Fungitoxicity of Carbamic and Thiocarbamic Acid Esters

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FUNGITOXICITY OF CARBAMIC AND THIOCARBAMIC ACID ESTERS

Saul Rich and James G. Horsfall[1]

Our laboratory has been particularly interested in derivatives of carbamic and thiocarbamic acids since 1938, when we tested our first group of organic compounds for fungitoxicity. In this first group was ethyl-N-phenylthionocarbamate, whose isopropyl ester later proved to be a very active herbicide (Shaw and Swanson, 1953). Our interest in the carbamates and their sulfur analogues was later intensified by the discovery in our laboratory of the fungitoxicity of the ethylenebisdithiocarbamates (Dimond, *et al.,* 1943). The derivatives of carbamic and thiocarbamic acids are a rich source of fungitoxicants, weed killers, and plant growth regulators. As such, they are particularly well suited for studies relating molecular configuration to biological activity.

Previous research on the biological activity of the oxygen containing derivatives has been largely in the field of antimitosis and herbicides. On the other hand, previous research on the biological activity of the sulfur-containing derivatives has been in the area of antifungal materials. Except for a brief paper by Davies and Sexton (1946) little has been done to meld the two. This, we hope to do.

One of the general features of research to date is that all of the oxygen analogues have been tested as esters. On the contrary, the sulfur analogues have usually been tested as metallic salts with very little emphasis on esters.

We shall compare the fungitoxicity of the oxygen and sulfur esters and go as far as the data will permit in relating differences in activity to possible differences in the ability of these compounds to permeate spores.

MATERIALS AND METHODS

We have assembled data on 174 derivatives. The data on fungitoxicity are displayed in the tables. The compounds were obtained from commercial sources, from the Chemical-Biological Coordination Center of the National Academy of Sciences, from various industrial research laboratories, or from the Eastman Kodak Company. The sources are listed in the tables. The compounds have been assayed without further purification.

In all cases we have used the spore germination technique of assaying potency of the test compounds as described by Horsfall and Rich (1951).

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[1] We wish to express our thanks for helpful suggestions in the preparation of the manuscript to our colleagues A. E. Dimond and Raymond J. Lukens and to W. E. Craig, C. P. Lo, and H. F. Wilson of the Rohm and Haas Co., Philadelphia, Pa.

We use two test fungi, *Stemphylium sarcinaeforme* and *Monilinia fructicola.* All compounds are dissolved in a suitable solvent, usually acetone, at 10, 1.0, 0.1, and 0.01 grams per liter, and 0.2 ml is pipetted with a graduate syringe into duplicate depression or culture slides to give 1300, 130, 13, and 1.3 μgm/cm^2 when dried.

The depression is filled with a spore suspension and the spores settle at random onto the dried deposit in the bottom. The concentration of spores is so adjusted as to give 50 spores per low power field of the microscope.

The spores are incubated in moist chambers overnight at about 25°C. and examined next morning with a binocular microscope. Fifty spores in each duplicate are examined and the percentage not germinating is recorded. The one or two per cent of natural mortality is disregarded. If the proportion of natural mortality is higher than one or two per cent, the test is discarded and the compound is rerun.

In comparing compounds we shall use a "toxicity index" which is the sum of the percentage kill figures for the four doses. This is a relative number with a possible maximum of 400.

Normally, we like to use ED 50 values and slopes of dosage-response curves in evaluating fungicides. In this paper, we report the results of a fishing trip in which we have dropped our hook into a wide variety of waters to see where the fish are. Thus, we examine a wide range of compounds and not a detailed study of a few.

In a few places, we do discuss ED 50 values but essentially we shall rely on the toxicity index.

It should be mentioned that the technique described will not adequately appraise the fungitoxicity of compounds with high vapor pressure. In other words, rapidly volatile toxicants will escape when the slides are dried down and may well appear to be non-toxic. If slowly volatile compounds happen to be highly toxic, however, they will kill the check spores and thus be detected.

In presenting a paper on fungitoxicity, one is always confronted with the question as to whether an ungerminated spore is dead or merely temporarily inhibited. To some extent the problem is not critical because in practice, recovery cannot occur as long as the spore remains in contact with the toxicant. To avoid conflict in terminology, however, we shall avoid the term fungicidal or fungistatic, and use fungitoxic.

THE PROBLEM OF PERMEATION

We may reasonably assume that these compounds act inside the fungus cell or spore. This assumption would be less defensible were we dealing with mycelium growing on food that had been treated with the test compounds. In that case the test compound could be acting to prevent absorption of food and thus acting to starve the fungus.

The data, however, do not permit us to distinguish surface activity from internal activity. They do not permit a distinction between adsorption and absorption. This distinction is always a most difficult one to draw in fungicide research. The spores are too small to deal with individually. One cannot easily dissect off the cell wall and analyze the cell contents, although Owens and Miller (1957) have made progress on this problem by using ultrasonic vibrations.

EXPERIMENTAL DATA

The toxicity data are recorded in three tables in an appendix. Table 1 contains the data on all oxygen containing analogues, Table 2 the dimethyldithiocarbamate esters, and Table 3 the bisdithiocarbamate esters. The compounds are arranged in the tables by accession number for convenience in referring to them in the text and in the figures. The names appear in the tables, the structures in the text figures.

In discussing the compounds, we shall deal chiefly with structure-activity relationships. Accordingly, the structures of related compounds and their toxicity indexes are grouped into text figures and discussed that way. The accession number will enable one to refer to the original data in the relevant data table in the appendix.

FUNGITOXICITY OF OXYGEN ANALOGUES

Data on all of the oxygen containing carbamate esters are set forth in Table 1. These will be referred to in the text as the oxygen analogues to distinguish them from the sulfur analogues.

Differential Action on the Test Organisms

Monilinia is vastly more sensitive to the carbamates than is *Stemphylium*. All carbamate esters are at least as toxic to *Monilinia* as to *Stemphylium* and most are significantly more so.

A possible explanation for this differential action is that *Monilinia* produces esterases that hydrolyze the ester linkage and form carbamic acid inside the cell. *Stemphylium* is less efficient in doing so. Shaw and Swanson (1953) similarly show that several species of higher plants vary in their sensitivity to carbamate toxicity.

Effect of the Ester Moiety

Effect of the size of the ester moiety. Since carbamic acids are unstable, we, perforce, had to deal with esters. Most of the tested compounds are ethyl or isopropyl esters; a few are alkyl and aryl esters. On the basis of the shaped-charge hypothesis (Rich and Horsfall, 1952) we may assume that permeation into the fungus cell is related to the length of the alkyl chain in the ester. A few years ago, we investigated this possibility with the esters of nicotinic acid (Horsfall and Rich, 1951). For those esters the potency increases for *Stemphylium* as the chain lengthens up to 6 carbons and then decreases sharply. The potency increases for *Monilinia* up to 8 carbons and then decreases sharply.

Data available for comparable esters in the carbamate series are set forth in Figure 1. In the unsubstituted carbamate series, potency rises from methyl (No. 1189) through ethyl (No. 429) to butyl (No. 1581). Unfortunately, we do not have available in this series an ester of a longer chain alcohol than butyl.

Considering now N-phenylcarbamates, the potency against *Stemphylium* is in the following order: methyl (No. 4L) < ethyl (No. 993) <

Figure 1. Effect of the size of the ester moiety

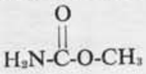
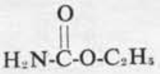
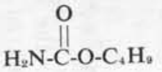
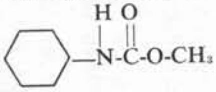
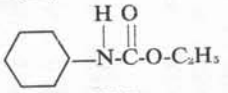
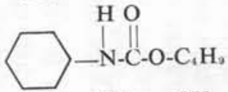
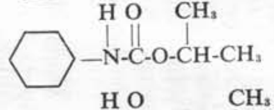
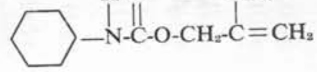
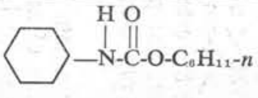
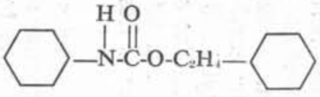
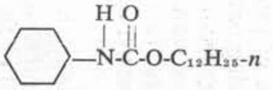
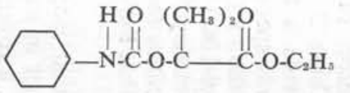
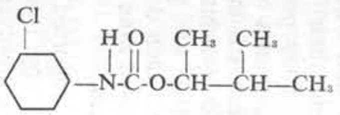
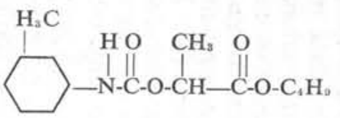
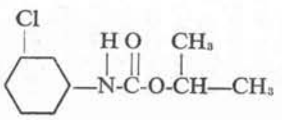
Number	Name	Structure	Toxicity Index *Stemphylium*	 *Monilinia*
		Compounds with unsubstituted nitrogen		
1189	Methyl carbamate	 $H_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}CH_3$	0	0
429	Ethyl carbamate	 $H_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}C_2H_5$	0	6
1581	Butyl carbamate	 $H_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}C_4H_9$	93	89
		Compounds with an N-phenyl substitution		
4L	Methyl N-phenylcarbamate		179	310
993	Ethyl N-phenylcarbamate		169	188
1872	Butyl N-phenylcarbamate		190	258
2690	Isopropyl N-phenylcarbamate		191	205
3336	2-Methallyl N-phenylcarbamate		215	204

Figure 1. Effect of the size of the ester moiety (continued)

Number	Name	Structure	Toxicity Index *Stemphylium*	 *Monilinia*
5306	*n*-Hexyl N-phenylcarbamate		82	400
3416	Phenethyl N-phenylcarbamate		34	244
5305	*n*-Dodecyl N-phenylcarbamate		17	127
3402	N-Phenylcarbamic acid, ethyl β-methyl lactate ester		22	274
3900	2-(3-Methylbutyl) N-(3-chlorophenyl)carbamate		65	261
4799	N-(3-Methylphenyl)carbamic acid, butyl lactate ester		0	239
2687	Isopropyl N-(3-chlorophenyl)carbamate		72	200

isopropyl (No. 2690) = butyl (No. 1872) < 2-methallyl (No. 3336) > *n*-hexyl (No. 5306) > phenethyl (No. 3416) > *n*-dodecyl (No. 5305). The phenethyl, *n*-hexyl, and *n*-dodecyl lipophilic groups may well be too large for *Stemphylium* so that permeation and toxicity is reduced. On the other hand the potency for *Monilinia* continues to rise in the same series (except also for the methyl homologue) to the *n*-hexyl homologue but falls sharply to the *n*-dodecyl. Thus, the optimum size is bigger for *Monilinia* than for *Stemphylium*. This result agrees with many others that we have obtained on these two organisms (Horsfall and Rich, 1951 and 1953). The optimum lipophilic group is invariably larger for *Monilinia* than for *Stemphylium* as would be expected because *Monilinia* contains much more fat in its spores than *Stemphylium* according to Miller and Richter (1960).

Although Shaw and Swanson (1953) do not allude to the point specifically, data from their Table 2 illustrate the herbicidal action of various sized esters. They provide a single number to summarizing the foliar toxicity of carbamates to 8 species of green plants. The toxicity of N-phenylcarbamate esters is in the following order: ethyl-520 < *n*-propyl-690 < isopropyl-660 < *n*-butyl-1000 < *sec*-butyl-1330 > 2-ethylhexyl-690 > lauryl-680. Here, too, potency rises with the size of the ester to the butyl or *sec*-butyl and then declines to the 11-carbon ester. For purposes of comparison, we might note that the benzyl ester is less phytotoxic than any of the alkyl esters.

Sexton (1953) reported that isopropyl N-phenylcarbamate is more effective than the *n*-propyl isomer in suppressing germination of oat seeds. Sexton shows further, however, a reversal of the above trend for length of hydrocarbon tail in the ester — isopropyl = ethyl > *n*-propyl = *n*-butyl. This is an interesting anomaly. Rather than lipid solubility, water solubility may enhance the activity of these compounds against oat seeds.

We have some data on the effect of branching in the alkyl chain of the ester. In our fungitoxicity data the 3-carbon branched chain (isopropyl, No. 2690) is more active than the 2-carbon unbranched chain (ethyl, No. 993) and the 4-carbon branched chain (No. 3336) is as active, possibly more so, than the 4-carbon straight chain (No. 1872). As shown in the next section the unsaturation in the chain of No. 3336 has little effect on the activity.

There are two esters (Nos. 3402 and 4799) that are analogues of lactic acid, a branched chain compound. These are bland to *Stemphylium* but respectably fungitoxic compounds to *Monilinia*.

This is a bit unusual. Normally attaching a branch to a hydrocarbon tail reduces fungitoxicity (Horsfall, 1956). The data indicate that these particular compounds may be acting in the water phase of the spore.

In the case of the phytotoxicity data of Shaw and Swanson *n*-propyl is more toxic than the isopropyl (branched) ester, but the *sec*-butyl is more toxic than the straight chain isomer.

Schneider (1957) gives a few data on fungitoxicity in culture to two wilt fungi. In his data ethyl N-phenylcarbamate (our No. 993) is more active than isopropyl N-(3-chlorophenyl)carbamate (our No. 2687). This is the opposite both to our results on fungi, and to those of Shaw and Swanson on green plants. It should be noted, of course, that Schneider dealt with a growing thallus, we with germinating conidia.

Effect of aryl groups in the ester moiety. As we have just seen, the phenethyl ester (No. 3416) is a reasonably good "shaped charge," especially for *Monilinia*. This suggests an examination of esters that contain other aryl nuclei. The data appear in Figure 2.

We have three phenyl containing esters. One of these is the phenethyl analogue (No. 3416) already noted. It is the most toxic of the three to *Monilinia*. A dicholorophenoxy derivative (No. 3462) and the dimethylaminocarvacryl ester (No. 1180) are both weaker. The weakness of the latter is due in part to the fact that it is an N-methyl, not an N-phenyl compound. Figure 6 below shows that the toxicity is weak for compounds with small N-alkyl groups.

There are three heterocyclic ester analogues in Figure 2 (Nos. 3346, 3391, and 3983). Two of these are startling exceptions to the rule that carbamates are weak spore killers. One of these is No. 3983, which has a 2-heptadecenyl-2-imidazoline group in the ester. The non-conforming high potency of this analogue may well be due to the well-known high potency of the 2-alkyl substituted 2-imidazoline moiety (Wellman and McCallan, 1946). On that account we have bracketed our compound in the table with the heterocyclic nucleus itself (No. 762A), and the potency is essentially the same. Evidently, the ester (No. 3983) is hydrolyzed in the cell, liberating the carbamic acid and the imidazoline.

The other striking exception is No. 3391 (the 2-furfuryl ester). It is worth noting that Mitchell *et al.* (1958) have reported that this compound is highly effective as an internal chemotherapeutant to mitigate the symptoms of southern bean mosaic—and this without phytotoxicity. This compound would seem to be worthy of further trial in plant pathology.

Effect of unsaturation in the alkyl ester moiety. We have data (Figure 3) on 11 unsaturated alkyl esters, all as N-phenyl derivatives. Of these, 9 have unsaturated 3-carbon chains and 2 have unsaturated 4-carbon chains. In all cases the unsaturation occurs between the second and third carbon in the chain.

Five (Nos. 3336, 3596, 5298, 5301, and 5304) contain double bonds and six (Nos. 4256, 4242, 4260, 4440, 5323, and 3774) contain triple bonds.

The two 4-carbon compounds (Nos. 5323 and 3774) may be compared with the available 4-carbon saturated butyl homologue (No. 1872). No. 3774 is about equally toxic with the butyl homologue. No. 5323 is somewhat more directly comparable, but it is chlorinated on the ring and chlorinated on the number 4 carbon as well. It is considerably more fungitoxic than the butyl analogue. We cannot distinguish between the lipophilic effect of the chlorine atom and the toxic effect of the triple bond.

Then, too, the 3-carbon compounds cannot be directly checked because we have available no propyl (saturated) homologue. Data given in Figure 2 suggest, however, that the propyl derivative should be intermediate between the ethyl (No. 993) and the butyl (No. 1872) homologues. If so, then unsaturation does not improve potency appreciably—compare Nos. 5304, 5301, and 3336 with No. 993 and 1872.

There is a fairly direct comparison among the chlorinated derivatives. In this case the 3-chloroallyl compound (No. 3596) is no more fungitoxic than the 2-chloroethyl homologue (No. 3226). It should be more fungitoxic since it has one more carbon.

Figure 2. Effect of aryl groups in the ester moiety

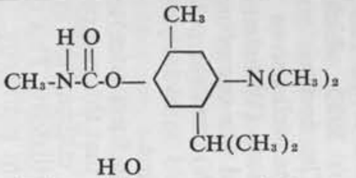
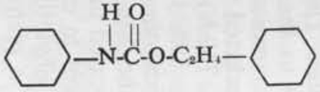
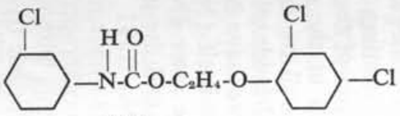
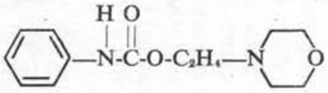
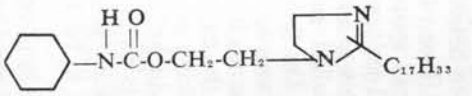
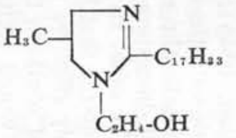
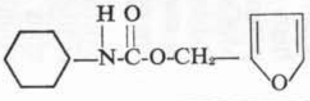
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
1180	5-Dimethylaminocarvacryl N-methylcarbamate		75	129
3416	2-Phenethyl N-phenylcarbamate		34	244
3462	2-(2,4-Dichlorophenoxyethyl) N-(3-chlorophenyl) carbamate		11	136
3346	1-(N-Morpholinyl)-2-ethyl N-phenylcarbamate		100	100
3983	2-[1-(x-Heptadecenyl)-2-imidazolyl] ethyl N-phenylcarbamate		271	356
762A	2-(8-Heptadecenyl)-1-(2-hydroxyethyl)-(4 or 5)-methyl-2-imidazoline		350	400
3391	Furfuryl N-phenylcarbamate		219	290

Figure 3. Effect of unsaturation in the alkyl ester of N-phenyl derivatives

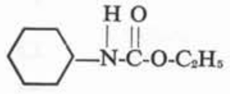
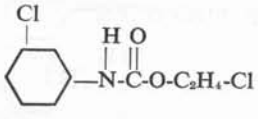
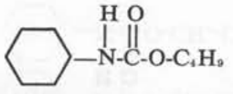
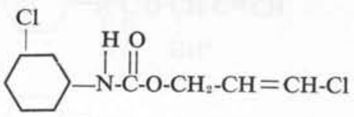
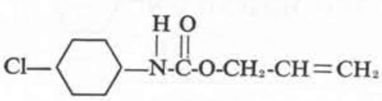
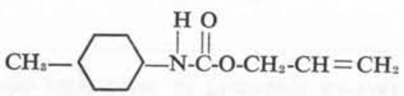
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
		Saturated analogues for comparison		
993	Ethyl N-phenylcarbamate		169	188
3226	2-Chloroethyl N-(3-chlorophenyl) carbamate		275	300
1872	Butyl N-phenylcarbamate		190	258
		Unsaturated 3-carbon analogues		
3596	3-Chloroallyl N-(3-chlorophenyl) carbamate		271	200
5298	Allyl N-(4-chlorophenyl)carbamate		254	335
5301	Allyl N-(4-methylphenyl)carbamate		200	235

Figure 3. Effect of unsaturation in the alkyl ester of N-phenyl derivatives (continued)

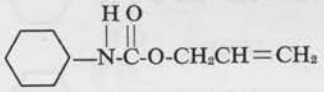
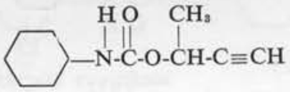
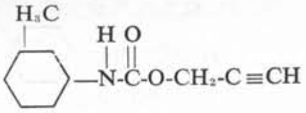
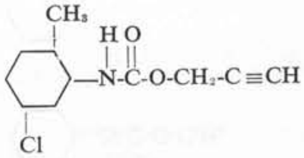
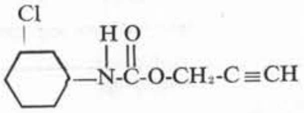
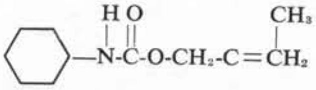
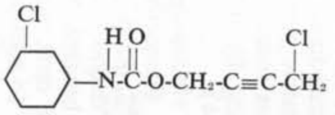
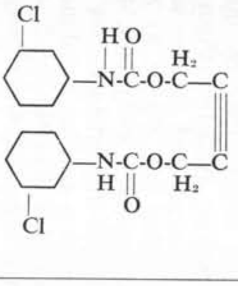
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
5304	Allyl N-phenylcarbamate		105	111
4256	3-(1-Butynyl) N-phenylcarbamate		200	200
4242	2-Propynyl N-(3-methylphenyl)carbamate		113	205
4260	2-Propynyl N-(5-chloro-2-methylphenyl)carbamate		0	314
4440	2-Propynyl N-(3-chlorophenyl)carbamate		113	313

Figure 3. Effect of unsaturation in the alkyl ester of N-phenyl derivatives (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
		Unsaturated 4-carbon analogues		
3336	2-Methylallyl N-phenylcarbamate		215	204
5323	1-(4-Chloro-2-butynyl) N-(3-chlorophenyl)carbamate		267	303
3774	2-Butyne-1,4-bis(N-(3-chlorophenyl)carbamate)		198	222

Thus, the best conclusion that we can draw is that unsaturation in the alkyl chain does not improve the fungitoxicity of a carbamate ester.

