived from Cumene and p-Cymene

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Two 5-chloro-4-aryl-1,2-dithiol-3-ones were synthesized and found to have high activity. These new compounds were prepared in a three-step process from cumene or p-cymene, sulfur, chlorine, and water. Greenhouse foliage and soil fungicide tests indicated that the materials are fungitoxic to a wide variety of pathogens at low concentrations. Subsequent field tests, primarily with the cumene derivative, showed the compounds to have considerable promise in soil and seed treatment applications. Foliage field tests were less successful, partly because of phytotoxicity at high rates and partly because of lack of persistence under field conditions.

MORE effective and economical fungicides are being sought in many laboratories, as indicated by the large number of patents issued annually on compounds with fungicidal activity. During a research program whose objective was to find such fungicides, two 5-chloro-4-aryl-1,2-dithiol-3-ones (I and II) derived from cumene and p-cymene, respectively, were synthesized and found to have a high degree of activity (2).
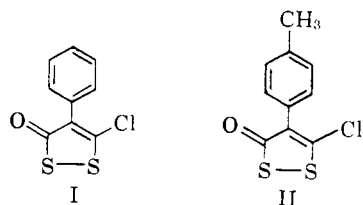
Compound I has been evaluated for several years under code as Hercules 3944, and compound II as Hercules 4223. These materials have very similar activity, but the former was chosen for more extensive evaluation because it is prepared from the lower cost raw material, cumene, and has slightly higher over-all fungicidal activity. In these tests, the compounds have shown considerable promise as seed treatment and soil fungicides.

Experimental

Synthesis of Compounds. These two new compounds were synthesized by the sequence of reactions shown in Figure 1.

The intermediates (IV) may be prepared from cumene and p-cymene, or from the corresponding α-methylstyrenes, by reaction with sulfur as described by Fields (5). To obtain pure, crystalline I and II, the intermediates (IV) must be purified before proceeding with their chlorination; otherwise, oils are obtained from which the pure final products can be isolated only by elaborate chromatographic procedures. Usually one extraction and crystallization of IV from acetone is adequate purification.

These intermediates may be further purified by recrystallization from benzene.

Chlorination of the 4-aryl-1,2-dithiole-3-thiones (IV) in refluxing chloroform solution with three moles of chlorine yields the trichlorinated intermediates (V). These chlorinations are rapid and exothermic except toward the end of the addition; chlorine is passed into the liquid phase at a rate to maintain gentle reflux. The trichlorinated intermediate from the 4-phenyl derivative separates, and more intermediate can be isolated by the addition of hexane to the cooled filtrate. The 4-p-tolyl intermediate requires addition of hexane to the cooled reaction mixture to precipitate the trichlorinated product. Isolation of these chlorinated intermediates is necessary since hydrolyzing them in the reaction mixture without isolation gives oils from which the separation of pure I and II is very difficult.

The trichlorinated intermediates (V) are filtered and immediately added with vigorous stirring to a 2 : 1 benzene-water mixture. As the benzene- and water-insoluble trichlorinated intermediates hydrolyze, the products (I and II) that are formed dissolve in the benzene. These products are then isolated by separating the benzene layer, washing it twice with water, and drying it over sodium sulfate. The solvent is removed by distillation under reduced pressure, leaving residual oils which solidify on cooling. The products so obtained are usually analytically pure, and the yield is 50 to 60% based on IV. 5-Chloro-4-phenyl-1,2-dithiol-3-one (I), obtained by this procedure, is a reddish yellow crystalline compound which melts at 98°–100° C., is soluble in most organic solvents, and insoluble in water. It may be further purified by recrystallization from ethanol to a light yellow crystalline compound which melts at 99°–100° C. Analysis: 15.3% chlorine and 28.0% sulfur. Calculated: 15.5% chlorine and
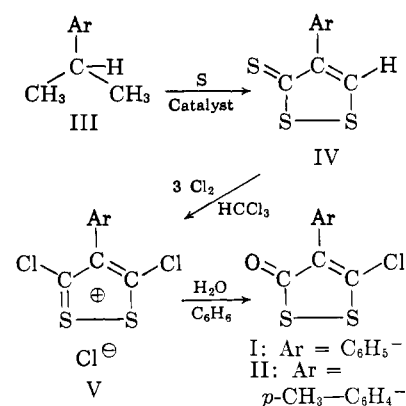

Figure 1. Reactions used to prepare 5-chloro-4-aryl-1,2-dithiol-3-ones

28.0% sulfur. The molecular weight found for this compound by the Rast method was 240; the theoretical value is 228.5. Its ultraviolet spectrum in isooctane (0.04 gram per liter) shows maxima at 228 (log ϵ = 4.0170) and 321 (3.8363), and minima at 261 (3.8745) and 282 mμ (3.3263).