Schneider (1957) found no difference between the fungitoxicity of a triple bond ester (2-propynyl N-phenylcarbamate) and that of ethyl N-phenylcarbamate on two fungi in culture. Similarly in Fig. 3, the 2-propynyl N-(3-methylphenyl)carbamate (No. 4242) has the same or less toxicity than butyl N-phenyl carbamate (No. 1872). The approximate double bond analogue of No. 4440 is No. 5298 [2-allyl N-(4-chlorophenyl)carbamate] and it is more fungitoxic, especially to *Stemphylium*. Similarly, the approximate double bond analogue of No. 4242 is No. 5301 [2-allyl N-(4-methylphenyl)carbamate]—and it also is more toxic.

Effect of electronegative groups in the ester moiety. We have suggested above that deesterification, i.e., hydrolysis by fungal enzymes may be involved in the action of the carbamates. A device for testing this hypothesis is to add an electronegative group near the ester linkage. Such a group should withdraw electrons from the ester linkage, weaken it, and increase fungitoxicity by making hydrolysis more likely. Several comparisons are available (Figure 4).

Chlorine and fluorine are electronegative atoms. One may compare (in Section I of Figure 4) the fluoroethyl analogues of ethyl N-phenylcarbamate (No. 993). Nos. 4632, 4646, and 4647 are all more toxic than the fluoro-free analogue on *Monilinia,* the sensitive fungus. Apparently fluorination can be overdone, because No. 4647 with 3 fluorine atoms is less toxic than No. 4632 with only one. Substituting a naphthyl for the phenyl ring (No. 4660) seems to reduce activity of the fluorinated ethyl ester. Doubtless, this is due to excess lipid solubility induced by the larger ring structure.

One may compare (in Section II of Figure 4) various halogenated esters of isopropyl N-(3-chlorophenyl)carbamate (No. 2687). Thus, the 1,3-dichloro analogue (No. 3335), the 1-chloro-3-isopropoxy analogue (No. 4424), the 2-chloroethyl analogue (No. 3226), and the 2-fluoro analogue (No. 4648) are all more active on both organisms than the non-halogenated esters. Similarly, (Section III, Figure 4) chlorine seems to increase the activity of the allyl ester (No. 5304 vs. No. 3596) and the butyl ester (No. 1872 vs. No. 5323).

An old proverb says that you cannot make a silk purse out of a sow's ear. Ethyl carbamate (No. 429, Section IV, Figure 4) is non-toxic, and fluorination of the ethyl ester does not make it toxic, as witness the monofluoro (No. 4658) and the trifluoro (No. 4654) analogues.

Shaw and Swanson (1953) give some data on the biological effect on green plants of chlorine in the alkyl ester. In their data, 3-chloropropyl N-phenylcarbamate is less active as a herbicide than the unchlorinated analogue, *n*-propyl N-phenylcarbamate. This suggests (a) that chlorine on the γ-end of the propyl chain is too far removed from the ester linkage to be effective, or (b) that toxicity to higher plants does not depend upon hydrolysis to the free acid.

The idea of electronegativity can be pursued further with a cyano and a nitro group (Section V, Figure 4). The cyano compound (No. 3222) is less toxic than its cyano-free analogue. (No. 2690). The nitro group occurs in compound No. 3337. There is no directly comparable nitro-free analogue but perhaps No. 3336 will suffice. If so, then the nitro

Figure 4. Effect of electronegative groups in the ester moiety

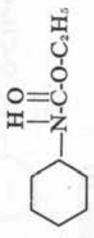
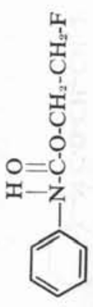
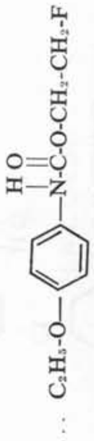
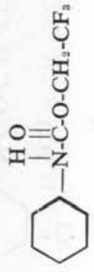
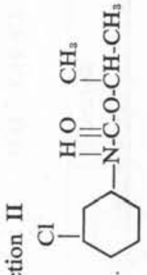
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
		Section I		
993	Ethyl N-phenylcarbamate		169	188
4632	2-Fluoroethyl N-phenylcarbamate		185	319
4646	2-Fluoroethyl N-(4-ethoxyphenyl)carbamate		47	235
4647	2,2,2-Trifluoroethyl N-phenylcarbamate		111	236
4660	2-Fluoroethyl N-(1-naphthyl)carbamate		16	162
		Section II		
2687	Isopropyl N-(3-chlorophenyl)carbamate		72	200

Figure 4. Effect of electronegative groups in the ester moiety (continued)

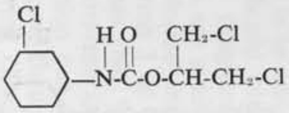
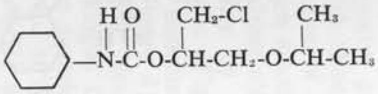
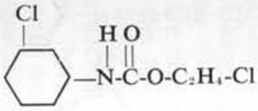
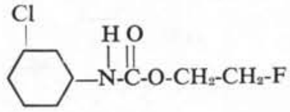
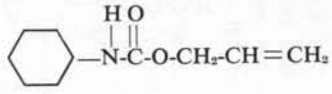
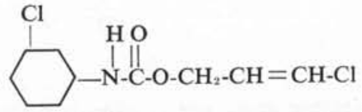
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3335	1,3-Dichloroisopropyl N-(3-chlorophenyl)carbamate		246	321
4424	(1-Chloro-3-isopropoxy)isopropyl N-phenylcarbamate		91	362
3226	2-Chloroethyl N-(3-chlorophenyl)carbamate		275	300
4648	2-Fluoroethyl N-(3-chlorophenyl)carbamate		200	344
		Section III		
5304	Allyl N-phenylcarbamate		105	111
3596	3-Chlorallyl N-(3-chlorophenyl) carbamate		271	200

Figure 4. Effect of electronegative groups in the ester moiety (continued)

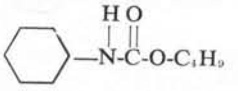
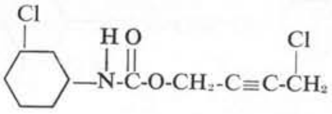
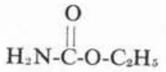
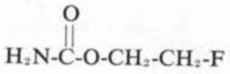
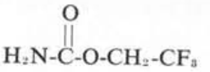
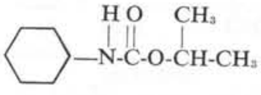
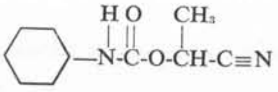
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
1872	Butyl N-phenylcarbamate		190	258
5323	1-(4-Chloro-2-butynyl) N-(3-chlorophenyl)carbamate		267	303
		Section IV		
429	Ethyl carbamate	 $H_2N-\overset{\overset{O}{\|}}{C}-O-C_2H_5$	0	6
4658	2-Fluoroethylcarbamate	 $H_2N-\overset{\overset{O}{\|}}{C}-O-CH_2-CH_2-F$	0	0
4654	2,2,2-Trifluoroethylcarbamate	 $H_2N-\overset{\overset{O}{\|}}{C}-O-CH_2-CF_3$	0	0
		Section V		
2690	Isopropyl N-phenylcarbamate		191	205
3222	1-Cyanoethyl N-phenylcarbamate		107	153

Figure 4. Effect of electronegative groups in the ester moiety (continued)

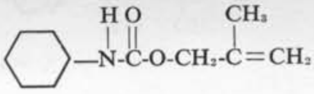
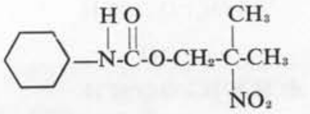
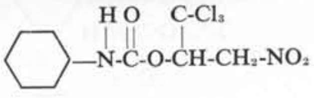
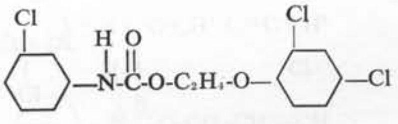
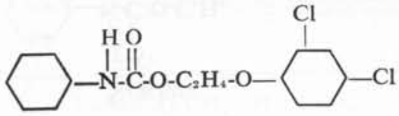
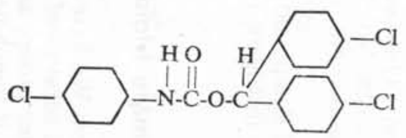
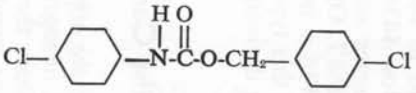
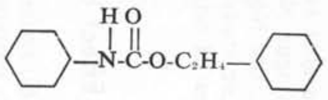
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3336	2-Methylallyl N-phenylcarbamate		215	204
3337	2-Methyl-2-nitropropyl N-phenylcarbamate		0	132
4257	(1,1,1-Trichloro-3-nitro)isopropyl N-phenylcarbamate		234	200
	Section VI			
3462	2-(2,4-Dichlorophenoxyethyl) N-(3-chlorophenyl) carbamate		11	136
3567	2-(2,4-Dichlorophenoxyethyl) N-phenylcarbamate		0	165

Figure 4. Effect of electronegative groups in the ester moiety (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
5299	4,4'-Dichlorobenzhydryl N-(4-chlorophenyl) carbamate		0	154
5300	4-Chlorobenzyl N-(4-chlorophenyl)carbamate		140	137
3416	2-Phenethyl N-phenylcarbamate		34	244

group also reduces fungitoxicity. The significance of this is not clear, especially in the light of further evidence to be adduced below on the importance of electronegative groups in toxicity. It is interesting that the chlorine of No. 4257 seems to restore the quenching effect of the nitro group. As shown later in Figure 7, a nitro group on the N-phenyl ring also reduces potency.

In Section VI of Figure 4 we show four carbamates with chlorine attached to aryl esters. These are Nos. 3462, 3567, 5299, and 5300. They may be compared with the chlorine-free analogue (No. 3416). It is clear that adding electronegative chlorine atoms to rings in the ester has not added potency, except for No. 5300 for *Stemphylium.*

Effect of electropositive groups in the ester moiety. Two amide-like derivatives of the carbamates (Nos. 4436 and 4429) are shown in Figure 5. The closest comparable analogues seem to be No. 2690 and the N-(3-chlorophenyl) analogue No. 2687. Of the two No. 4429 is highly fungitoxic to *Monilinia,* but No. 4436 is not.

Certainly, more study of this type of compound is needed. We make brief mention below of similar derivatives in Figure 15 in the DDC series.

Effect of the Carbamate Moiety

Effect of single substitution on the nitrogen. We have compounds in which one valence of the carbamate nitrogen is substituted and others in which both have been substituted. Since the ester group, as we have seen, generally improves permeation, one wonders if lipophilic groups on the nitrogen may not act likewise. Data are shown in Section I of Figure 6.

The data are best illustrated with the ethyl ester series. The size of the N-substituent makes little difference to *Stemphylium* which is not particularly sensitive to the carbamate, but potency for *Monilinia* does seem to rise in a predictable fashion as the size and presumably lipid solubility of the N-substituent increases. This again is in line with our general conclusion that *Monilinia* is more sensitive to lipophilc molecules than is *Stemphylium.* If, however, the lipophilic groups are too large (i.e. compare No. 5303 with No. 3416 in Fig. 1), potency is reduced.

Effect of electronegative groups in the carbamate moiety. We have seen in Figure 4 that electronegative halogens in the ester moiety enhance toxicity of carbamates. Later in Figure 14 and Figure 21 we shall show that electronegative carbonyls in the ester act similarly on dithiocarbamates. How about electronegative groups in the carbamate moiety?

In compound No. 2873 (Section II of Figure 6) we have an electronegative carbonyl attached to the nitrogen of a butyl carbamate. It may be compared with No. 1581 without the carbonyl. Clearly the carbonyl attached to the nitrogen reduces fungitoxicity, although neither analogue is very active. This is not unexpected. Very seldom is the structure

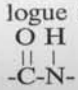

$\overset{O}{\overset{\|}{-C}}\overset{H}{\overset{|}{-N-}}$ toxic to our fungi.

Figure 5. Effect of electropositive groups in the ester moiety

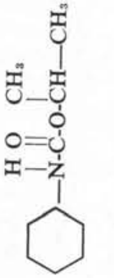
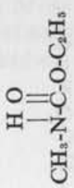
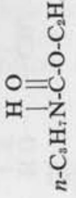
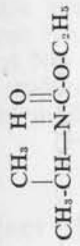
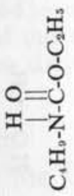
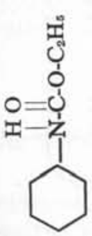
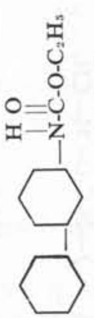
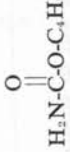
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
2690	Isopropyl N-phenylcarbamate		191	205
4436	Acetylmethylisocyano N-phenyl carbamate		107	214
2687	Isopropyl N-(3-chlorophenyl) carbamate		72	200
4429	Dimethylisocyano N-(2,5-dichlorophenyl) carbamate		0	363

Figure 6. Effect of lipophilicity of nitrogen substituents

Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
		Section I		
2339	Ethyl N-methylcarbamate	 $CH_3\text{-}\overset{\overset{H}{\vert}}{N}\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_2H_5$	0	0
1190	Ethyl N-propylcarbamate	 $n\text{-}C_3H_7\overset{\overset{H}{\vert}}{N}\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_2H_5$	0	0
1191	Ethyl N-isopropylcarbamate	 $CH_3\text{-}\overset{\overset{CH_3}{\vert}}{CH}\text{—}\overset{\overset{H}{\vert}}{N}\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_2H_5$	50	100
1194	Ethyl N-butylcarbamate	 $C_4H_9\text{-}\overset{\overset{H}{\vert}}{N}\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_2H_5$	0	50
993	Ethyl N-phenylcarbamate		169	188
3453	Ethyl N-(2-biphenylyl)carbamate		38	300
5303	Benzyl N-(*n*-dodecyl)carbamate		16	0
		Section II		
1581	Butyl carbamate	 $H_2N\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_4H_9$	93	89
2873	Butyl N-acetylcarbamate	 $H_3C\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}\overset{\overset{H}{\vert}}{N}\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}O\text{-}C_4H_9$	22	21

Effect of N-phenyl analogues. The largest number of available single substitutions is in the N-phenyl series. One possibility of enhancing the lipid solubility is to add hydrocarbons to the ring. The data appear in Figure 7.

Figure 7. Effect of N-phenyl analogues

Number	Structure: N-phenyl substituent	Structure: Ester	Toxicity index *Stemphylium*	Toxicity index *Monilinia*
2690	None	Isopropyl	191	205
3573	3-Methyl	"	167	300
4242	3-Methyl	2-Propynyl	113	205
3570	3-Methoxy	Isopropyl	150	225
3456	2-Vinyl(-CH=CH$_2$)	"	136	316
3580	3,5-Dimethyl	"	30	168
3575	2,3-Dimethyl	"	16	238
3568	2,4-Dimethyl	"	15	195
3569	2,5-Dimethyl	"	0	207
4801	2,5-Dimethoxy	"	23	215
3231	2-Methoxy-5-nitro	"	23	119
3574	2,6-Dimethyl	"	122	200
3461	2-Methoxy-5-methyl	Chloroethyl	19	206
3453	2-Phenyl	Ethyl	38	300
4260	2-Methyl	2-Propynyl	0	314
3464	2-Methoxy	Butyl lactate	0	149

Figure 7 illustrates three points about the N-phenyl group: (a) small substituents on the ring do not add potency, (b) a 5-nitro group reduces activity, and (c) a 2-substitution quenches the potency to *Stemphylium* without simultaneously affecting *Monilinia* very much.

The action of the 5-nitro group can be seen by comparing the action on *Monilinia* of the 2-methoxy-5-nitro compound (No. 3231) with the 2,5-dimethyl analogue (No. 3569) and the 2,5-dimethoxy analogue (No. 4801). The effect of a nitro group on the ring must have generality because the data of Sexton (1953) and Shaw and Swanson (1953), show the same quenching action on heribicidal carbamates.

The effect of 2-substitution on *Stemphylium* is very striking. By contrast its lack of effect on *Monilinia* is equally striking. In 10 out of 11 cases, a 2-substitution quenches what little toxicity there is to *Stemphylium*. The only exception is the 2,6-dimethyl analogue (No. 3574). Perhaps this compound needs further attention. The effect of the 2-substitution on toxicity to *Stemphylium* is an important point in the general theory to be set up below in the section on general discussion of the oxygen analogues. Suffice it to say here, that we suggest that the 2-substituent squeezes the N-hydrogen and hinders its participation in the fungitoxic reaction.

Sexton's (1953) data on oat germination agree with our data on *Stemphylium*. He shows that the 2-methoxy and 2-chloro N-phenylcarbamates are less effective than the unsubstituted analogue.

Shaw and Swanson (1953) report an opposite effect on foliage toxicity. They found that a 2-substitution on the N-phenyl ring increases phytotoxicity. They say that "active compounds result from substitution in the 2-position."

Ring chlorination often enhances lipid solubility and permeation. We have a few compounds in which the N-phenyl group has been chlorinated. Four sets of comparisons are given in Figure 8.

Isopropyl N-phenylcarbamate (No. 2690) may be considered as a starting point for one comparison. Neither a 3-methyl (No. 3573) nor a 3-chloro (No. 2687) substitution on the N-phenyl ring adds any toxicity. The 3-chloro may actually reduce activity on *Stemphylium.*

We can also study the effect of 3-chloro-substitution on the N-phenyl ring by comparing the two 2,4-dichlorophenoxyethyl esters. The 3-chloro N-phenyl analogue (No. 3462) is no more toxic than the unsubstituted analogue (No. 3567).

Here our data depart drastically again from those of Shaw and Swanson (1953) on herbicides. In our case a 3-substitution adds nothing, but they report that ". . . substitution in the 3-position . . . produces the greatest activity." Sexton's data on oat germination agree with those of Shaw and Swanson.

On the other hand 4-substitution in the N-phenyl nucleus does seem to increase the activity of the allyl esters. With the unsubstituted ring, the unsubstituted allyl ester (No. 5304) has a toxicity value of 111 for *Monilinia.* A 4-methyl substitution (No. 5301) has a toxicity value of 235 and a 4-chloro substitution (No. 5298) has a toxicity value of 335 for the same fungus. The same trend occurs also for *Stemphylium.*

Here again we depart from the herbicide data. Shaw and Swanson (1953, p. 62) say that ". . . very little activity [of the isopropyl series] is obtained by substitution in the 4-position" and Sexton's (1953) data on oat germination show that substitution in the 4-position actually reduces activity.

We have no unsubstituted propynyl N-phenyl carbamates, but we have a 3-methyl (No. 4242), a 4-chloro (No. 4440) and a 5-chloro-2-methyl (No. 4260) derivative. The toxicity values are 205, 313, and 314, respectively for *Monilinia.* The 2-methyl substituent in No. 4260 as mentioned earlier in Figure 7 quenches essentially all activity on *Stemphylium* irrespective of the chlorine substituent.

Effect of attaching heterocycles to the nitrogen atom. We have just seen that an N-phenyl group seems to add potency to carbamate esters. What about a heterocyclic group instead? From Figure 9 we can see that none of the compounds with a pyridine, a thiazole, a tetrazole, or a furan group is more toxic than the N-phenyl analogues (No. 993 and No. 2690). In fact, they are far less toxic. They quench the activity in the ethyl ester series.

Effect of N to N substitution. In the carbazic acid analogues of the carbamate esters, the nitrogen of the carbamate moiety is bonded to another nitrogen in an azide linkage. Then a phenyl group or other substituent is attached to the second nitrogen atom.

Data on the four available compounds are compared in Figure 10 to similar carbamates. The data suggest a slight possible advantage for the azide linkage.

Figure 8. Effect of chlorinating the N-phenyl nucleus

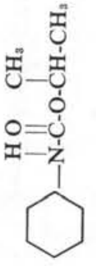
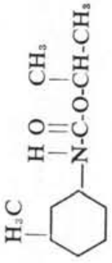
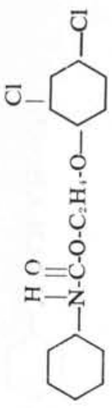
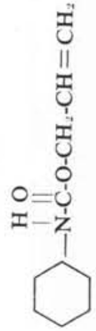
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
2690	Isopropyl N-phenylcarbamate		191	205
3573	Isopropyl N-(3-methylphenyl)carbamate		190	200
2687	Isopropyl N-(3-chlorophenyl)carbamate		72	200
3567	2-(2,4-Dichlorophenoxyethyl) N-phenylcarbamate		0	165
3462	2-(2,4-Dichlorophenoxyethyl) N-(3-chlorophenyl) carbamate		11	136
5304	Allyl N-phenylcarbamate		105	111

Figure 8. Effect of chlorinating the N-phenyl nucleus (continued)

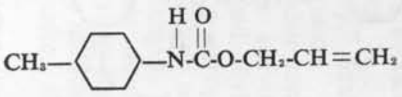
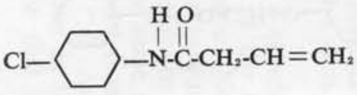
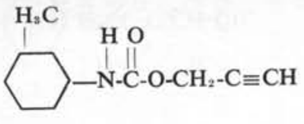
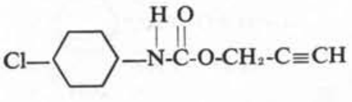
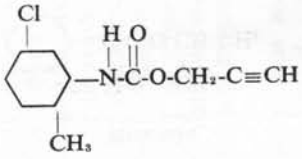
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
5301	Allyl N-(4-methylphenyl)carbamate		200	235
5298	Allyl N-(4-chlorophenyl)carbamate		254	335
4242	2-Propynyl N-(3-methylphenyl)carbamate		113	205
4440	2-Propynyl N-(4-chlorophenyl)carbamate		113	313
4260	3-Propynyl N-(5-chloro-2-methylphenyl)carbamate		0	314

Figure 9. Effect of attaching heterocycles to the nitrogen atom

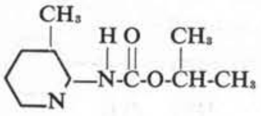
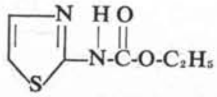
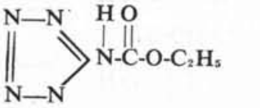
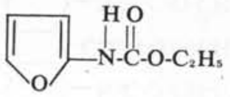
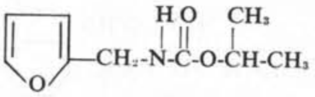
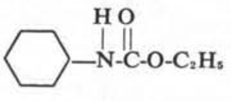
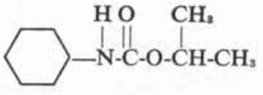
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3401	Isopropyl (3-methyl-2-pyridyl) carbamate		23	107
2902	Ethyl N-(2-thiazolyl)carbamate		0	0
3421	Ethyl N-[5-(IH-tetrazolyl)]carbamate		0	10
5302	Ethyl N-(2-furanyl)carbamate		22	2
3225	Isopropyl N-(2-furfuryl)carbamate		100	100
993	Ethyl N-phenylcarbamate		169	188
2690	Isopropyl N-phenylcarbamate		191	205

Figure 10. Effect of N to N substitution

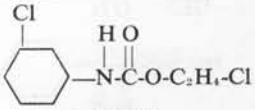
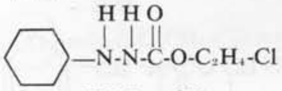
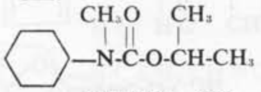
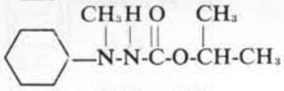
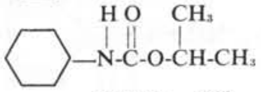
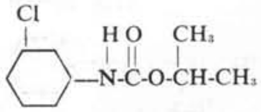
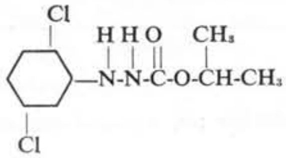
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
3226	2-Chloroethyl N-(3-chlorophenyl)carbamate		275	300
3257	2-Chloroethyl β-phenylcarbazate		219	316
3230	Isopropyl N-methyl-N-phenylcarbamate		58	100
3268	Isopropyl β-methyl-3-phenylcarbazate		113	200
2690	Isopropyl N-phenylcarbamate		191	205
3572	Isopropyl β-phenylcarbazate		134	216
2687	Isopropyl N-(3-chlorophenyl)carbamate		72	200
3577	Isopropyl β-(2,5-dichlorophenyl)carbazate		202	306

Figure 11. Effect of double substitution on the nitrogen atom

Number	The two nitrogen substituents	The Ester	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
4670	Ethyl, ethoxy	Ethyl	0	16
1193	Diethyl	Ethyl	0	0
1195	Dipropyl	Ethyl	0	0
1196	Dibutyl	Ethyl	0	50
3230	Methyl, phenyl	Ethyl	58	100
3579	Methyl, phenyl	Butyl lactate	117	324
3260	Methyl, 2-methylphenyl	Ethyl	100	100
3576	Ethyl, phenyl	Ethyl	97	246
3459	Allyl, phenyl	Ethyl	80	132
3458	2-Crotonyl, phenyl	Ethyl	22	200
3581	Butyl, phenyl	Ethyl	15	148
3251	Bisphenyl	Ethyl	78	225
994	Benzyl, phenyl	Ethyl	0	26
3571	Benzyl, 3-methylphenyl	Isopropyl	0	8
1192	In a morpholine ring	Ethyl	52	80
3334	In a morpholine ring	Isopropyl	0	0
3256	In a pyrrolidine ring	Isopropyl	12	19
3454	In a piperidine ring	Isopropyl	0	32
3457	In a 2-ethyl, 2-methyl, piperidine ring	Isopropyl	15	121
3466	In a 2,4-dimethyl-1,4-piperazine ring	Diisopropyl	75	167

Effect of double substitution on the nitrogen. Nineteen of our compounds contain a carbamate nitrogen atom that is doubly substituted. Data are presented in Figure 11. In six of these the nitrogen is part of a ring structure.

In this series we strike gold when digging for a mode of action, at least for a mode of action on *Stemphylium.* Essentially all of the disubstituted compounds are inactive on *Stemphylium.* As listed in Figure 11, they are a page full of negative compounds for that test fungus. This means that a labile N-hydrogen is necessary for the fungicidal action of carbamates on *Stemphylium.*

Double substitution of the nitrogen atom seems less important to *Monilinia* than to *Stemphylium.* Four doubly substituted compounds show a toxicity index of 200 or more for *Monilinia.*

Three of these are in the neighborhood of 200. These are N-ethyl, N-phenyl (No. 3576), N-2-crotonyl, N-phenyl (No. 3458) and N,N-bisphenyl (No. 3251). One seems to be especially toxic to *Monilinia.* This is the butyl lactate ester of the N-methyl, N-phenyl carbamate (No. 3579). This compound was so toxic that we gave it a repeat test with the same results. The compound clearly warrants further study.

The occurrence of four toxic compounds in the N-di-substituted series suggests that a labile N-hydrogen is not as necessary for toxicity to *Monilinia* as to *Stemphylium.* Although it may not be necessary for toxicity to *Monilinia,* it adds to toxicity when present.

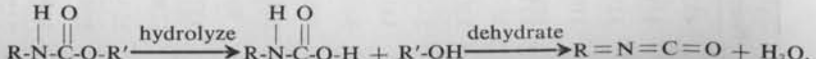
The dependence on a free N-hydrogen for fungitoxicity to *Stemphylium* stands in striking contrast to the effect on toxicity to *Monilinia* or to green plants. Most of the carbamate weed killers have doubly substituted nitrogen atoms. In fact Woodford *et al.* (1958) suggest that disubstitution is imperative for a weed killer. Disubstitution is surely not imperative for toxicity to *Monilinia* but it does not necessarily inhibit it, either.

Effect of isocyanates. Toxicologists, especially those dealing with fungitoxicants, like to assume that the compound at hand must change to something else in order to be active. Sulfur, for instance, they have said, must be converted to H_2S, nabam to diisothiocyanate.

Although we normally eschew conformity, we might conform here and begin by assuming that carbamates are converted to isocyanates and thus are made toxic. This possibility is intriguing at first because of the dependence of toxicity at least to *Stemphylium* on a labile N-hydrogen. No isocyanate could form without a labile N-hydrogen.

The possibility is made more appealing by the exciting current research into urethane foams, urethane rubber, and the like. The chemistry of these takes off from an isocyanate base as discussed by Dombrow (1957).

On the other hand the possibility is counter-indicated by the chemistry of the case. To postulate the action of an isocyanate, one would have to derive a satisfying equation such as follows:



$$\text{R-}\overset{\text{H}}{\underset{|}{\text{N}}}\text{-}\overset{\text{O}}{\underset{\|}{\text{C}}}\text{-O-R}' \xrightarrow{\text{hydrolyze}} \text{R-}\overset{\text{H}}{\underset{|}{\text{N}}}\text{-}\overset{\text{O}}{\underset{\|}{\text{C}}}\text{-O-H} + \text{R}'\text{-OH} \xrightarrow{\text{dehydrate}} \text{R}=\text{N}=\text{C}=\text{O} + \text{H}_2\text{O}.$$

If this reaction is to go, water must first be added and then removed. We are unable to see how it can be removed in the aqueous system of the spore, if for no other reason than that isocyanates are avid water seekers.

This in fact is the basis for the chemistry of urethane foams. When a regulated amount of water is added to an isocyanate the free amine and CO_2 are liberated. The liberated amine reacts with some of the residual isocyanates to give a polymer and the CO_2 causes the batch to "rise" just like bread.

The nice isocyanate hypothesis should not be discarded without trial, however. Figure 12 contains the data on six isocyanates and their available carbamate analogues.

With the possible exception of No. 4751, no isocyanate shows any very striking toxicity to either test organism. This evidence seriously weakens any isocyanate theory of toxicity. Of course, the evidence does not realy negate an isocyanate hypothesis. The isocyanates may be too volatile, too unstable, or even too impermeable. They might conceivably be toxic if they could be delivered to the site of action. Still, the data do weaken the isocyanate hypothesis.

Discussion of Oxygen Analogues

All the cards in the carbamate poker hand have now been drawn. All the chips are down. What shall we call our hand? What can we conclude about the chemistry of fungitoxic action of the carbamates?

Perhaps we should review briefly what we have learned.

(1) That *Monilinia* is much more sensitive to carbamates than *Stemphylium.*

(2) The evidence seems reasonably clear in view of our earlier research (Rich and Horsfall, 1952) that permeation is involved, i.e., that the action is inside the cell. There is an optimum balance between polarity and lipid solubility. This differs for the two test organisms. For equal toxicity, lipid solubility must be greater for *Monilinia* than for *Stemphylium* and this agrees with other work on these two test organisms (Horsfall and Rich, 1951, 1953).

This may be evidence of adsorption and not permeation but we lean toward the idea that it indicates permeation.

(3) The evidence seems to be pretty clear, too, that deesterification, i.e., hydrolysis is needed. This evidence comes largely (a) on the imidazoline analogue (No. 3983), and (b) from the data on electronegative groups in the ester moiety that aid deesterification.

(4) Since the esters are reasonably stable in water the evidence suggests that deesterification occurs within the cell under the influence of fungus esterases. Byrde and Woodcock (1956) have done much with the action of fungus esterases on fungitoxic esters.

(5) The products of hydrolysis are an alcohol and a carbamic acid. Could these be fungitoxic? Isopropyl esters are among the most fungitoxic, and isopropanol, according to Ogawa and Lyda (1960) is more toxic to *Monilinia* than ethanol or methanol. We doubt, however, that isopropanol is very important in toxicity of isopropyl esters because the dose range is pretty low.

Figure 12. Effect of isocyanates

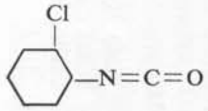
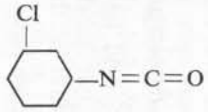
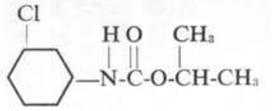
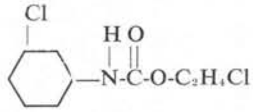
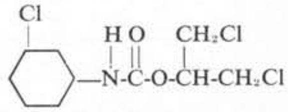
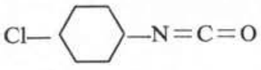
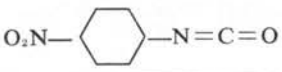
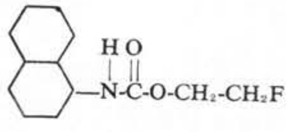
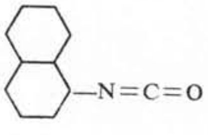
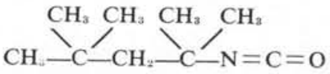
Number	Name	Structure	Toxicity Index	
			Stemphylium	Monilinia
		Section I		
4751	2-Chlorophenyl isocyanate		35	216
4753	3-Chlorophenyl isocyanate		85	124
2687	Isopropyl N-(3-chlorophenyl)carbamate		72	200
3226	2-Chloroethyl N-(3-chlorophenyl)carbamate		275	300
3335	1,3-Dichloroisopropyl N-(3-chlorophenyl)carbamate		246	325
4750	4-Chlorophenyl isocyanate		74	109
600	4-Nitrophenyl isocyanate		0	0

Figure 12. Effect of isocyanates (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	Monilinia
		Section II		
4660	2-Fluoroethyl N-(1-naphthyl)carbamate			
608	1-Naphthyl isocyanate			
		Section III		
1194	Ethyl N-butylcarbamate	 $C_4H_9\text{-}\overset{H}{N}\text{-}\overset{O}{C}\text{-O-}C_2H_5$	0	50
4495	1,1,3,3-Tetramethylbutyl isocyanate	 $CH_3\text{—}\overset{CH_3\ CH_3}{C}\text{—}CH_2\text{—}\overset{CH_3\ CH_3}{C}\text{—}N{=}C{=}O$	61	128

The carbamic acid possibility is more intriguing. Once formed inside the spore, the acid presumably decomposes in the normal fashion to an amine and CO_2.

The decomposition of the carbamic acid would be pH dependent with a pKA on the acid side. If so, this opens an interesting possibility to account for the greater sensitivity to carbamates of *Monilinia* than *Stemphylium*. As Horsfall (1956) has reported, *Monilinia* lives at a much lower pH than *Stemphylium*. Thus, we would expect that the acid would be more unstable in *Monilinia* than in *Stemphylium,* and, thus, we would expect more amine to be formed in *Monilinia* than in *Stemphylium*.

The resulting amine could very easily combine with carboxyl, hydroxyl, or sulfhydryl groups in the cell and thus put them out of business. If the N-hydrogen is required for *Stemphylium*, then this test fungus demands a primary amine, whereas a secondary amine is also effective on *Monilinia.*

No. 3335 in Figure 13 is interesting in this connection. All of what we have just said would lead us to say that the activity of No. 3335 is probably due to 3-chloroaniline. And yet we tested this compound many years ago (Horsfall, 1945) and it is not fungitoxic when offered directly to fungus spores.

Now this does not prove that the activity of No. 3335 is *not* due to 3-chloroaniline. We still have the permeation problem. This always "rears its ugly head" when we try to establish structure activity relationships. No. 3335 probably permeates well because of its strong lipophilic properties, and then decomposes to 3-chloroaniline *in situ*. 3-Chloroaniline alone is probably inactive because it cannot permeate into the cell. It needs a lipophilic group. 3-Chloroaniline can be made fungitoxic by adding a lipophilic phenoxy group in the 4-position (No. 1236, Figure 13). This gives a toxic index of 200 for *Stemphylium* and 300 for *Monilinia*. Similarly, Horsfall, Chapman and Rich (1951) have shown that one can make aniline itself fungitoxic by substituting a lipophilic phenyl group in the 4-position (No. 359, Figure 13).

Thus, we conclude that aniline formed *in vivo* probably accounts for the toxicity of N-phenylcarbamate esters and that the ester serves as a wagon to carry the aniline into the cell.

(6) The foregoing being so, we come to the requirement of a mobile N-hydrogen for the toxicity of a carbamate to *Stemphylium* but not always to *Monilinia*. An ideal test compound would be the dimethyl homologue of 4-phenoxy-3-chloroaniline. It has no mobile hydrogen and should be non-toxic.

Lacking that compound to test, some similar compounds (Figure 13) can illustrate this point. Benzidine (No. 534) is 4,4′-diaminodiphenyl, which can be considered as a bianiline. It is fungitoxic. If, however, the amines are doubly substituted with C_2H_5 groups to give tetraethylbenzidine (No. 1235), the activity is lost.

Bis-(4-aminophenyl) methane (No. 437) is a similar compound in which the two anilines are separated by a methane bridge. It, too, is fungitoxic (Horsfall, Chapman, and Rich, 1951) but the fungitoxicity to *Stemphylium* is lost if the two amine groups are doubly substituted (No. 639).

Thus, the aniline data agree with the carbamate data showing the necessity of a mobile N-hydrogen for toxicity to *Stemphylium*. In that sense the data also lend further evidence to the idea that toxicity requires deesterification of the carbamate ester *in vivo*.

(7) Still, we cannot ignore the fact that the ester can be toxic in its own right.

The possibility still remains that the primary amino group is directly toxic to both organisms either by direct addition, by hydrogen bonding, or by enolization with the adjacent carbonyl group to form an alcoholic -OH group which might be toxic.

We have a small bit of data on the first two of these three—i.e., direct action of the -NH- group without any fussy requirement of deesterification. This is found in the activity of No. 1220 (Figure 13). This compound is an aniline with the lipid solubility provided by a 7-carbon tail attached directly to the nitrogen. It is toxic to both test organisms just as No. 3335 is. Thus, we need not necessarily postulate a change to a more toxic form. We need only a permeative form.

On balance, however, the evidence seems to favor deesterification. The action of the electronegative groups seem to tip the balance of evidence in that direction rather than toward direct action of the ester itself.

(8) And, thus, in summary the data say that the carbamate esters are toxic (a) because they are lipophilic enough to permeate the spore, (b) once inside they are deesterified, possibly with the aid of fungus esterases, (c) the carbamic acid thus formed decomposes to the free amine, and (d) the amine reacts with metabolites to inhibit the fungus.

FUNGITOXICITY OF SULFUR ANALOGUES

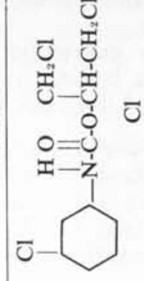
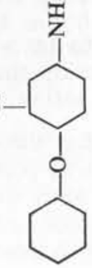
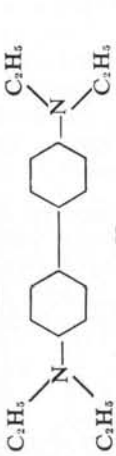
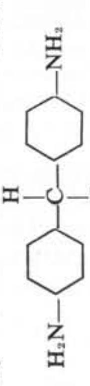
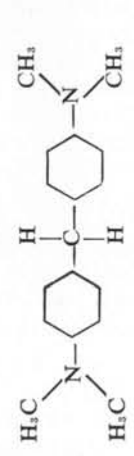
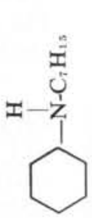
So far, we have been discussing only the oxygen containing carbamates. Let us now turn to their sulfur analogues. The only paper with much work on the structure-activity relatives of sulfur-containing carbamic acid esters is that of Pluijgers (1959). We shall meld his data with ours.

As mentioned in the introduction, we were first exposed back in 1938 to the fungitoxicity of the carbamates through ethyl N-phenylthionocarbamate (No. 1257). In the meantime we have collected and tested as many thiono-, thiol-, and dithio- carbamates as possible. One of these, first screened in 1940, eventuated into the commercially useful fungicides, nabam, zineb, and maneb (See Dimond, Heuberger, and Horsfall, 1943).

We shall discuss in this paper the single and double esters plus the isothiocyanates of the sulfur analogues of dithiocarbamate derivatives of dimethylamine and ethylenediamine. We shall report our data on metallic salts in a later paper.