That the chlorine in I was on the dithiole and not on the aromatic ring was shown by a comparison of its nuclear magnetic resonance spectrum with that of the intermediate (IV; R = C_6H_5-). The latter has two kinds of hydrogen in the expected 5 : 1 ratio, whereas the former has but one kind of hydrogen. The spectra were taken in $CDCl_3$, the latter as an 8% solution and the former as a 20% solution, at 60 megacycles per second, with benzene as the external reference; lines on the lower side of benzene have negative values—compound I: −54 c.p.s.; compound IV: −60 c.p.s. (5–6 protons), −116 c.p.s. (1 proton). These spectra were taken with a Varian HR-60 spectrometer.

In a typical run, 380 grams of I was obtained from 588 grams (2.8 moles) of IV (R = C_6H_5), 3500 ml. of chloroform, and 655 grams (9.2 moles) of

Table I. Cotton Soil Fungicide Assay

	Percentage Stand at P.P.M. Rate		
Soil Treatment	40	80	160
Compound I	72	90	92
Captan	66	80	84
Terrachlor	60	86	76
Thiram	34	80	78
Check (untreated)	4		

Table II. Persistence Data on Various Soil Fungicide Treatments Using Cotton Seed

		Percentage Stand at 14-Day Planting Intervals			
Soil Treatment	Concn., P.P.M.	1	2	3	4
Compound I	40	79	3	0	0
	80	92	64	33	0
Zineb	40	41	4	1	0
	80	58	0	1	0
Captan	40	77	0	0	0
	80	96	33	0	0
Check (untreated)		6	1	0	0

chlorine. The chlorine was added over a 4-hour period.

The preparation of 5-chloro-4-(p-tolyl)-1,2-dithiol-3-one (II) was similar. From 628 grams (2.8 moles) of 4-(p-tolyl)-1,2-dithiole-3-thione, 354 grams of II was obtained. The crude, reddish yellow crystalline product (m.p. 63°–70° C.) was recrystallized from ethanol to give a pure, light yellow product (m.p. 75° C.). This product contained 14.6% chlorine and 26.4% sulfur. Theoretical values were 14.8% chlorine and 26.5% sulfur.

Fungicide Assays. Standard spore germination assays were made by the test tube dilution technique and the test fungi *Alternaria oleracea*, *Monolinia fruticola*, and *Venturia inaequalis* at 1, 10, 100, and 1000 p.p.m. concentrations (*12*). Subsequent tests showed that both compounds had ED_{50}'s of 0.3 p.p.m. against the first two test fungi and 0.1 p.p.m. against the last. Foliage disease assays were made according to standard procedures with tomato early blight and tomato late blight fungi at 0.1% concentrations (*11*). Both compounds gave complete control of these pathogens at that concentration. An interesting fumigant phenomenon was observed in these tests. When treated tomato plants inoculated with either *Alternaria solani* or *Phytophthora infestans* were placed in a 90-cubic foot incubation chamber with untreated but inoculated plants, the diseases were controlled on the latter as well as on the former. This apparent fumigant action was also observed in spore germination assays despite physical measurements which indicated that these compounds have negligible vapor pressures at the temperatures involved. This effect may perhaps be due to volatile fragments from slow decomposition of the compounds.

Foliage field tests were carried out in Florida for the control of potato late blight (*18*). Compounds I and II were applied every 6 to 7 days as 45% wettable powders at 2 pounds active compound per 100 gallons of water. Approximately 120 gallons of spray per acre were used. Both compounds checked the disease for 1 to 2 weeks after it appeared, but then became ineffective. Further, some phytotoxicity was observed. The lack of persistence may have been due to light-instability since dilute solutions of I in clear glass bottles were found to

decompose slowly when exposed to sunlight. This decomposition was determined by monitoring the ultraviolet spectrum of the solution. Solutions similarly stored in brown or red glass bottles were comparatively stable. An effort to circumvent these problems by formulating the compounds in polyvinyl acetate was only partially successful in prolonging activity and reducing phytotoxicity.

Greenhouse soil fungicide assays were carried out by planting pea seed in soil infested with *Pythium debaryanum* and *Phthium ultimum*, which cause pre-emergence damping-off. Infested soil was thoroughly mixed with the test compound at the desired test concentrations, usually at 40, 80, and 160 p.p.m. Then 10 pea seeds were planted in five replicates of this soil at a depth of 1 inch; 14 days after planting, the number of emerged plants was determined per replicate, and compared with untreated checks and with replicates treated similarly with presently used commercial materials. To determine the persistence of the test compounds in the soil, the plants were pulled and the replicates reseeded. After each 14-day period, the effect was evaluated as before.

Soil fungicide tests were also made in soil infested with *Rhizoctonia solani* and planted to cotton seed as described above.

Table I summarizes results from a typical soil fungicide test. Results from a typical persistence test are given in Table II.

Discussion

The chlorination of 1,2-dithioles has not been studied previously except for the work of Spindt *et al.* (*17*). These investigators reported that the chlorination of certain 4-alkyl-substituted 1,2-dithiole-3-thiones resulted in 3,3-dichloro-1,2-dithioles that were hydrolyzable to the corresponding 1,2-dithiol-3-ones. No trichlorinated 1,2-dithioles or chlorine-containing 1,2-dithiol-3-ones were reported by these workers. Recently, however, some chlorinated 1,2-dithiol-3-ones have been prepared by other methods (*1*, *15*).

The inherent fungitoxicity of these

compounds was first indicated in the spore germination assays. Greenhouse foliage tests showed that both compounds completely controlled tomato early and late blight at 0.1% concentrations. However, subsequent foliage field tests were less successful, apparently because of too rapid deterioration of the compound under field conditions. There was some evidence that ultraviolet light accelerated this deterioration. Also, the compounds were phytotoxic to some foliage at high rates of application. Formulation of the compounds in nonvolatile liquids and in polymeric compositions was partially successful in prolonging activity and reducing phytotoxicity.

The correlation between greenhouse and field results in soil and seed treatment applications was considerably better. The compounds, especially I which was tested more extensively, proved to be effective against a variety of seed- and soil-borne pathogens, including many of the important *Pythium*, *Rhizoctonia*, and *Fusarium* species. Typical data are given in Tables I and II. Detailed evaluation reports on these materials are published elsewhere (*3*, *4*, *6*, *9*, *10*, *13*, *14*, *16*).

These compounds appear to have a low order of mammalian toxicity. Compound I has an acute oral LD_{50} in rats of >10,000 mg. per kg. of body weight, the highest concentration tested. Acute dermal tests on rabbits resulted in only minor skin irritation at 10,000 mg. per kg. Inhalation tests using mice, rats, and guinea pigs indicated no apparent toxicity. Oral feeding tests at 1 and 5% levels in the diet of rats did not adversely affect the animals. The toxicity tests were performed by other laboratories (*7*, *8*).

Compounds I and II have been formulated as dusts, wettable powders, and emulsifiable concentrates with no difficulties.

Acknowledgment

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FUNGICIDE DECOMPOSITION

The Degradation of Organomercury Fungicides in Soil

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Metallic mercury vapor and trace amounts of phenylmercury acetate (PMA) were present in the air surrounding PMA-treated soil. About equal amounts of the vapors of metallic mercury and a volatile ethylmercury compound were present when ethylmercury acetate was used. With the use of methylmercury compounds, methylmercury vapor was present with trace amounts of mercury vapor. The chloride was about twice as volatile as the dicyandiamide. A large portion of the organic mercurial applied to the soil was found to be in the organomercury form after the lapse of 30 to 50 days. Moisture in soil decreased the amount of escaping organic mercury vapor.

DECOMPOSITION of mercurial fungicides in contact with soil has long been known (*1, 2, 9*). The escape of metallic and organic mercury vapors and the amount of organic mercurial remaining in soil, however, have not been investigated except through indirect biological techniques, because of inadequacy of chemical methods. Booer (*1*), basing his conclusions on biological phytotoxicity experiments, postulated a mechanism for organic mercury decomposition in soil. He suggested that organic mercury compounds reacted with the clay micelle in soil to form an intermediate which subsequently gave a dialkylmercury or diphenylmercury and a mercury-clay compound. Based on this hypothesis, the dialkylmercury compounds would escape into the atmosphere while diphenylmercury would accumulate in the soil. Metallic mercury would result from the further degradation of the mercury-clay compound. However, repeated attempts in this laboratory to detect the disubstituted organic mercury compounds formed in soil through degradation failed, indicating that decomposition was not by Booer's mechanism.

More recently, work has been done on the absorption and inactivation of organomercurials by microorganisms that tolerate and even thrive on mercurials (*3, 8*). It has been postulated that inactivation occurred by the uptake of fungicide by microorganisms, followed by metabolic breakdown and by possible utilization of portions of the byproducts. However, whether or not biological inactiviation and mercury evolution occur together has not been determined.

This paper presents chemical data on the nature of residual mercurials in soil and in the atmosphere surrounding the treated soil to further elucidate the phenomena of degradation in soil.

Experimental

Soil Treatment, Sampling, and Vapor Collection. Puyallup sandy loam, the principal bulb-growing soil and the most extensive agricultural soil in Pierce County, Wash., was used in these experiments. It is an alluvial soil occurring on the floor of the Puyallup and Stuck River Valleys. This soil, taken from the field as required, was air dried several days and passed through a 30-mesh seive to remove rocks and roots. A 650-gram portion of the soil was spread out on a plastic sheet and sprayed with a measured amount of an aqueous mercurial sufficient to give a concentration in soil of about 100 μg. mercury per gram of dry soil. The soil was transferred to a large beaker, and water was added in small increments, while mixing, to bring the moisture contents to the approximate desired level. The soil was mixed until analytically uniform. Where autoclaved soil was used, it was heated 3 hours at 15 pounds steam pressure prior to the addition of mercurials in the manner above. A 50-gram portion of the soil was set aside in a sealed container for analysis within 24 hours.

Soil treated with phenylmercury acetate (PMA) or ethylmercury acetate (EMA) was placed in unglazed clay pots and immediately placed under a bell jar-type adapter connected to an aeration train composed of a carbonate-phosphate and an acid permanganate absorber, previously described (*4*) for fractionation of the vapor into the metallic mercury and monosubstituted organomercury compound. A wet test