The first, or dialkyl dithiocarbamate, is made by reacting dimethylamine or its homologues with CS_2 and NaOH. We shall refer to this as the DDC series. The second, or alkylene bisdithiocarbamate, is made by reacting ethylenediamine or its homologues with CS_2 and NaOH. Because the latter series is based on the disodium salt, nabam, we shall refer to it as the nabam series.

Figure 13. Effect of amine analogs of carbamates

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3335	1,3-Dichloroisopropyl N-(3-chlorophenyl) carbamate		246	321
1236	3-Chloro-4-phenoxyaniline		200	300
359	4-Aminobiphenyl		ca 200	ca 300
534	Benzidine		100	118
1235	N,N,N',N'-Tetraethylbenzidine		5	0
437	Bis(4-aminophenyl) methane		104	111
639	Bis(4-dimethylaminophenyl) methane		0	129
1220	N-Heptylaniline		200	200

EFFECT OF DDC ESTERS

The DDC series of fungicides was first reported by Tisdale and Williams in 1934. We will discuss herein the possibility that DDC esters may hydrolyze to form the free acid or the dithiocarbamate ion as Klöpping and van der Kerk (1951) have suggested.

All available data on DDC esters and isothiocyanates are given in Table 2.

Effect of Monosulfide Esters of DDC

We mean by single esters, those that are esters of a single thiocarbamic acid. Double esters to be discussed below are the mono-sulfides and disulfides.

Effect of thiono-, thiol-, and dithiocarbamate esters. The data on the several types of sulfur containing analogues are set forth in Figure 14. A general impression from examining Figure 14 is that the sulfur derivatives are unexpectedly weak fungicides.

Most of those that have activity in excess of 200, especially for *Stemphylium,* are N-phenyl derivatives with a labile hydrogen, Nos. 1117 H, 9 L, 2799, and 1257. This conclusion agrees with that for the oxygen analogues as discussed above. Three other analogues all with disubstituted nitrogen atoms have toxicity values of 200 or more for *Monilinia.* These are Nos. 2314, 2882, and 2336. All are dithio derivatives. Two of these are 2-hydroxyethyl derivatives (Nos. 2314 and 2336).

We would like to be able to separate the four possible carbamate types -$\overset{O}{\overset{\|}{C}}$-O-, -$\overset{O}{\overset{\|}{C}}$-S-, -$\overset{S}{\overset{\|}{C}}$-O-, and -$\overset{S}{\overset{\|}{C}}$-S-. Unfortunately, we do not have as many wholly comparable types as we would like.

The only complete series is the methyl N-phenyl-series as shown in Section I of Figure 14. These are all pretty toxic to *Monilinia* and reasonably toxic to *Stemphylium* as well. It appears that the dithiocarbamate member is the most toxic to *Stemphylium* and the oxygen derivative the least. The data on the thiol derivative suggest that it is the weakest of the four on *Monilinia.*

Section II of Figure 14 lists a comparison of oxygen, 2-thiols, and a dithio derivative. The four compounds available (Nos. 1193, 5290, 5325, and 18 L) all have disubstituted nitrogen atoms and, hence, all are very weak on *Stemphylium.* No. 5290 and 5325, the thiol derivatives have toxicity values for *Monilinia* of 129 and 227, respectively. This may be due to their lipid solubility. The lipid solubility of the propyl substituents of these two may add as much to the potency as the thiol sulfur. Still, it gives a little evidence that the thiol derivative in Section I really is more toxic to *Monilinia* than the available data indicate. The electronegative chlorine atom in No. 5325 shows its effect on fungitoxicity.

Antognini *et al.* (1957) have reported strong herbicidal action from No. 5290, which is ethyl N,N-di-*n*-propyl-thiolcarbamate.

Figure 14. Effect of thiono, thiol, and dithiocarbamate esters

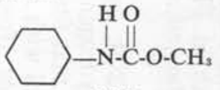
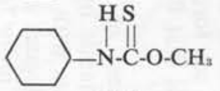
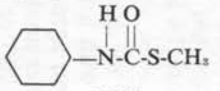
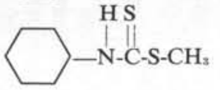
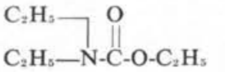
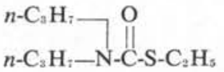
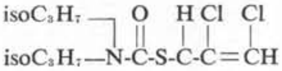
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
		Section I		
4 L	Methyl N-phenylcarbamate		179	310
1117 H	Methyl N-phenylthionocarbamate		200	350
9 L	Methyl N-phenylthiolcarbamate		201	233
2799	Methyl N-phenyldithiocarbamate		272	300
		Section II		
1193	Ethyl N,N-diethylcarbamate	 $C_2H_5\text{—}\overset{C_2H_5\text{—}}{N}\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	0	0
5290	Ethyl N,N-di-*n*-propylthiolcarbamate	 $n\text{-}C_3H_7\text{—}\overset{n\text{-}C_3H_7\text{—}}{N}\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}C_2H_5$	0	129
5325	2,3-Dichloroallyl N,N-diisopropylthiolcarbamate	 $\text{iso}C_3H_7\text{—}\overset{\text{iso}C_3H_7\text{—}}{N}\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}\overset{H}{\overset{|}{C}}\text{-}\overset{Cl}{\overset{|}{C}}=\overset{Cl}{\overset{|}{CH}}$	35	227
18 L	Methyl N,N-dimethyldithiocarbamate	 $CH_3\text{—}\overset{CH_3\text{—}}{N}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}CH_3$	10	0

Figure 14. Effect of thiono, thiol, and dithiocarbamate esters (continued)

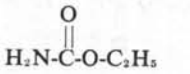
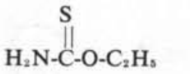
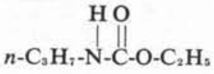
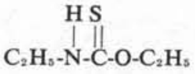
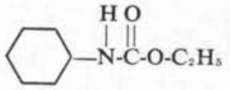
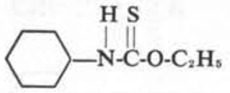
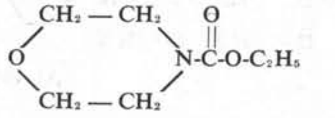
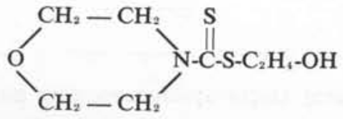
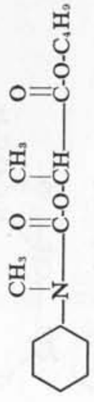
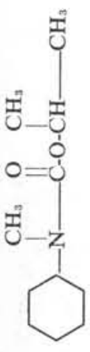
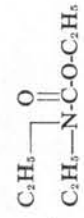
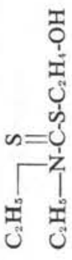
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
		Section III		
429	Ethyl carbamate	 $H_2N\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	0	6
1251	Ethyl thionocarbamate	 $H_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	5	0
1190	Ethyl N-propylcarbamate	 $n\text{-}C_3H_7\text{-}\overset{H}{\overset{|}{N}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	0	0
1255	Ethyl N-ethylthionocarbamate	 $C_2H_5\text{-}\overset{H}{\overset{|}{N}}\text{-}\overset{S}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	44	92
993	Ethyl N-phenylcarbamate		169	188
1257	Ethyl N-phenylthionocarbamate		250	250
1192	Ethyl N-morpholinylformate		52	80
2314	4-Morpholinecarbodithioic acid, 2-hydroxyethyl ester		50	202

Figure 14. Effect of thiono, thiol, and dithiocarbamate esters (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
	Section IV			
3579	N-methyl-N-phenylcarbamic acid, butyl lactate ester		117	324
2882	Dimethyldithiocarbamic acid, methyl propionate ester	 $(CH_3)_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{CH_3}{\overset{\vert}{C}H}\text{—}\overset{O}{\overset{\|}{C}}\text{-}OCH_3$	100	252
3230	Isopropyl N-methyl-N-phenylcarbamate		58	100
3044	N-methyl N-phenyldithiocarbamic acid, acetic acid ester		156	133
1193	Ethyl N,N-diethylcarbamate	 $(C_2H_5)_2N\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	0	0
2336	Diethyldithiocarbamic acid, 2-hydroxyethyl ester	 $(C_2H_5)_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}C_2H_4\text{-}OH$	115	202

So far as the thiono compounds are concerned, we have four available comparisons with their oxygen counterparts, one in Section I of Figure 14 and three listed in Section III of Figure 14.

Ethyl carbamate (No. 429) and ethyl thionocarbamate (No. 1251) are nontoxic, and, thus, indistinguishable. It is interesting, however, that Berry (1958) controlled decay in oranges with ethyl thionocarbamate.

In the other three comparisons, the thiono derivative is more fungitoxic than the oxygen analogue to *Monilinia* and the first two are more toxic to *Stemphylium*. The most toxic thiono compound in Section III is ethyl N-phenylthionocarbamate (No. 1257). It is comparable with methyl N-phenylthionocarbamate (No. 1117H) in Section I.

The weakest of these three thionocarbamates is the ethyl N-ethyl derivative (No. 1255). This presumably is because the N-ethyl substitution permeates less readily than the N-phenyl compound.

The data on thiono derivatives seem quite clear—they are more toxic than their oxygen counterparts. Data of Shaw and Swanson (1953) show that thiono derivatives of isopropyl N-phenyl series are more toxic to green foliage than their oxygen counterparts.

We have only four thiolcarbamates (Nos. 9 L, 5290, and 5325 in Section I of Figure 14 and No. 642 in Figure 16). It is hard to assess their relative toxicities. It almost looks as if the other moieties in the molecule are exerting the major effect on toxicity.

There are three isolated pairs of reasonably close dithiocarbamate-carbamate comparisons listed in Section IV of Figure 14. These are No. 2882 and 3579, 3044 and 3230, and 2336 and 1193. In the second two cases the dithiocarbamate ester is more fungitoxic than its oxygen counterpart. No. 2882 is weaker, however, because it has an N-methyl group instead of the N-phenyl group of the oxygen analogue.

In general, then, we may conclude that although the within-series differences are small, the trend in toxicity seems to be as in the following order $\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-} < \text{-}\overset{S}{\overset{\|}{C}}\text{-}O\text{-} < \text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-} < \text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}$. Possibly, we should list $\text{-}\overset{S}{\overset{\|}{C}}\text{-}O\text{-}$ and $\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}$ as equal.

Pluijgers (1959) investigated the fungicidal action of many esters of DDC on five fungi growing in culture. His data show several comparisons of interest. Although he reported on no straight oxygen analogues, he did make four comparisons of $\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}$ and $\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}$. $(CH_3)_2N\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}\overset{S}{\overset{\|}{C}}\text{-}N(CH_3)_2$ was less toxic than $(CH_3)_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{S}{\overset{\|}{C}}\text{-}N(CH_3)_2$. No distinction is possible between $\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}$ and $\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}$ in the dimethylamino series where the ester is $\text{-}CH_2\text{-}COOC_2H_5$ because neither of the pair was toxic enough to register on his screen. The $\text{-}\overset{O}{\overset{\|}{C}}\text{-}S\text{-}$ group was more toxic, however, than $\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}$ in the dimethylamine series where the ester was methyl and less toxic where the ester was $-CH_2COOH$.

From Pluijgers' data, one can make four comparisons between $-\overset{S}{\overset{\parallel}{C}}-O-$ and $-\overset{S}{\overset{\parallel}{C}}-S-$. The latter is more toxic than the former where the structure is $(CH_3)_2N-\overset{S}{\overset{\parallel}{C}}-S-CH_2-COOH$, $(C_2H_5)_2N-\overset{S}{\overset{\parallel}{C}}-S-CH_2COOH$, $(n\text{-}C_4H_9)_2N-\overset{S}{\overset{\parallel}{C}}-S-CH_2COOH$, and equal in toxicity where the structure is $(CH_3)_2N-\overset{S}{\overset{\parallel}{C}}-S-CH_2CH_2COOH$.

In all of these cases the differences are small. Except for the methyl N,N-dimethyldithiocarbamate pair, the $-\overset{S}{\overset{\parallel}{C}}-S-$ is apparently more toxic than $-\overset{O}{\overset{\parallel}{C}}-S-$ or $-\overset{S}{\overset{\parallel}{C}}-O-$. Pluijgers' data do not permit a choice in the one comparison of $-\overset{S}{\overset{\parallel}{C}}-O-$ and $-\overset{O}{\overset{\parallel}{C}}-S-$ because neither was toxic enough to register.

In general, we can say that Pluijgers' data agree with ours to the extent that $-\overset{S}{\overset{\parallel}{C}}-S-$ is the most toxic of the series.

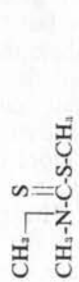
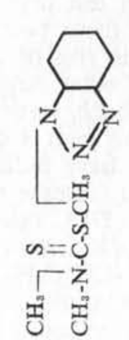
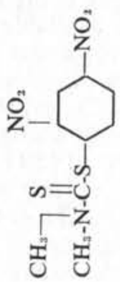
Davies and Sexton (1946) made a few comparisons on *Penicillium digitatum* in culture for methyl and ethyl esters in the N-phenyl series. In the methyl ester group the $-\overset{O}{\overset{\parallel}{C}}-O-$ was the most toxic and the $-\overset{O}{\overset{\parallel}{C}}-S-$, $-\overset{S}{\overset{\parallel}{C}}-O-$ and $-\overset{S}{\overset{\parallel}{C}}-S-$ were equal. In the ethyl ester group, $-\overset{O}{\overset{\parallel}{C}}-O-$ and $-\overset{S}{\overset{\parallel}{C}}-S-$ were equal and more toxic than the $-\overset{S}{\overset{\parallel}{C}}-O-$ analogue. (The $-\overset{O}{\overset{\parallel}{C}}-S-$ was not tested in the ethyl group.)

We should emphasize that the differences among all seem to be small. One must take his choice.

Effect of the size of the ester moiety. We are impressed with the unexpectedly and generally weak fungitoxicity of the family of DDC esters. This may well be due to the small lipid solubility either of the esters or of the N-substitutions. For example, the toxicity of oxygen analogues is weak, too, if the hydrocarbon tail in the ester is no more than two carbons in length (See Figure 1 above), and we have only three thio esters with more than two carbons (Figure 15).

The 2,4-dinitrophenylester (No. 1246) of dimethyldithiocarbamic acid is of particular interest because it clearly is more toxic than the methyl ester (18 L). This recalls to mind the quenching effect of the

Figure 15. Effect of the size of the ester moiety

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
18 L	Methyl N,N-dimethyldithiocarbamate	 $CH_3-N(CH_3)-\overset{S}{\overset{\parallel}{C}}-S-CH_3$	10	0
2624	1-Benzotriazolylmethyl N,N-dimethyldithiocarbamate		14	332
1246	2,4-Dinitrophenyl N,N-dimethyldithiocarbamate		160	167

nitro group when attached to an alkyl ester of the oxygen analogues. The nitro group will be discussed further in the second section below on electronegative compounds.

Another interesting comparison is the 1-benzotriazolylmethyl ester of dimethyldithiocarbamic acid (No. 2624), and the methyl ester (No. 18 L). The methyl ester of dimethyldithiocarbamic acid is non-toxic to either test organism. The 1-benzotriazolymethyl ester (No. 2624), however, is very toxic to *Monilinia* but non-toxic to *Stemphylium*. The latter compound may well be sufficiently fat soluble for permeation into *Monilinia* but too fat soluble for entering *Stemphylium*. In that sense it confirms the comparative effects of 29 L and 3134 (see Figure 22 below). Another possibility is that the deesterification would release both a dithiocarbamate and a benzotriazole moiety. We have tested, however, benzotriazole itself and it is equally toxic to both test organisms. Thus, the fat-soluble explanation seems the better of these two.

As a final point about the size of the ester moiety, we should say that we have available several other large esters but that all have strong electronegative groups that probably serve to confuse the lipophilic picture. These will be discussed in the next section on electronegative groups. Thus, what little evidence we have indicates that increasing the size of the ester moiety exerts a small increase in the activity of DDC esters.

Pluijgers' (1959) data on DDC esters are more complete than ours. His order of potency for the DDC esters follows: methyl < ethyl < isopropyl < $-CH_2CH_2-S-CH_3$ < $-CH_2C_6H_5$. Thus, Pluijgers finds the benzyl ester to be the best of the DDC esters, but it was the weakest of the two we tried for the nabam series (see below). Perhaps this is not unexpected. The evidence continues to pile up that the two series display different kinds of activity.

The effect of lipophilic substituents on the nitrogen atom will be discussed later.

Effect of electronegative groups in the ester moiety. As we have seen, chlorine in the oxygen esters, especially if conjugated to the acid moiety, improves fungitoxicity greatly. We have only one chlorinated thiocarbamate (No. 5325) available for study. This is the 2,3-dichloroallyl ester of N,N-diisopropylthiolcarbamate (See Section II of Figure 14). The only chlorine-free analogue available for comparison (also Figure 14) is No. 5290, which is the ethyl ester of the N,N-dipropylthiolcarbamate. The chlorine does seem to boost the activity.

As we mentioned earlier in discussing Figure 15, the 2, 4-dinitrophenyl ester of dimethyldithiocarbamic acid (No. 1246) appears to be more toxic than the methyl ester (18 L). Pluijgers' (1959) data show a striking effect of a 4-nitro substituent in the benzyl ester. Instead of increasing toxicity, the nitro group quenches it altogether. And the same is true with the 4-chlorophenyl analogue. Now in the benzyl ester the ring is separated from the sulfur by a methylene bridge. The electronegativity of the *para* substituted $-NO_2$ group could place stress on the sulfur bridge in the phenyl derivative but not in the benzyl homologue.

Carbonyl groups in the proper place in the ester can also exert tension on the ester linkage. We have drawn together all applicable DDC compounds in Figure 16.

Figure 16 is comprised of three sections. Section I contains the three available non-carbonyl bearing analogues to use as checks. Section II contains those compounds with carbonyls immediately adjacent to the sulfur bridge of the carbamate moiety. And Section III contains those compounds where the carbonyl is separated from the sulfur by one or more carbons.

The hypothesis to be tested in Figure 16 is that compounds in Section II with carbonyls juxtaposed to the sulfur should be more toxic than those in Section I without carbonyls in the ester or those in Section III where the carbonyls are at a distance from the sulfur bridge.

We can examine Figure 16 also for evidence on a hypothesis set up earlier that *Monilinia* is better able to split a carbamate ester than *Stemphylium*. If a carbonyl aids in cleaving an ester, it should aid an inefficient organism more than an efficient one.

Considering these hypotheses, it is clear that compounds with juxtaposed carbonyls (Section II) are generally more toxic than those in Section I or III and that this applies more to *Stemphylium* than to *Monilinia*.

As an example, compare No. 2336 in Section I to its appropriate analogue in Section II (No. 2656) and in Section III (No. 4264). The toxicity indexes for *Stemphylium* are 115, 269, and 100, respectively. Those for *Monilinia* are 202, 282, and 200. Compound 2314 in Section I has a comparable analogue in Section II (No. 3486). The toxicity indexes for *Stemphylium* are 50 and 158, for *Monilinia* 202 and 154. The Section III analogue of No. 2314 is No. 2322. This one is complicated by the pentachlorophenol moiety. Even so it is less toxic for *Stemphylium* but may be not significantly so than No. 3486 in Section II. It seems to be really more toxic to *Monilinia* than No. 3486.

To return to the general comparison of Section II and Section III, none of the 7 compounds in Section III (separated carbonyls) reaches a toxicity value of 200 for *Stemphylium*, whereas 6 of the 14 in Section II (juxtaposed carbonyls) are 200 or more. Two of these are near 300 and two of those below 200 are 194 and 184.

The three unexpectedly weak compounds in Section II are Nos. 3489, 3491, and 3495. These compounds need further study.

At any rate we may conclude from Figure 16 that carbonyls properly placed in the ester do in fact improve toxicity especially to *Stemphylium*. The probable explanation is that the electronegative group weakens the sulfur linkage and helps to deesterify the compound. This is further evidenced by the greater effect on *Stemphylium* than on *Monilinia*.

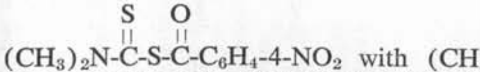
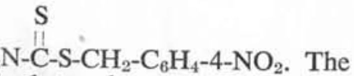
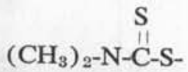
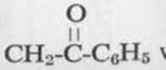
Pluijgers' (1959) data give confirmation of these conclusions about the action of the carbonyls. The carbonyl effect is shown by comparing  $(CH_3)_2N-\overset{\overset{S}{\|}}{C}-S-\overset{\overset{O}{\|}}{C}-C_6H_4-4-NO_2$ with  $(CH_3)_2N-\overset{\overset{S}{\|}}{C}-S-CH_2-C_6H_4-4-NO_2$. The former contains the juxtaposed carbonyl. The latter does not. The former is fungitoxic at about 0.5 to 5 parts per million. The latter is not toxic at 500 parts per million. The quenching effect of inserting a methyl bridge between the acid sulfur and the carbonyl may be seen in  $(CH_3)_2-N-\overset{\overset{S}{\|}}{C}-S-CH_2-\overset{\overset{O}{\|}}{C}-C_6H_5$ which is not more active than the analogue with no carbonyl.

Figure 16. Effect of electronegative groups in the ester moiety

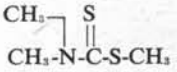
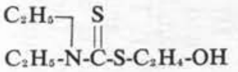
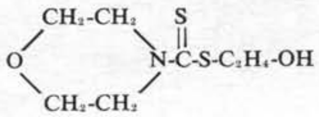
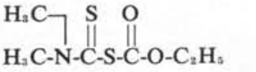
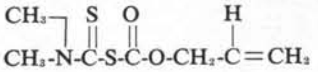
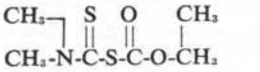
			Toxicity Index	
Number	Name	Structure	*Stemphylium*	*Monilinia*
		Section I		
18 L	Methyl N,N-dimethyldithiocarbamate	 $CH_3\text{-}\overset{CH_3}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}CH_3$	10	0
2336	Diethyldithiocarbamic acid, 2-hydroxyethyl ester	 $C_2H_5\text{-}\overset{C_2H_5}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}C_2H_4\text{-}OH$	115	202
2314	4-Morpholinecarbodithioic acid, 2-hydroxyethyl ester		50	202
		Section II		
2656	Carbethoxy dimethyldithiocarbamate	 $H_3C\text{-}\overset{H_3C}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_5$	269	282
3143	Carballyloxy dimethyldithiocarbamate	 $CH_3\text{-}\overset{CH_3}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{C}}=CH_2$	194	248
3122	Carbisopropoxy dimethyldithiocarbamate	 $CH_3\text{-}\overset{CH_3}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\vert}{CH_3}}$	333	288
3489	Isopropoxycarbonyl N,N-diisopropyldithiocarbamate	 $isoC_3H_7\text{-}\overset{isoC_3H_7}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\vert}{C}H}\text{-}CH_3$	79	155

Figure 16. Effect of electronegative groups in the ester moiety (continued)

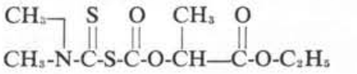
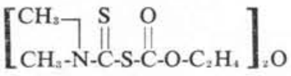
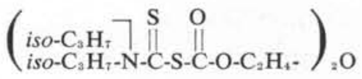
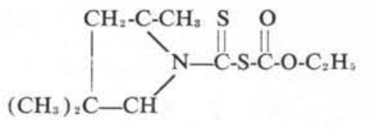
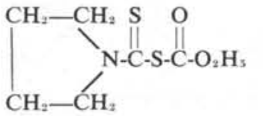
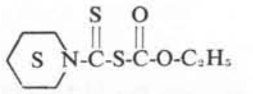
			Toxicity Index	
Number	Name	Structure	*Stemphylium*	*Monilinia*
3491	Isopropoxycarbonyl N-isononyldithiocarbamate	 $iso\text{-}C_9H_{19}\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\vert}{C}H}\text{-}CH_3$	78	321
3495	1-Ethoxycarbonylethoxycarbonyl dimethyldithiocarbamate	 $CH_3\text{-}\overset{CH_3}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\vert}{C}H}\text{—}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_5$	121	166
3136	Carbo(diethyleneglycoloxy)bis(dimethyldithiocarbamate)	 $\left[CH_3\text{-}\overset{CH_3}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_4\right]_2O$	200	200
3629	3-Oxapentylene-1,5-dioxycarbonyl N,N-diisopropyldithiocarbamate	 $\left(iso\text{-}C_3H_7\text{-}\overset{iso\text{-}C_3H_7}{N}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_4\text{-}\right)_2O$	184	225
3131	Ethoxycarbonyl 2,4,4-trimethyltetramethylenedithiocarbamate		228	300
3149	Carbethoxy tetramethylenedithiocarbamate		177	189
3144	Carbethoxy pentamethylene dithiocarbamate		137	199

Figure 16. Effect of electronegative groups in the ester moiety (continued)

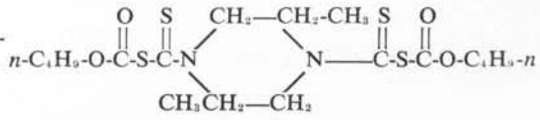
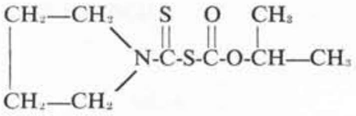
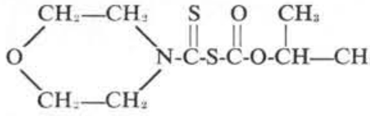
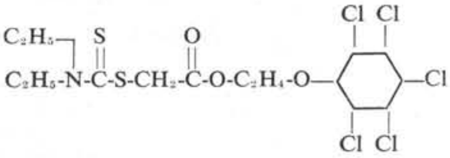
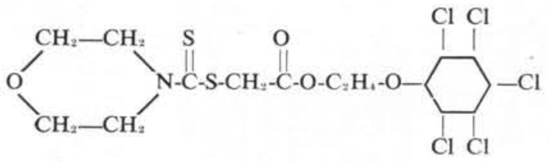
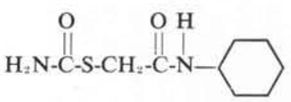
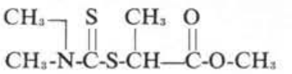
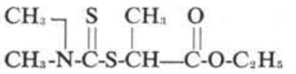
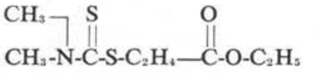
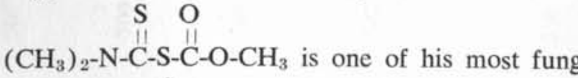
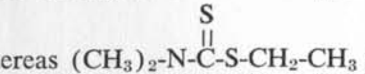
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3627	Di-*n*-butoxycarbonyl 2,5-dimethylpiperazine-1,4-biscarbodithioate		222	310
3488	Isopropoxycarbonyl tetramethylenedithiocarbamate		278	383
3486	Isopropoxycarbonyl 4-morpholine carbodithioate		158	154
	Section III			
4264	Dimethyldithiocarbamic acid, ethyl acetate ester	 $(CH_3)_2N\text{-}C(=S)\text{-}S\text{-}CH_2\text{-}C(=O)\text{-}O\text{-}C_2H_5$	100	200
2312	Diethyldithiocarbamic acid, 2-(pentachlorophenoxy) ethyl acetate ester		0	223

Figure 16. Effect of electronegative groups in the ester moiety (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
2322	4-Morpholinecarbodithioic acid, 2-(pentachlorophenoxy)ethyl actetate ester		133	276
642	α-Mercaptoacetanilide carbamate		188	162
2882	Dimethyldithiocarbamic acid, methyl propionate ester	 $(CH_3)_2N\text{-}C(=S)\text{-}S\text{-}CH(CH_3)\text{-}C(=O)\text{-}O\text{-}CH_3$	100	252
4268	α-Dimethyldithiocarbamic acid, ethyl propionate ester	 $(CH_3)_2N\text{-}C(=S)\text{-}S\text{-}CH(CH_3)\text{-}C(=O)\text{-}O\text{-}C_2H_5$	157	200
4266	β-Dimethyldithiocarbamic acid, ethyl propionate ester	 $(CH_3)_2N\text{-}C(=S)\text{-}S\text{-}C_2H_4\text{-}C(=O)\text{-}O\text{-}C_2H_5$	100	200

Pluijgers has still another example of the effect of a carbonyl in the ester.  $(CH_3)_2\text{-N-}\overset{\overset{S}{\|}}{C}\text{-S-}\overset{\overset{O}{\|}}{C}\text{-O-CH}_3$ is one of his most fungitoxic compounds whereas  $(CH_3)_2\text{-N-}\overset{\overset{S}{\|}}{C}\text{-S-CH}_2\text{-CH}_3$ is one of the weakest.

Pluijgers explains the action as we do, that the free acid is probably formed without explicitly stating that the effect of the electronegative group is to weaken the ester linkage.

We can conclude, then, that the thiocarbamates confirm the carbamates and that an electronegative group in the ester improves activity especially on *Stemphylium,* presumably by encouraging deesterification. This point will be discussed further when we take up the monosulfides and the disulfides.

Effect of electropositive groups in the ester moiety. One of our test compounds, (No. 1223, Figure 17) has an amino group attached to the sulfur of the carbamic acid. It may be compared with the methyl analogue (No. 2799). It is clearly much less toxic especially to the less sensitive organism, *Stemphylium.* Presumably the dithiocarbamic acid does not form as readily from the amino compound as it does from the methyl analogue.

Smale *et al.* (1956) give some data on an electropositive grouping in a DDC ester. They show that cysteine will essentially quench the toxicity of sodium dimethyldithiocarbamate. Obviously here we have the typical DDC-sulfhydryl reaction to give  $(CH_3)_2\text{-N-}\overset{\overset{S}{\|}}{C}\text{-S-CH}_2\text{-}\overset{\overset{NH_2}{|}}{CH} - \text{COOH}$. Here the quenching group is probably the $-NH_2$. Without the $-NH_2$ group, the compound approximates No. 4226 of Figure 16, which is reasonably fungitoxic.

Effect of a single substitution on the nitrogen. In contrast to the carbamates, we have only a few thiocarbamates in the DDC series with but a single substituent on the nitrogen. These few are assembled in Figure 18. It is clear that the phenyl ring (No. 1257 and 1117 H) is a much better substituent on the nitrogen atom than an ethyl group (No. 1255) for the thiono analogue. This was shown earlier (Figure 6) to be true for the carbamates as well.

Similarly, it seems that a 9-carbon chain (No. 3491) is inferior to a 2-furfuryl substituent (No. 3496) for *Stemphylium.*

Effect of double substitution on the nitrogen. In discussing the oxygen analogues (Figure 11) we concluded that eliminating the labile N-hydrogen by doubly substituting the nitrogen quenched or highly curtailed the toxicity especially to *Stemphylium.*

This problem is more difficult to test with the thiocarbamate esters (Figure 19) because of the absence of really suitable singly substituted analogues. However, we can make two reasonably direct comparisons. Single substituted 9 L is vastly more fungitoxic than doubly substituted No. 5290, but on the other hand 9 L contains an N-phenyl ring which as we have already said adds greatly to toxicity. Similarly, singly substi-

Figure 17. Effect of an electropositive group attached to the sulfur atom

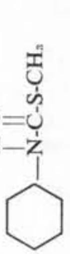
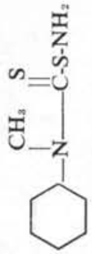
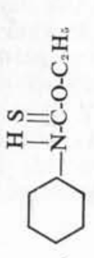
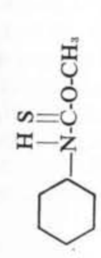
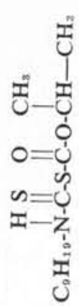
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
2799	Methyl N-phenyldithiocarbamate		272	300
1223	S-(Methylphenylthiocarbamyl) hydrosulfamine		0	220

Figure 18. Effect of a single substitution on the nitrogen atom

Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
		Section I		
1255	Ethyl N-ethylthionocarbamate	 $C_2H_5\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_5$	44	92
1257	Ethyl N-phenylthionocarbamate		250	250
1117 H	Methyl N-phenylthionocarbamate		200	350
		Section II		
3491	Isopropoxycarbonyl N-isononyldithiocarbamate	 $C_9H_{19}\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\vert}{CH}}\text{—}CH_2$	78	321
3496	Isopropoxycarbonyl N-furfuryldithiocarbamate		202	293

tuted No. 1255 is more fungitoxic than doubly substituted 18 L. Here, also the case is not clear-cut, because No. 1255 is a thiono compound and 18 L is a dithio derivative.

For the rest we shall have to be content with examining the 20 doubly substituted DDC derivatives and comparing them one with the other. These are grouped into three levels of toxicity in Sections II, III, and IV of Figure 19. The non-toxic ones are those with toxicity values up to about 50, weakly toxic with values up to about 200, and strongly toxic with values over 200. With three strong exceptions the groupings are the same for the two test organisms. The three exceptions are Nos. 2312, 2314, and 5325, which appear in the non-toxic group (Section II). They are not toxic to *Stemphylium*, but are strongly toxic to *Monilinia*. We have no ready explanation for this difference. Nos. 2312 and 5325 are highly chlorinated esters. By the rules discussed earlier, their esters should break off easily and this should make them toxic to both test fungi.

The groupings display an interesting characteristic of the data. Except for No. 5325, there are no easily opened esters in the non-toxic group. There are 5 out of the 10 in the weakly toxic group, but all are easily opened in the toxic group. By easily opened, we mean that they contain electronegative groups so placed as to put strain on the sulfur bridge.

Whatever else one could say about Figure 19, one thing is clear. Doubly substituted DDC esters are much more likely to be fungitoxic even to *Stemphylium* than their oxygen containing counterparts listed in Figure 11.

It would be easy to conclude that the larger number of toxic compounds in the sulfur series than in the oxygen series is due to the sulfur. Such a conclusion is too facile. The toxic DDC esters in Figure 16 all have strong electronegative carbonyls in the ester. No such compound appears in Figure 11 for the oxygen cousins.

Perhaps, the chemists will make oxygen containing compounds with electronegative carbonyls in the ester. They should be worthy of study as fungicides.

Effect of monosulfide and disulfide esters of DDC. The dithiocarbamates undergo oxidation to form monosulfides $(=N\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}N=)$, and disulfides $(=N\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}S\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}N=)$. These make interesting compounds to study because they demonstrate further the effect of electronegative groups in the ester moiety. Here the C=S (thione) groups rather than the carbonyls are the electron sinks that serve to break the sulfur bridge.

Hence, these esters should be more active than those that lack electronegative groups. As will be seen, they are the most fungitoxic of all the compounds discussed in this paper.

All of the data are given in Table 2 in the appendix. We have only one straight chain monosulfide. The two valences on each nitrogen are substituted with methyl groups to give bis-(dimethylthiocarbamyl) sulfide or tetramethylthiuram monosulfide (TMTM, No. 411 in Figure 20). It has a mean index of 297 for *Stemphylium* and 356 for *Monilinia*. Even though

Figure 19. Effect of double substitution on the nitrogen atom

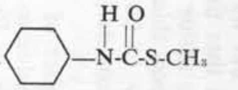
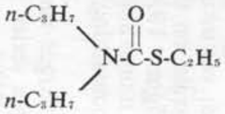
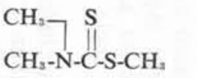
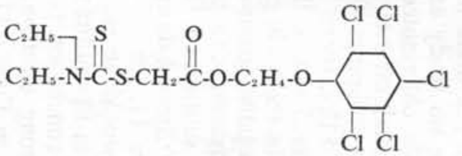
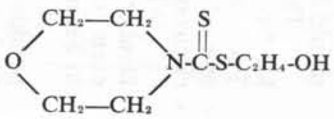
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
		Section I		
9 L	Methyl N-phenylthiolcarbamate		201	233
5290	Ethyl N,N-di-*n*-propylthiolcarbamate	 $(n\text{-}C_3H_7)_2N\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}S\text{-}C_2H_5$	0	129
1255	Ethyl N-ethylthionocarbamate	 $C_2H_5\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}O\text{-}C_2H_5$	44	92
18 L	Methyl N,N-dimethyldithiocarbamate	 $(CH_3)_2N\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}CH_3$	10	0
		Section II Non-toxic to *Stemphylium*		
2312	Diethyldithiocarbamic acid, 2-(pentachlorophenoxy)ethyl acetate ester		0	223
2314	4-Morpholinecarbodithioic acid, 2-hydroxyethyl ester		50	202

Figure 19. Effect of double substitution on the nitrogen atom (continued)

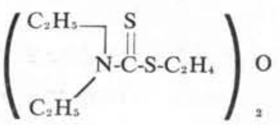
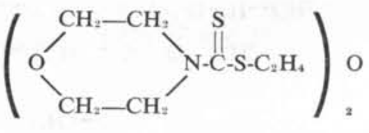
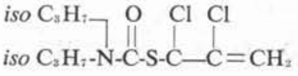
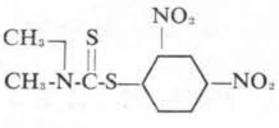
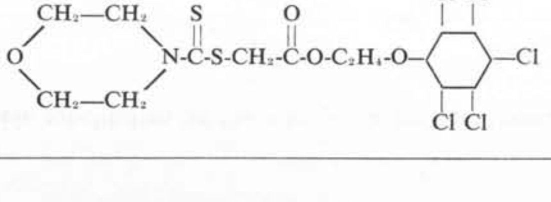
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
2321	Diethyldithiocarbamic acid, 2,2′-oxydiethyl diester	 $\left((C_2H_5)_2N\text{-}\overset{S}{\overset{\Vert}{C}}\text{-}S\text{-}C_2H_4\right)_2O$	0	0
2357	4-Morpholinecarbodithioic acid, 2,2′-oxydiethyl diester		0	0
5325	2,3-Dichloroallyl N,N-diisopropylthiolcarbamate	 $(iso\ C_3H_7)_2N\text{-}\overset{O}{\overset{\Vert}{C}}\text{-}S\text{-}\overset{Cl}{\overset{\vert}{C}}\text{—}\overset{Cl}{\overset{\vert}{C}}=CH_2$	35	227
		Section III Weakly toxic to both organisms		
1246	2,4-Dinitrophenyl N,N-dimethyldithiocarbamate		160	167
2322	4-Morpholinecarbodithioic acid, 2-(pentachlorophenoxy)ethyl acetate ester		133	276

Figure 19. Effect of double substitution on the nitrogen atom (continued)

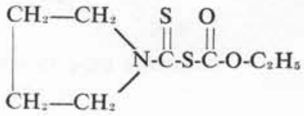
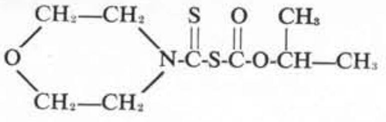
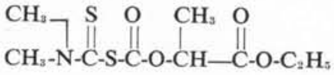
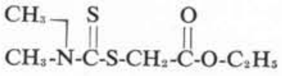
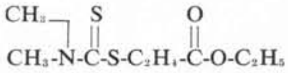
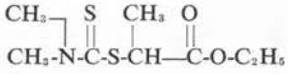
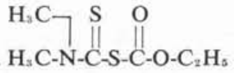
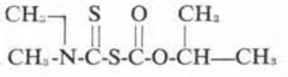
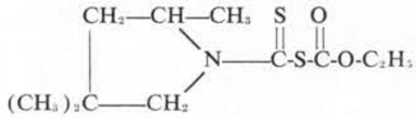
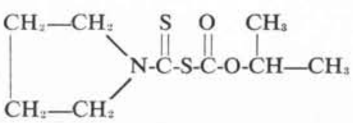
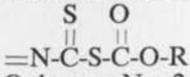
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
2336	Diethyldithiocarbamic acid, 2-hydroxyethyl ester	 $C_2H_5\text{-}N(C_2H_5)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}C_2H_4\text{-}OH$	115	202
3149	Carbethoxy tetramethylenedithiocarbamate		177	189
3486	Isopropoxycarbonyl 4-morpholine carbodithioate		158	154
3489	Isopropoxycarbonyl N,N-diisopropyldithiocarbamate	 $iso\ C_3H_7\text{-}N(iso\ C_3H_7)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\|}{C}H}\text{—}CH_3$	79	155
3495	1-Ethoxycarbonyl ethoxycarbonyl dimethyldithiocarbamate	 $CH_3\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\|}{C}H}\text{—}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	121	166
4264	Dimethyldithiocarbamic acid, ethyl actetate ester	 $CH_3\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	100	200

Figure 19. Effect of double substitution on the nitrogen atom (continued)

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
4266	β-Dimethyldithiocarbamic acid, ethyl propionate ester	 $CH_3\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}C_2H_4\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	100	200
4268	α-Dimethyldithiocarbamic acid, ethyl propionate ester	 $CH_3\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{CH_3}{\overset{\|}{C}H}\text{—}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	157	200
	Section IV Strongly toxic to both organisms			
2656	Carbethoxy dimethyl dithiocarbamate	 $H_3C\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	269	282
3122	Carbisopropoxy dimethyldithiocarbamate	 $CH_3\text{-}N(CH_3)\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{CH_3}{\overset{\|}{C}H}\text{—}CH_3$	333	288
3131	Ethoxycarbonyl 2,4,4-trimethyl tetramethylenedithiocarbamate		228	300
3488	Isopropoxycarbonyl tetramethylenedithiocarbamate		278	383

TMTM is more fungitoxic than most of the carbamates discussed above, like them it is more toxic to *Monilinia* than to *Stemphylium*.

At this point we can refer again to the series of compounds mentioned earlier in the section on electronegative groups. These may be called monosulfides in a sense because they contain the following nucleus  $=\text{N-}\overset{\overset{S}{\|}}{C}\text{-S-}\overset{\overset{O}{\|}}{C}\text{-O-R}$. Data on all of these were given above in Figure 19. Only one, No. 2656, is reproduced in Figure 20 as a sample. It approaches TMTM in fungitoxicity. The others vary around TMTM.

The thiuram disulfides are also given in Figure 20. The disulfides, of course, have the sulfur-to-sulfur linkage. We tested the tetramethyl, tetraethyl, and morpholine derivatives. There is little difference between the methyl (No. 24) and ethyl (No. 505) homologues, but the morpholine analogue (No. 317) seems to be definitely less fungitoxic.

An interesting analogue of morpholine thiuram disulfide is No. 1578. It may be considered as a morpholinethiuram disulfide without the disulfide bridge. The nucleus is  $=\text{N-}\overset{\overset{S}{\|}}{C}\text{-}\overset{\overset{S}{\|}}{C}\text{-N=}$ instead of  $=\text{N-}\overset{\overset{S}{\|}}{C}\text{-S-S-}\overset{\overset{S}{\|}}{C}\text{-N=}$. Since there is no sulfur bridge to open, one might expect that there would be no toxicity and there is none.

Lastly, we have one disulfide that is based on a chlorobenzene sulfonic acid, No. 2311. It is more fungitoxic than morpholinethiuram disulfide, but less toxic than tetramethylthiuram disulfide (No. 24).

Montgomery and Shaw (1943) showed that the disulfide (No. 24) is more toxic than the monosulfide (No. 411). This is true here for *Stemphylium*.

A little work has been done on the enzyme systems that are affected by bis(dithiocarbamyl)disulfide, TMTD. Sisler and Cox (1951) reported that it inhibited exogenous but not endogenous respiration. They expanded these observations later (1952) and said that it inhibited use of glucose and of fructose-1,6-diphosphate by yeast. On the other hand, it does not affect fermentation of 3-phosphoglyceric acid and pyruvic acid by yeast.

Sulfhydryl compounds like cysteine and glutathione inhibit the effects of TMTD. They conclude that TMTD inhibits use of glucose by yeast by preventing conversion of fructose-1,6-diphosphate to the 3-carbon intermediates.

Effect of isothiocyanates of DDC. Data on isothiocyanates are given in Table 2 and in Figure 21. We have included in Figure 21, a rhodanine (No. 2948) and a thiadiazinethione (Mylone-No. 4935) because they are described as transforming into isothiocyanates by van der Kerk (1959).

Earlier in this paper, we concluded that isocyanates probably play no role on fungitoxicity of the oxygen analogues, (a) because isocyanates themselves are not very toxic and (b) because the formation of an isocyanate involves a dehydration step and this is highly unlikely in an aqueous medium.

Conceivably an isothiocyanate could be different because removal of H_2S is postulated rather than removal of H_2O. This reaction would be attractive to some because of the high enthusiasm in some quarters for the action of H_2S in accounting for fungitoxicity of sulfur containing compounds.

Figure 20. Effect of monosulfide and disulfide esters of DDC

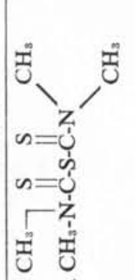
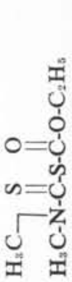
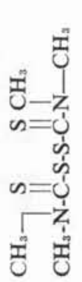
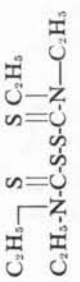
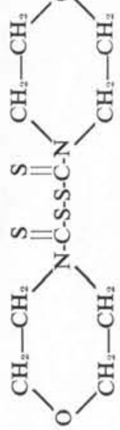
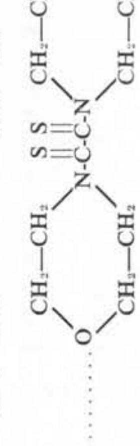
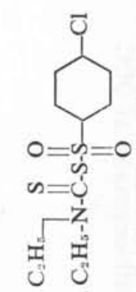
Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
411	Bis(dimethylthiocarbamyl) sulfide		297	356
2656	Carbethoxydimethyl dithiocarbamate		269	282
24	Bis(dimethylthiocarbamyl) disulfide		342	328
505	Bis(diethylthiocarbamyl) disulfide		322	328
317	Dimorpholinethiuram disulfide		268	239
1578	Dithioxalodimorpholide		6	0
2311	Diethyldithiocarbamic acid, anhydrosulfide with *p*-chlorothiolbenzenesulfonic acid		296	386

Figure 21. Effect of isothiocyanates of DDC

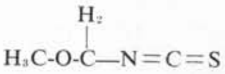
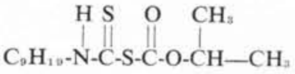
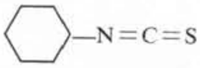
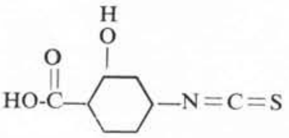
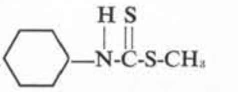
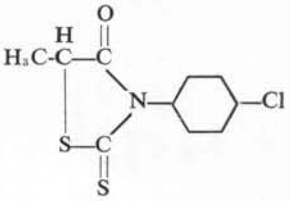
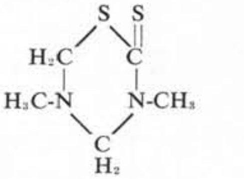
Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
3040	Methoxymethyl isothiocyanate	 $H_3C\text{-}O\text{-}\overset{H_2}{C}\text{—}N{=}C{=}S$	100	200
63	Allyl isothiocyanate	$H_2C{=}CH{=}CH\text{-}CH_2\text{-}N{=}C{=}S$	136	295
2633	*n*-Butoxymethyl isothiocyanate	$n\text{-}C_4H_9\text{-}O\text{-}CH_2\text{-}N{=}C{=}S$	77	50
1690A	*t*-Octyl isothiocyanate	$t\text{-}C_8H_{17}\text{-}N{=}C{=}S$	400	400
1255	Ethyl N-ethylthionocarbamate	 $C_2H_5\text{-}\overset{H}{N}\text{-}\overset{S}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5$	44	92
3491	Isopropoxycarbonyl N,isononyldithiocarbamate	 $C_9H_{19}\text{-}\overset{H}{N}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{CH_3}{CH}\text{—}CH_3$	78	321
723	Phenyl isothiocyanate		83	239
3244	4-Isothiocyanosalicylic acid		228	349

Figure 21. Effect of isothiocyanates of DDC (continued)

Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
2799	Methyl N-phenyldithiocarbamate		272	300
2948	3-(*p*-Chlorophenyl) 5-methyl rhodanine		400	400
4935	3,5-Dimethyltetrahydro-1,3,5-2H-thiadiazine-2-thione		358	400

If the reaction does go to completion by liberating H_2S, then isothiocyanates should be more than usually toxic to *Monilinia* in comparison with *Stemphylium*. This is because *Monilinia*, according to McCallan and Wilcoxon (1931), is much more sensitive to H_2S than *Stemphylium*. Even a brief glance at Figure 21 will show, however, that the reverse is true. The compounds are more toxic than expected to *Stemphylium*.

Thus, it is hard to make a case for a role for isothiocyanates in dithiocarbamate toxicity by testing the isothiocyanate derivatives themselves. This is not to say, of course, that isothiocyanates are not fungitoxic because they surely are. Examination of Figure 21 shows that with only one exception (No. 2633) all isothiocyanates are as toxic as or more toxic than the best isocyanate in Figure 12. This is particularly striking for *Stemphylium* which, relative to *Monilinia* is considerably more sensitive to isothiocyanates than to isocyanates. In Figure 21 are shown two isothiocyanates (Nos. 1690A and 3244), and two compounds said to decompose to isothiocyanates (Nos. 2948 and 4935) with toxicity indexes for *Stemphylium* greater than 200. None of the six isocyanates show a value even as high as 100.

The central theme of this paper is the fungitoxicity of carbamates and dithiocarbamates, not so much the toxicity of their isocyanates or isothiocyanate analogues. Wedding and Kendrick (1959) found quite different toxicological effects between N-methyldithiocarbamate and methylisothiocyanate. In other words, their data, like ours, lend little credence to a view that an isothiocyanate, however toxic itself, is involved in the activity of dithiocarbamates.

Discussion of DDC Esters

There are many similarities between the dithiocarbamate esters and their dioxygen analogues. Electronegative groups in the esters seem to act similarly and suggest the same conclusion that deesterification enhances the fungitoxicity. Then, too, it seems no more necessary to invoke any involved conversion to an isothiocyanate derivative than for the carbamates.

The big difference seems to be in the matter of the effect of doubly substituted nitrogen atoms. Doubly substituted carbamates are bland to *Stemphylium* but dithiocarbamate analogues are not bland. They are toxic. This poses a puzzle.

Please recall, however, that doubly substituting the nitrogen of the oxygen carbamates does not quench the toxicity to *Monilinia*, only to *Stemphylium*. Thus, it seems that *Stemphylium* acts toward dithiocarbamates as *Monilinia* does to carbamates or dithiocarbamates.

In the case of carbamates, we postulated that a carbamate is hydrolyzed to the free acid which decomposes to an amine and CO_2; that the amine is the toxic moiety; that a secondary amine is satisfactory for *Monilinia* but that a primary amine is required for *Stemphylium*.

The dithiocarbamate esters must, somehow, act differently. The amine can hardly be the whole story, because it should be the same whether it is recovered from an oxygen or from a sulfur containing carbamate. If this were not so, methyl-N-phenyldithiocarbamate (see Figure 14) would not be so much more toxic than methyl-N-phenylcarbamate and ethyl-N-phenylthionocarbamate would not be so much more toxic than ethyl-N-phenylcarbamate.

We have considered various possibilities to account for this.

1. We can preserve the amine hypothesis by assuming that dithiocarbamates permeate more rapidly and, thereby, carry more amine in than carbamates, but there is no evidence for this.

2. We can postulate that the CS_2 formed from the dithiocarbamate provides the necessary extra toxicity. We should remember, too, when thinking of a possible role for CS_2 that thiono and thiol analogues are less fungitoxic than the straight dithiocarbamates. The thiono and thiol compounds, upon hydrolysis, would each liberate $O{=}C{=}S$ instead of $S{=}C{=}S$.

We really need a wider selection of thiono and thiol analogues, especially some with strong electronegative groups at the proper place in the ester. The chief difficulty with a CS_2 hypothesis is that CS_2 is considered to be a very weak fungitoxicant (Rich and Horsfall, 1950).

CS_2 is weak when tested by offering it directly to spores. There is an outside possibility that the CS_2 molecule does not permeate even though it surely is fat soluble enough. Perhaps it is too fat soluble like some of the molecules discussed herein. We are postulating already that a properly designed carbamate is a good wagon to carry the toxophore in. In this case it carries the CS_2 in just as it carries the amine in and sets it free deep in the heart of the fungus cell.

CS_2 is known to react with amino groups and there are a plethora of such groups inside the cell for it to react with. We do not know. In any case when we suggest CS_2 and an amine we are returning to Parker-Rhodes who postulated just that in 1943.

3. Chelation is another possibility. According to Martell and Calvin (1952, p. 169-171) N chelates more readily than O with Cu^{I} and CU^{II}. S chelates more readily than O with Cu^{I}, but O chelates more readily than S with Cu^{II}. The less substitution on O and N the greater is their ability to chelate. However, the greater the substitution on S the greater its ability to chelate; i.e. $R_2S > RSH > H_2S$.

Before leaving the DDC derivatives, we might recall the very unsettled matter of polymodal curves first reported by Dimond *et al.* (1941).

At present, the most satisfactory explanation for the polymodal curve of DDC is based on Goksøyr's theory (1955). Presumably, the increasing doses of DDC chelate with the fixed amount of copper in the medium to give different chelate forms. These chelate forms differ in their fungitoxicity. The lower concentrations of DDC^-, insufficient to saturate the copper, produce the half chelate: $Cu(DDC)^+$. The half chelate is the most toxic form of the copper-DDC series and poisons at the lower doses. This is the first zone of inhibition. Additional DDC^- then saturates the toxic half chelate to produce the nontoxic full chelate: $Cu(DDC)_2$. As the nontoxic $Cu(DDC)_2$ is formed at the expense of the $Cu(DDC)^+$, toxicity falls and the fungus can grow. This is the zone of reversal. Finally, after saturating the metals in the medium, additional doses of DDC^- begin to poison the fungus as free DDC^- ions. This is the second zone of inhibition. The toxic mechanisms of the first zone appears to be different from that of the second zone. By adding other chelators, Sijpesteijn and Janssen (1959) alleviated fungitoxicity in the first zone but not in the second. They concluded that the alleviation was caused by additional chelators competing with DDC$^-$ for the limited amount of copper in the medium. Hence, metals are necessary for the toxicity of DDC$^-$ in the first zone but not in the second zone.

None of these hypotheses is wholly convincing. We conclude that the sulfur makes the difference. What it does we do not know.

It seems strange that most of the weed killer research has centered around the oxygen analogues. Van der Kerk *et al.* (1955) investigated the action of the thioglycolic acid and its thiol and thiono analogues. They showed that  $(CH_3)_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH$ is a growth regulant for green plants. If, however, they changed the C=S group to C=O activity is lost, but not when the -C-S-group was changed to -C-O-C.

EFFECT OF NABAM ESTERS

We have separated the derivatives of nabam from those of DDC because of evidence that they may function by different biological mechanisms. The data on all the available nabam esters are brought together in Table 3.

Effect of Simple Nabam Esters

We tested (Figure 22) three simple esters of nabam, ethylenebisdithiocarbamic acid, and two oxygen analogues.

As in the case of the DDC esters, the oxygen analogues of nabam (Nos. 15 L and 16 L) are very much less fungitoxic than the sulfur compounds. So far as the nabam esters themselves are concerned, we tested the methyl (29 L), the benzyl (No. 3134) and the benzoyl (No. 3138) esters. The benzyl ester surely does not improve activity. In fact it quenches the activity for *Stemphylium* possibly by overdoing the factor of lipid solubility. In the case of carbamates (Table 1) the phenethyl ester (No. 3416) is more fungitoxic than the methyl (No. 4 L) for *Monilinia*. Here the benzyl, that is the phenyl methyl ester is much less toxic. This could be because the mode of action differs, or only because the whole molecule is much larger in the nabam series. The benzoyl ester is just as strong as the benzyl ester is weak, but the benzoyl ester contains a strong electronegative carbonyl group to aid deesterification.

Collins and Wiese (1955) present data on the toxicity of a few nabam esters to fungi pathogenic to man. The order of potency follows: diallyl > bis-2-hydroxyethyl > bis-3-hydroxypropyl > di-*n*-propyl > dibenzyl. The diallyl ester leads. It is interesting that Davies and Sexton (1946) state that the allyl ester of the dialkyl series is also the most fungitoxic that they tried.

From our data and those of Collins and Wiese (1955) it seems fairly clear that increasing the lipid solubility of the ester reduces potency. This result, be it noted, is out of agreement with the carbamate esters. The nabam molecule is so large already that a further increase in size seems to be incompatible with high activity.

Figure 22. Effect of simple nabam esters

Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
29 L	Dimethyl ethylenebis(dithiocarbamate)	 $(\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{C}{\overset{\|}{C}}\text{-}S\text{-}CH_3)_2$	188	281
3134	Dibenzyl ethylenebis(dithiocarbamate)	 $\left(\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}CH_2\text{-}C_6H_{11}\right)_2$	0	206
3138	Dibenzoyl ethylenebis(dithiocarbamate)	 $\left(\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_{11}\right)_2$	390	400
15 L	Diethyl ethylenebiscarbamate	 $(\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}C_2H_5)_2$	78	187
16 L	Dimethyl ethylenebiscarbamate	 $(\text{-}CH_2\text{-}\overset{H}{\overset{\vert}{N}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_3)_2$	3	9

Effect of Monosulfide and Polysulfide Esters of Nabam

Nabam esters differ in a significant way from DDC esters in the type of monosulfide and disulfide formed. Nabam molecules, having a reactive group in either end can form a large ring structure. Such ring structures are shown in Figure 23. Presumably, these molecules can polymerize also end to end to form long chains.

DDC esters cannot form rings or polymerize into chains because they have only a single reactive group per molecule.

The nabam monosulfides, disulfides, and polysulfides are shown in Figure 23. There are two monosulfides (Nos. 4442 and 5346). Also are listed the disulfide (No. 5345), the trisulfide (No. 4579), and the tetrasulfide (No. 5363). Then we have tetrasulfides based on a propylene (3-carbon instead of 2-carbon nucleus No. 5362), on a phenylene diamine nucleus (909 H), and on a piperazine nucleus (No. 5361).

In the nabam series we find the most fungitoxic of all the esters tested. The ED 50 of ethylenethiocarbamyl monosulfide (ETM No. 5346) to *Stemphylium* is 0.045 μgm/cm² of treated surface—a very powerful spore killer.

In the nabam series, too, we come at long last to a carbamate that is more toxic to *Stemphylium* than to *Monilinia*. Figure 23 shows this for both ethylenebis(thiocarbamyl)monosulfide (No. 5346) and ethylenebis(thiocarbamyl)disulfide (ETD No. 5345). Rich and Horsfall (1950) pointed out several years ago that nabam itself is more toxic to *Stemphylium* than to *Monilinia.*

The difference between organisms is important. It adds another unit to the already impressive pile of evidence that dithiocarbamates of the nabam series differ in biological properties from the DDC series.

Stemphylium is about 40 times as sensitive to the monosulfide as *Monilinia.* If, however, the number of sulfur atoms in the ring is increased to two (No. 5345) the ratio falls from 40 to 1 to about 3 to 1. By the time the trisulfide and tetrasulfide are reached in the series, *Monilinia* is more sensitive than *Stemphylium.*

According to the ED 50 data the fungitoxicity falls in the following order for *Stemphylium*: monosulfide, disulfide, tetrasulfide, and still further to the propylene thiuram tetrasulfide. Insufficient data are available to decide where the trisulfide fits, but presumably it lies in between. This feature of the series suggests at first that permeation into *Stemphylium* declines as the lipid solubility is increased by adding more and more lipophilic sulfur. We remind ourselves again, however, that if permeation were the explanation, then potency to *Monilinia* should increase concomitantly, but it does not. As we know, generally *Monilinia* succumbs to the more lipophilic molecules, *Stemphylium* to the less lipophilic. Obviously this striking reversal for the two organisms warrants further research.

Rich and Horsfall (1954) have shown that the trisulfide and tetrasulfide are effective foliage protectants. Here, we must point out again, that these sulfides tend to polymerize and we do not know in specific samples how much has polymerized. Polymerization presumably reduces permeation and thus fungitoxicity. Klöpping (1951) and Ludwig and Thorne (1960) show that monomeric ethylenebis(thiocarbamyl)disulfide is more toxic than the polymeric form.

It seems significant that ethylenebis(thiocarbamyl)monosulfide is

Figure 23. Effect of nabam monosulfides and polysulfides

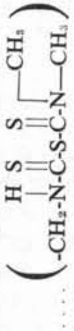
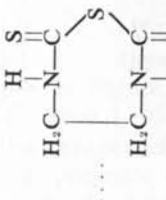
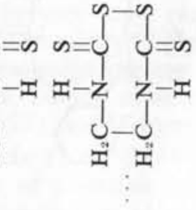
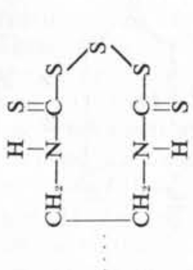
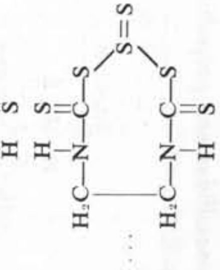
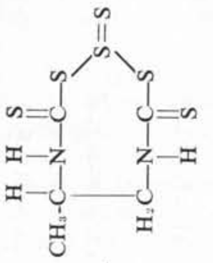
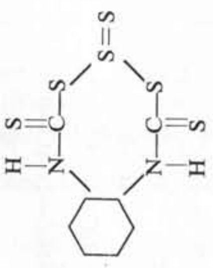
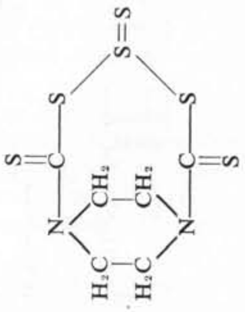
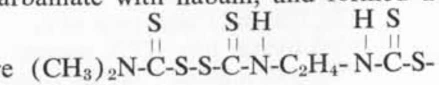
Number	Name	Structure	ED 50 gm/cm²		Toxicity Index	
			Stem.	Moni.	Stem.	Moni.
4442	Ethylenebis(dimethylthiocarbamyl) sulfide	 $\left(-CH_2-\overset{H}{\overset{\mid}{N}}-\overset{S}{\overset{\parallel}{C}}-S-\overset{S}{\overset{\parallel}{C}}-\overset{CH_3}{\overset{\mid}{N}}-CH_3\right)_2$	. . .	. . .	300	375
5346	Ethylenebis(thiocarbamyl)monosulfide		0.045	0.18	400	400
5345	Ethylenebis(thiocarbamyl)disulfide		0.16	0.39	300	323
4579	Ethylenebis(thiocarbamyl)trisulfide		. . .	. . .	359	400
5363	Ethylenebis(thiocarbamyl)tetrasulfide		3.63	. . .	328	377

Figure 23. Effect of nabam monosulfides and polysulfides (continued)

Number	Name	Structure	ED 50 gm/cm² Stem.	ED 50 gm/cm² Moni.	Toxicity Index Stem.	Toxicity Index Moni.
5362	Propylenebis(thiocarbamyl)tetrasulfide		4.26	...	280	395
909 H	1,4-Phenylenebis(thiocarbamyl)tetrasulfide		2.21	...	...	...
5361	Piperazinebis(thiocarbamyl)tetrasulfide		...	...	100	400

more toxic to both test organisms than the disulfide, because this is the reverse of the DDC series where ethylenebis(thiocarbamyl)disulfide is more fungitoxic than the monosulfide (See Figure 20 and also Kirby and Frick 1957). This is more evidence that the two series act differently.

Another disulfide in the nabam series was made by Bakkeren (1958) who reacted sodium dimethyldithiocarbamate with nabam, and formed a disulfide with the following structure  $(CH_3)_2N\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}S\text{-}\overset{S}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}C_2H_4\text{-}\overset{H}{\overset{|}{N}}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}$  $S\text{-}\overset{S}{\overset{\|}{C}}\text{-}N(CH_3)_2$. Van der Kerk (1959) reports that this compound has reached commercial adoption in Holland. It is similar to our No. 4442 (Figure 23). Both are examples of activity obtained by surrounding the sulfur atom with electronegative groups as Horsfall and Rich proposed several years ago (1953).

This leads us to explore the five nabam esters that have an electronegative carbonyl in the ester. The basic structure is  $(\text{-}CH_2\text{-}\overset{H}{\overset{|}{N}}\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}\overset{O}{\overset{\|}{C}}\text{-}R)_2$ and the data are displayed in Figure 24. Three (Nos. 3135, 3138, and 3148) of the five are in the very toxic range of nearly 400. These data provide further evidence that toxicity is greatly enhanced when the sulfur bridge is bracketed by electronegative groups. The electronegative esters of nabam shown in Figure 24 are closely related to those reported by Williams and Graham (1955) and Torgeson *et al.* (1960).

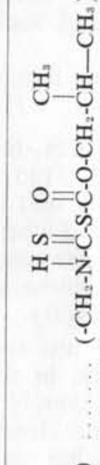
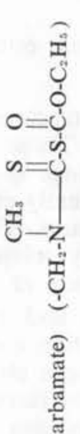
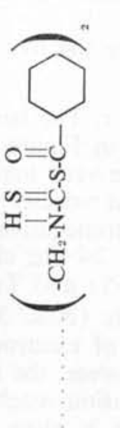
Two of the compounds (Nos. 3146 and 3147) are comparatively weak despite the presence of electronegative carbonyls in the ester. In these weak compounds, however, the nitrogen atom is doubly substituted. The result recalls the conclusion reached by Barratt and Horsfall (1947) that doubly substituting the N atom in nabam quenches its activity to *Stemphylium*.

With this result we come full circle in this paper so far as *Stemphylium* is concerned. In the carbamate series, doubly substituting the nitrogen atom quenches the activity to *Stemphylium*. In the DDC series this has no important effect on *Stemphylium*, and here in the nabam series it does have an effect.

Ethylenebis(thiocarbamyl)monosulfide (ETM, No. 5346) has generated a lot of enthusiasm as the compound most likely to succeed in explaining the fungitoxicity of nabam, a compound that is water soluble, highly ionizable, and highly fungitoxic. Ludwig *et al.* (1954) first proposed ETM when they isolated it from aerated water solutions of nabam. This was an important break-through. This, they said, can explain how a hydrophilic compound like nabam becomes lipophilic and, thus, can permeate the fungus cells and can cling to a leaf. The discovery of ETM was foreshadowed, however, by Barratt and Horsfall (1947) who said that zineb gained potency on standing in humid air. They postulated a new compound. Recently Grandi and Ciferri (1959) in Italy have shown that zineb gains potency when leached with water (presumably aerated water).

The trouble with Ludwig and Thorn's theory is that ethylenebis(thiocarbamyl)disulfide (ETD No. 5345) rather than ETM is the first compound that forms when nabam oxidizes. Barratt and Horsfall (1947)

Figure 24. Effect of electronegative carbonyls in nabam esters

Number	Name	Structure	Toxicity Index	
			Stemphylium	*Monilinia*
3135	Dicarboisobutoxyethylenebis(dithiocarbamate)	 $(-CH_2-\overset{H}{\overset{\vert}{N}}-\overset{S}{\overset{\Vert}{C}}-S-\overset{O}{\overset{\Vert}{C}}-O-CH_2-\overset{CH_3}{\overset{\vert}{CH}}-CH_3)_2$	350	350
3146	Dicarbethoxy N,N'dimethylethylenebis(dithiocarbamate)	 $(-CH_2-\overset{CH_3}{\overset{\vert}{N}}-\overset{S}{\overset{\Vert}{C}}-S-\overset{O}{\overset{\Vert}{C}}-O-C_2H_5)$	50	268
3138	Dibenzoyl ethylenebis(dithiocarbamate)		390	400
3147	Dibenzoyl N,N'-dimethylethylenebis(dithiocarbamate)		184	224
3148	Dicarbophenoxyethylenebis(dithiocarbamate)		397	360

studied this compound and so did Klöpping (1951) but strangely, neither proposed it as the active derivative of nabam.

Both ETM and ETD meet our requirement that, like nabam, the active compound must be more toxic to *Stemphylium* than to *Monilinia* (see Rich and Horsfall 1950). We consider that monomeric ETD must play an important role in the fungitoxicity of nabam. We are pleased to note that Ludwig and Thorne (1960) now also lean toward ETD.

They speak of an equilibrium between ETD and nabam somewhat equivalent to that one now so well known between sodium dimethyldithiocarbamate and tetramethylthiuram disulfide. They also reopen the problem of the possible polymodal curve for nabam and zineb as reported by Dimond, Heuberger, and Horsfall (1943) and Zentmyer and Erspamer (1954). Dr. Harry Keil tells us verbally that he, too, has seen polymodal curves for zineb especially on *Monilinia* spores.

In our tests on ETD we have observed strong J-shaped curves. This suggests that we are seeing a fragment of a polymodal curve first reported by Dimond *et al.* (1941) for tetramethylthiuram disulfide. The possible polymodal curve for nabam and ETD needs much more work. If, these two are actually in equilibrium, they may well generate such a curve. The conditions for a stable equilibrium may be so delicate, however, as to account for the rarity of a polymodal curve. Nabam, we know, is much more unstable than sodium dimethyldithiocarbamate.

A little work has been done on the biological systems affected by ethylenebis(thiocarbamyl)monosulfide. According to Chefurka (1957) it is a potent inhibitor of the dehydrogenases for 6-phosphogluconate and glucose-6-phosphate.

Effect of Diisothiocyanates of Nabam

We have discussed already the effect of isocyanates in the oxygen series and the isothiocyanates in the DDC series and have concluded that the isocyanate or isothiocyanate structures are unnecessary to account for the activity of the respective carbamates.

Nabam esters presumably can be converted to isothiocyanates, too, by the same mechanisms as for the DDC series, but in this case we produce a diisothiocyanate because nabam esters have two reactive groups.

In our original paper (Barratt and Horsfall, 1947) on the action of nabam, we suggested that ethylene diisothiocyanate (No. 2431, Figure 25) might be the effective compound, but decided even then that its formation is unlikely and, hence, that it is an unlikely explanation of the action of nabam.

Thus, we ruled out diisothiocyanate in our first paper on the basis of chemical probabilities. Its formation just seemed unlikely. Since then biological evidence has accumulated. Hundreds, perhaps thousands, of tons of nabam have been applied to crops by farmers without significant complaint of dermatitis, even though isothiocyanates are well known skin irritants. If diisothiocyanate forms easily from nabam on or off the skin, nabam would have never attained its present commercial success.

An occasional farmer especially in Italy does develop a skin rash. Perhaps, on these rare occasions a diisothiocyanate does form. On the other hand, a few people develop a skin rash to nearly any synthetic chemical.

Diisothiocyanates are highly fungitoxic as the data in Figure 22 so dramatically show. In fact the two tested compounds completely kill the test organisms at all concentrations so far tried.

Klöpping (1951) convinced himself that ethylene diisothiocyanate accounts for the fungitoxicity of nabam (a) because it is highly fungitoxic (see Figure 25) and (b) because it has a "biological spectrum" similar to that of nabam, i.e., it kills the same organisms and fails to kill the same organisms as nabam. Klöpping ignored, however, his own demonstration that nabam is much more potent than isothiocyanates as a respiration inhibitor.

Sijpesteyn and van der Kerk (1954) continued Klöpping's argument for diisothiocyanate and advanced another that *both nabam and diisothiocyanate react with sulfhydryl groups.* To some extent this is circular reasoning.

To say that diisothiocyanate is a highly fungitoxic compound that reacts with -SH groups is to say that diisothiocyanate is a highly fungitoxic compound that reacts with -SH groups. Captan is a sulfur containing, highly fungitoxic compound that can combine with sulfhydryl compounds, too (Lukens, 1959) but this is no proof that it is the fungitoxic derivative of nabam.

Van der Kerk (1959) continued his isothiocyanate argument to explain the activity of the fungitoxic rhodanines especially N-(4-chlorophenyl) rhodanine (our No. 2948 in Table 2). He shows that the heterocyclic ring in this compound opens to form a dithiocarbamic acid and then an isothiocyanate. Then he shows that this, too, reacts with -SH groups—but so does any dithiocarbamic acid. There is no need to postulate an isothiocyanate to account for the activity.

Ludwig *et al.* (1955) tended to accept Klöpping's diisothiocyanate hypothesis when they demonstrated that ethylenebis(thiocarbamyl)monosulfide (ETM) as well as nabam (Ludwig and Thorne, 1960) can form diisothiocyanate.

Recent evidence, however, appears to reduce further the importance of isothiocyanates in the nabam series. Owens (1960) found that a lethal dose of nabam causes the accumulation of citrate in *Neurospora sitophila,* but has little effect on pyruvate synthesis. Methyl isothiocyanate, however, has no effect on citrate synthesis but does cause pyruvate to accumulate. Owens concludes that nabam types inhibit aconitase, while methyl isothiocyanate inhibits dehydrogenases.

Klöpping (1951) and Wedding and Kendrick (1959) also found quite different toxicological effects between sodium N-methyldithiocarbamate (vapam) and methyl isothiocyanate. Sodium N-methyldithiocarbamate may be considered as a nabam molecule chopped in half between the two ethylene carbons.

That a fungicide may produce isothiocyanates does not mean that this is its only or even primary mechanism of action. The DDC types and the nabam types may have many toxic mechanisms in common. Owens (1960) groups the DDC type ziram with nabam and maneb as having similar toxic effects on organic acid metabolism of *N. sitophila.* Ludwig and Thorne (1960) also note the similarities between DDC types and nabam types. The nabam types, however, appear to have additional chemical versatility that has made them the more useful of the two series.

Figure 25. Effect of diisothiocyanates of nabam

Number	Name	Structure	Toxicity Index *Stemphylium*	Toxicity Index *Monilinia*
2431	Ethylene diisothiocyanate	$S=C=N\text{-}C_2H_4\text{-}N=C=S$	400	400
889	Tetramethylene diisothiocyanate	$S=C=N\text{-}C_4H_8\text{-}N=C=S$	400	400

Discussion of Nabam Esters

Nabam esters like the oxygen carbamate esters and the DDC esters probably enter the cell because they are lipophilic molecules. There they presumably are deesterified to ethylenebisdithiocarbamic acid which reacts with sulfhydryl and possibly amine groups in the living tissue and, thus, destroy their contribution to the life process.

Diisothiocyanates are probably not involved (a) because they need not be postulated and (b) because they would be skin irritants if they formed.

The nabam types have attained commercial superiority in general over DDC types because the former performs essentially all the feats that DDC does and more besides.

SUMMARY

1. We have been interested in carbamates and dithiocarbamates since 1938. This paper summarizes our researches on the fungitoxic properties of some 174 esters, sulfides, disulfides, isocyanates, and isothiocyanates.

2. The experimental data are recorded as the inhibition of sporė germination of two test fungi, *Stemphylium sarcinaeforme and Monilinia fructicola.*

3. The objectives of the paper are: (a) to show relations of structure to permeation and fungitoxic action, (b) probable effects of deesterification, (c) the possible significance of isocyanates and isothiocyanates, and (d) to relate the fungicidal data to herbicidal data.

4. *Monilinia* is strikingly more inhibited by the esters of essentially all types than *Stemphylium*. In some ways, then, *Stemphylium* mirrors the effect of altered structures differently from *Monilinia*. Only two compounds in the whole paper are more toxic to *Stemphylium* than to *Monilinia*. These are the nabam internal esters, ethylenebis(thiocarbamyl) monosulfide and ethylenebis(thiocarbamyl) disulfide.

5. Among the oxygen analogues, increasing the size of the ester increases potency, presumably by increasing permeability. If the size be too big, however, potency is diminished. This seems to be true, too, for herbicides.

6. Electronegative groups properly spaced in the ester increase potency, presumably by increasing susceptibility to deesterification. Data on herbicides are equivocal on this point.

7. As with herbicides, N-phenyl substitutents seem to make the most fungicidal of the oxygen analogues. 2-substitution on the ring very seriously reduces potency to *Stemphylium* without much affecting the potency to *Monilinia*. Weeds seem to respond to the oxygen analogues more like *Monilinia* than like *Stemphylium* in this regard. If heterocyclic rings replace a benzene ring on the nitrogen, potency is reduced.

8. Doubly substituting the carbamate nitrogen essentially quenches the potency of carbamates to *Stemphylium* but affects very little the potency to *Monilinia*. Here again weeds seem to act more like *Monilinia* than like *Stemphylium*. Perhaps, we can rephrase the *Stemphylium* story more effectively by saying that a mobile N-hydrogen is required for carbamate toxicity to this fungus.

9. One is tempted at first to suggest that isocyanates account for the fungitoxicity of carbamates to *Stemphylium* because a mobile N-hydrogen is required for isocyanate formation. This facile conclusion is made untenable, however, by the following considerations: (a) a dehydration step is demanded in isocyanate formation and this is unlikely in an aqueous system in which spores live, (b) isocyanates at least when tested directly are weaker fungicides than parent carbamates. Presumably this means that they degrade spontaneously in the spore drop to the parent amine and alcohol. The alcohol would not be fungitoxic at the concentration concerned and the amine would not be very permeable.

Evidence is offered to suggest that the carbamate esters permeate the cell, are deesterified there to the acid which degrades to the amine and carbon dioxide. We assume that the amine is fungitoxic. It is not so if offered directly to the fungus in a spore drop. Data are cited to show, however, that the amine can be made fungitoxic by adding the proper lipophilic group which presumably promotes permeation.

10. Insofar as the DDC estsers are concerned, the sulfur analogues are considerably more fungitoxic than the oxygen counterparts.

11. Evidence on lipid solubility of the DDC esters is less complete than desired because we had for trial no esters of long chain alcohols.

12. Electronegative groups in the DDC esters are as important as they are in the oxygen analogues. Presumably here also they encourage deesterification inside the cell.

Some of the very important electronegative compounds are the sulfides and disulfides. These seem to be especially easily deesterified and these are highly fungitoxic.

13. Dithiocarbamates with doubly substituted nitrogen atoms seem toxic to *Stemphylium* whereas doubly substituted oxygen analogues are not toxic. This poses a puzzle.

14. Isothiocyanates seem no more necessary to explain fungitoxicity of DDC esters than their oxygen analogues.

15. The nabam esters differ again from the oxygen esters and the DDC esters. Here we find two esters, which like nabam itself, are more toxic to *Stemphylium* than to *Monilinia*. This is a dramatic exception to the general rule that carbamates and dithiocarbamates are more toxic to *Monilinia* than to *Stemphylium*.

16. The nabam esters differ, too, in that increasing the size of the ester moiety does not improve potency. Presumably, the nabam molecule is big enough in its own right to permeate well.

17. Nabam esters differ, also, in that the molecule has a carbamic acid moiety on each end. Thus, after deesterification, they are capable of polymerizing. This is not true of the DDC and oxygen analogues.

18. Several workers have reached for the diisothiocyanate to account for the powerful fungitoxicity of nabam and its derivatives. We are unable to subscribe to this hypothesis because: (a) It follows a fad of assuming that a compound owes its potency to a derivative. This seems needlessly to complicate the problem. (b) Isothiocyanates are so unstable that one has difficulty in accepting the likelihood that they will be formed in the presence of the multitudinous reactions that proceed simultaneously in a fungus spore. And (c) Isothiocyanates are postulated to form from another reactant, viz, dithiocarbamic acid. To say that isothiocyanates are formed, postulates that the reaction proceeds to isothiocyanate via dithiocarbamic acid and then returns to dithiocarbamic acid. (d) Diisothiocyanates would produce skin rashes on farmers that use nabam derivatives. Seldom does a user experience a skin rash.

19. Our general conclusion is that nabam esters produce essentially the fungitoxic effects of DDC esters and more besides.

20. Ignorance of the mode of action of dithiocarbamates is both widespread and profound.

Table I. Fungitoxicity of carbamate esters and isocyanates

Code No.	Name	Source[1]	*Stemphylium*					*Monilinia*				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
4 L	Methyl N-phenylcarbamate	R&H	100	70	4	5	179	100	70	65	75	310
15 L	Diethylethylenebis(carbamate)	"	70	8	0	0	78	100	87	0	0	187
16 L	Dimethylethylenebis(carbamate)	"	3	0	0	0	3	9	0	0	0	9
429	Ethyl carbamate	USIC	0	0	0	0	0	6	0	0	0	6
600	4-Nitrophenyl isocyanate	EK	0	0	0	0	0	0	0	0	0	0
608	1-Naphthyl isocyanate	EK	88	0	0	0	88	74	63	0	0	137
762A	2-(8-Heptadecenyl)-1-(2-hydroxyethyl)-(4 or 5)-methyl-2-imidazoline	C & C	100	100	100	50	350	100	100	100	100	400
993	Ethyl N-phenylcarbamate	EK	100	60	6	3	169	100	54	34	0	188
994	Ethyl N-phenyl-N-benzylcarbamate	EK	0	0	0	0	0	26	0	0	0	26
1180	5-Dimethylaminocarvacryl N-methyl carbamate	CBCC	75	0	0	0	75	100	29	0	0	129
1189	Methyl carbamate	SRI	0	0	0	0	0	0	0	0	0	0
1190	Ethyl N-propylcarbamate	SRI	0	0	0	0	0	0	0	0	0	0
1191	Ethyl N-isopropylcarbamate	SRI	50	0	0	0	50	100	0	0	0	100
1192	Ethyl N-morpholinyl formate	SRI	25	5	10	12	52	30	11	10	29	80
1193	Ethyl N,N-diethylcarbamate	SRI	0	0	0	0	0	0	0	0	0	0
1194	Ethyl N-butylcarbamate	SRI	0	0	0	0	0	50	0	0	0	50
1195	Ethyl N,N-dipropylcarbamate	SRI	0	0	0	0	0	0	0	0	0	0
1196	Ethyl N,N-dibutylcarbamate	SRI	0	0	0	0	0	50	0	0	0	50

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	Stemphylium					Monilinia				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
1581	Butyl carbamate	R&H	90	3	0	0	93	88	1	0	0	89
1872	Butyl N-phenylcarbamate	SRI	100	90	0	0	190	100	100	58	0	258
2339	Ethyl N-methylcarbamate	CBCC	0	0	0	0	0	0	0	0	0	0
2687	Isopropyl N-(3-chlorophenyl) carbamate	Co.S.	40	32	0	0	72	100	100	0	0	200
2690	Isopropyl N-phenylcarbamate	……	100	91	0	0	191	100	92	0	13	205
2873	Butyl N-acetylcarbamate	CBCC	22	0	0	0	22	21	0	0	0	21
2902	Ethyl N-(2-thiazolyl)carbamate	CBCC	0	0	0	0	0	diff. to read	0	0	0	0
3222	1-Cyanoethyl N-phenylcarbamate	Co.S.	100	7	0	0	107	100	20	33	0	153
3225	Isopropyl N-(2-furfuryl) carbamate	Co.S.	100	0	0	0	100	100	0	0	0	100
3226	2-Chloroethyl N-(3-chlorophenyl) carbamate	Co.S.	100	100	75	0	275	100	100	100	0	300
3230	Isopropyl N-methyl-N-phenyl-carbamate	Co.S.	58	0	0	0	58	100	0	0	0	100
3231	Isopropyl N-(2-methoxy-5-nirtophenyl)carbamate	Co.S.	23	0	0	0	23	48	36	35	0	119
3251	Ethyl N,N-diphenylcarbamate	Co.S.	75?	3?	0	0	78	100	77	47	1	225
3256	Isopropyl N-pyrrolidyl formate	CBCC	12	0	0	0	12	19	0	0	0	19
3257	2-Chloroethyl β-phenylcarbazide	Co.S.	100	99	20	0	219	100	100	86	30	316
3260	Isopropyl N-methyl-N-(2-methyl-phenyl)carbamate	Co.S.	100	0	0	0	100	100	0	0	0	100

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	Stemphylium					Monilinia				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
3268	Isopropyl β-methyl-3-phenyl-carbazide	Co.S.	100	13	0	0	113	100	100	0	0	200
3334	Isopropyl N-morpholinyl formate	CBCC	0	0	0	0	0	0	0	0	0	0
3335	1,3-Dichloroisopropyl N-(3-chlorophenyl)carbamate	Co.S.	100	100	46	0	246	100	100	100	21	321
3336	2-Methallyl N-phenylcarbamate	Co.S.	100	95	20	0	215	100	100	4	0	204
3337	2-Methyl-2-nitropropyl-N-phenylcarbamate	Co.S.	0	0	0	0	0	100	32	0	0	132
3346	1-(N-Morpholinyl)-2-ethyl N-phenylcarbamate	CBCC	100	0	0	0	100	100	0	0	0	100
3391	Furfuryl N-phenylcarbamate	CBCC	100	100	19?	0	219	100	100	90	0	290
3401	Isopropyl(3-methyl-2-pyridyl) carbamate	CBCC	23	0	0	0	23	100	7	0	0	107
3402	N-Phenylcarbamic acid, ethyl β-methyl lactate ester	CBCC	22	0	0	0	22	100	100	60	14	274
3416	2-Phenethyl N-phenylcarbamate	Co.S.	34	0	0	0	34	100	68	76	0	244
3421	Ethyl N-[5-(1H-tetrazolyl)] carbamate	CBCC	0	0	0	0	0	10	0	0	0	10
3453	Ethyl N-(2-biphenylyl)carbamate	R&H	24	12	2	0	38	100	100	100	0	300
3454	Isopropyl 1-piperidyl formate	CBCC	0	0	0	0	0	15	7	5	5	32
3456	Isopropyl N-(3-vinylphenyl) carbamate	Co.S.	79	54	3	0	136	100	100	81	35	316
3457	Isopropyl 1-(5-ethyl-2-methyl-piperidyl)formate	CBCC	15	0	0	0	15	100	11	7	3	121

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	Stemphylium 10.0	1.0	0.10	0.01	Index	Monilinia 10.0	1.0	0.10	0.01	Index
3458	Isopropyl N-2-butenyl-N-phenylcarbamate	Co.S.	22	0	0	0	22	100	100	0	0	200
3459	Isopropyl N-allyl-N-phenylcarbamate	Co.S.	59	17	4	0	80	80	47	5	0	132
3461	2-Chloroethyl N-(2-methoxy-5-methylphenyl)carbamate	Co.S.	13	6	0	0	19	100	50	50	6	206
3462	2-(2,4-Dichlorophenoxyethyl) N-(3-chlorophenyl)carbamate	Co.S.	0	11	0	0	11	100	11	0	25	136
3464	N-(2-Methoxy-5-methylphenyl) carbamic acid, butyl lactate ester	Co.S.	0	0	0	0	0	88	26	35	0	149
3466	Diisopropyl 2,5-dimethyl-1,4-piperazyl formate	CBCC	75	0	0	0	75	86	81	0	0	167
3567	2-(2,4-Dichlorophenoxyethyl) N-phenylcarbamate	CBCC	0	0	0	0	0	100	57	4	4	165
3568	Isopropyl N-(2,4-dimethylphenyl)carbamate	Co.S.	15	6	0	0	21	100	84	8	3	195
3569	Isopropyl N-(2,5-dimethylphenyl)carbamate	Co.S.	0	0	0	0	0	20	82	55	50	207
3570	Isopropyl N-(3-methoxyphenyl) carbamate	Co.S.	83	67	0	0	150	100	100	18	7	225
3571	Isopropyl N-benzyl-N-(3-methylphenyl)carbamate	Co.S.	0	0	0	0	0	3	3	1	1	8
3572	Isopropyl β-phenylcarbazate	Co.S.	94	40	0	0	134	100	69	47	0	216
3573	Isopropyl N-(3-methylphenyl) carbamate	Co.S.	87	93	10	0	190	100	100	0	0	200

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	Stemphylium 10.0	1.0	0.10	0.01	Index	Monilinia 10.0	1.0	0.10	0.01	Index
3574	Isopropyl N-(2,6-dimethylphenyl)carbamate	CBCC	88	34	0	0	122	100	100	0	0	200
3575	Isopropyl N-(2,3-dimethylphenyl)carbamate	Co.S.	8	4	3	1	16	100	98	40	0	238
3576	Isopropyl N-ethyl-N-phenylcarbamate	Co.S.	97	0	0	0	97	100	63	60	23	246
3577	Isopropyl β-(2,5-dichlorophenyl)carbazate	Co.S.	78	72	35	17	202	100	100	81	25	306
3579	N-Methyl N-phenylcarbamic acid, butyl lactate ester	Co.S.	19	62	36	0	117	100	100	92	32	324
3580	Isopropyl N-(3,5-dimethylphenyl) carbamate	Co.S.	30	0	0	0	30	78	71	19	0	168
3581	Isopropyl N-butyl-N-phenylcarbamate	Co.S.	15	0	0	0	15	100	48	0	0	148
3596	3-Chloroallyl N-(3-chlorophenyl)carbamate	Co.S.	100	88	83	0	271	100	50	50	0	200
3774	2-Butynl-1,4-bis(N-(3-chlorophenyl)carbamate)	CBCC	100	98	0	0	198	100	100	15	7	222
3900	2-(3-Methylbutyl) N-(3-chlorophenyl)carbamate	Co.S.	45	18	2	0	65	100	86	68	7	261
3983	2-[2-(x-heptadecenyl)imidazolyl] butyl N-phenylcarbamate	CBCC	100	100	50	21	271	100	100	97	59	356
4242	2-Propynyl N-(3-methylphenyl) carbamate	Co.S.	100	13	0	0	113	100	100	0	5	205
4256	3-(1-Butynyl) N-phenylcarbamate	CBCC	100	100	0	0	200	100	100	0	0	200

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium*					*Monilinia*				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
4257	(1,1,1-Trichloro-3-nitro)isopropyl N-phenylcarbamate	CBCC	100	100	34	0	234	100	100	0	0	200
4260	3-Propynyl N-(5-chloro-2-methylphenyl)carbamate	CBCC	0	0	0	0	0	100	100	100	14	314
4424	(1-Chloro-3-isopropoxy)isopropyl N-phenylcarbamate	CBCC	0	0	72	19	91	100	100	100	62	362
4429	Dimethylisocyano N-(2,5-dichlorophenyl)carbamate	CBCC	0	0	0	0	0	100	100	100	63	363
4436	Acetylmethylisocyano N-phenylcarbamate	CBCC	65	42	0	0	107	100	100	14	0	214
4440	2-Propynyl N-(3-chlorophenyl)carbamate	Co.S.	71	17	14	11	113	100	100	100	13	313
4495	1,1,3,3-Tetramethylbutyl isocyanate	CBCC	30	17	6	8	61	53	40	35	0	128
4632	2-Fluoroethyl N-phenylcarbamate	CBCC	100	70	15	0	185	100	100	44	75	319
4646	2-Fluoroethyl N-(4-ethoxyphenyl)carbamate	CBCC	47	0	0	0	47	100	100	35	0	235
4647	2,2,2-Trifluoroethyl N-phenylcarbamate	CBCC	100	11	0	0	111	100	100	16	20	236
4648	2-Fluoroethyl N-(3-chlorophenyl)carbamate	CBCC	100	100	0	0	200	100	100	94	50	344
4654	2,2,2-Trifluoroethylcarbamate	CBCC	0	0	0	0	0	0	0	0	0	0
4658	2-Fluoroethylcarbamate	CBCC	0	0	0	0	0	0	0	0	0	0
4660	2-Fluoroethyl N-(1-naphthyl)carbamate	CBCC	16	0	0	0	16	79	50	42	31	202

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[1] See Sources of Compounds following Table 3.

Table 1. Fungitoxicity of carbamate esters and isocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium*					*Monilinia*				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
4670	Ethyl N-ethyl-N-ethoxycarbamate	R&H	0	0	0	0	0	7	9	0	0	16
4750	4-Chlorophenyl isocyanate	EK	27	14	18	15	74	45	35	16	13	109
4751	2-Chlorophenyl isocyanate	EK	13	10	7	5	35	67	61	56	32	216
4753	3-Chlorophenyl isocyanate	EK	29	30	16	10	85	37	20	40	27	124
4799	N-(3-methylphenyl)carbamic acid, butyl lactate ester	CBCC	0	0	0	0	0	100	100	25	14	239
4801	Isopropyl N-(2,5-dimethoxyphenyl)carbamate	CBCC	23	0	0	0	23	100	100	15	0	215
5298	Allyl N-(4-chlorophenyl)carbamate	R&H	100	99	55	0	254	100	100	100	35	335
5299	4,4′-Dichlorobenzohydryl N-(4-chlorophenyl)carbamate	R&H	0	0	0	0	0	74	50	30	0	154
5300	4-Chlorobenzyl N-(4-chlorophenyl)carbamate	R&H	100	40	0	0	140	100	37	0	0	137
5301	Allyl N-(4-methylphenyl)carbamate	R&H	100	100	0	0	200	100	100	35	0	235
5302	Ethyl N-(2-furanyl)carbamate	R&H	13	5	4	0	22	2	0	0	0	2
5303	Benzyl N-(*n*-dodecyl)carbamate	R&H	3	2	5	6	16	0	0	0	0	0
5304	Allyl N-phenylcarbamate	R&H	95	9	1	0	105	100	11	0	0	111
5305	*n*-Dodecyl N-phenylcarbamate	R&H	13	0	2	2	17	82	45	0	0	127
5306	*n*-Hexyl N-phenylcarbamate	R&H	28	22	32	0	82	100	100	100	100	400
5323	1-(4-chloro-2-butynyl) N-(3-chlorophenyl)carbamate	Spencer	100	100	41	26	267	100	100	100	3	303

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[1] See Sources of Compounds following Table 3.

Table 2. Fungitoxicity of DDC esters, sulfides and isothiocyanates

Code No.	Name	Source[1]	*Stemphylium* 10.0	1.0	0.10	0.01	Index	*Monilinia* 10.0	1.0	0.10	0.01	Index
9 L	Methyl N-phenylthiolcarbamate	R&H	100	100	1	0	201	100	82	51	0	233
18 L	Methyl N,N-dimethyldithiocarbamate	”	10	0	0	0	10	0	0	0	0	0
24	Bis(dimethylthiocarbamyl) disulfide	Various	100	100	100	42	342	100	100	100	28	328
1117 H	Methyl N-phenylthionocarbamate	R&H	100	100	0	0	200	100	100	81	69	350
63	Allyl isothiocyanate	......	100	19	11	6	136	100	100	70	25	295
317	Dimorpholinethiuram disulfide	USDA	100	100	68	0	268	100	100	30	9	239
411	Bis(dimethylthiocarbamyl) sulfide	Various	100	91	58	48	297	100	100	93	63	356
505	Bis(diethylthiocarbamyl) disulfide	RTV	100	99	100	23	322	100	100	100	28	328
642	α-Mercaptoacetanilide carbamate	EK	92	74	20	2	188	95	50	15	2	162
723	Phenyl isothiocyanate	EK	63	20	0	0	83	100	81	58	0	239
1223	S-(Methylphenylthiocarbamyl) hydrosulfamine	CBCC	0	0	0	0	0	100	95	25	0	220
1246	2,4-Dinitrophenyl N,N-dimethyldithiocarbamate	CBCC	93	30	21	16	160	100	50	14	3	167
1251	Ethylthionocarbamate	SRI	5	0	0	0	5	0	0	0	0	0
1255	Ethyl N-ethylthionocarbamate	SRI	34	5	5	0	44	47	19	15	11	92
1257	Ethyl N-phenylthionocarbamate	SRI	100	100	50	0	250	100	100	50	0	250
1578	Dithioxalodimorpholide	R&H	6	0	0	0	6	0	0	0	0	0
1690A	*t*-Octyl isothiocyanate	R&H	100	100	100	100	400	100	100	100	100	400

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[1] See Sources of Compounds following Table 3.

Table 2. Fungitoxicity of DDC esters, sulfides and isothiocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium* 10.0	1.0	0.10	0.01	Index	*Monilinia* 10.0	1.0	0.10	0.01	Index
2311	Diethethyldithiocarbamic acid, anhydrosulfide with *p*-chlorothiolbenzenesulfonic acid	UCB	100	100	96	0	296	100	100	96	90	386
2312	Diethyldithiocarbamic acid, 2-pentachlorophenoxy)ethyl acetate ester	CBCC	0	0	0	0	0	100	100	23	0	223
2314	4-Morpholinecarbodithioic acid, 2-hydroxyethyl ester	CBCC	50	0	0	0	50	100	50	37	15	202
2321	Diethyldithiocarbamic acid, 2,2′-oxydiethyl diester	CBCC	0	0	0	0	0	0	0	0	0	0
2322	4-Morpholinecarbodithioic acid, 2-(pentachlorophenoxy)ethyl acetate ester	CBCC	60	55	18	0	133	98	83	65	30	276
2336	Diethyldithiocarbamic acid, 2-hydroxyethyl ester	CBCC	100	9	3	3	115	100	54	38	10	202
2357	4-Morpholinecarbodithioic acid, 2,2′-oxydiethyl diester	CBCC	0	0	0	0	0	0	0	0	0	0
2624	1-Benzotriazolylmethyl N,N-dimethyldithiocarbamate	R&H	14	0	0	0	14	98	98	97	39	332
2633	*n*-Butoxymethyl isothiocyanate	R&H	77	0	0	0	77	50	0	0	0	50
2656	Carbethoxy dimethyldithiocarbamate	R&H	100	100	69	0	269	100	100	82	0	282
2799	Methyl N-phenyldithiocarbamate	CBCC	99	97	75	1	272	100	100	100	0	300
2882	Dimethyldithiocarbamic acid, methyl propionate ester	CBCC	100	0	0	0	100	100	100	52	0	252

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[1] See Sources of Compounds following Table 3.

Table 2. Fungitoxicity of DDC esters, sulfides and isothiocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium*					*Monilinia*				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
2948	3-(*p*-Chlorophenyl)-5-methyl rhodanine	Stauffer	100	100	100	100	400	100	100	100	100	400
3040	Methoxymethyl isothiocyanate	R&H	100	0	0	0	100	100	100	0	0	200
3044	N-Methyl-N-phenyldithiocarbamic acid, acetic acid ester	R&H	100	56	0	0	156	77	56	0	0	133
3122	Carbisopropoxy dimethyldithiocarbamate	R&H	100	100	100	33	333	93	100	95	0	288
3131	Ethoxycarbonyl-2,4,4-trimethyl tetramethylenedithiocarbamate	R&H	100	100	28	0	228	100	100	100	0	300
3136	Carbo(diethyleneglycoloxy)bis-dimethyldithiocarbamate	R&H	100	100	0	0	200	100	100	0	0	200
3143	Carballyloxy dimethyldithiocarbamate	R&H	100	46	48	0	194	100	100	48	0	248
3144	Carbethoxy pentamethylenedithiocarbamate	R&H	100	37	0	0	137	100	80	19	0	199
3149	Carbethoxy tetramethylenedithiocarbamate	R&H	97	80	0	0	177	100	89	0	0	189
3244	4-Isothiocyano salicylic acid	CBCC	100	92	36	0	228	100	94	79	76	349
3486	Isopropoxycarbonyl-4-morpholine carbodithioate	R&H	100	39	19	0	158	100	54	0	0	154
3488	Isopropoxycarbonyl tetramethylenedithiocarbamate	R&H	100	100	78	0	278	100	100	100	83	383
3489	Isopropoxycarbonyl N,N-diisopropyldithiocarbamate	R&H	60	16	2	1	79	100	27	24	4	155
3491	Isopropoxycarbonyl N-isononyldithiocarbamate	R&H	45	33	0	0	78	100	93	79	49	321

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[1] See Sources of Compounds following Table 3.

Table 2. Fungitoxicity of DDC esters, sulfides and isothiocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium*					*Monilinia*				
			10.0	1.0	0.10	0.01	Index	10.0	1.0	0.10	0.01	Index
3495	1-Ethoxycarbonylethoxycarbonyl dimethyldithiocarbamate	R&H	83	38	0	0	121	100	46	20	0	166
3496	Isopropoxycarbonyl N-furfuryldithiocarbamate	R&H	100	100	2	0	202	100	100	73	20	293
3627	Di-*n*-butoxycarbonyl-2,5-dimethylpiperazine-1,4-bis-carbodithioate	R&H	66	61	55	40	222	100	100	80	30	310
3629	3-Oxapentylene-1,5-dioxycarbonyl N,N-diisopropyldithiocarbamate	R&H	100	57	14	13	184	100	100	25	0	225
4264	Dimethyldithiocarbamic acid, ethyl acetate ester	R&H	100	0	0	0	100	100	100	0	0	200
4266	β-Dimethyldithiocarbamic acid, ethyl propionate ester	R&H	100	0	0	0	100	100	100	0	0	200
4268	α-Dimethyldithiocarbamic acid, ethyl propionate ester	R&H	100	57	0	0	157	100	100	0	0	200
4935	3,5-Dimethyltetrahydro,-1,3,5-2H-thiadiazine-2-thione	C&C	100	100	100	58	358	100	100	100	100	400
5290	Ethyl N,N-di-*n*-propylthiolcarbamate	Stauffer	0	0	0	0	0	88	15	26	0	129
5325	2,3-Dichloroallyl N,N-diisopropylthiolcarbamate	Monsanto	0	7	18	10	35	100	100	21	6	227

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[1] See Sources of Compounds following Table 3.

Table 3. Fungitoxicity of nabam esters, sulfides and isothiocyanates

Code No.	Name	Source[1]	*Stemphylium* 10.0	1.0	0.10	0.01	Index	*Monilinia* 10.0	1.0	0.10	0.01	Index
29 L	Dimethyl ethylenebis (dithiocarbamate)	R&H	95	90	3	0	188	100	100	81	0	281
889	Tetramethylene diisothiocyanate	Dr. Klöpping	100	100	100	100	400	100	100	100	100	400
2431	Ethylene diisothiocyanate	R&H	100	100	100	100	400	100	100	100	100	400
3134	Dibenzyl ethylenebis (dithiocarbamate)	R&H	0	0	0	0	0	100	96	10	0	206
3135	Dicarboisobutoxy ethylenebis (dithiocarbamate)	R&H	100	100	100	50	350	100	100	100	50	350
3138	Dibenzoyl ethylenebis (dithiocarbamate)	R&H	100	100	100	90	390	100	100	100	100	400
3146	Dicarbethoxy N,N′-dimethyl-ethylenebis(dithiocarbamate)	R&H	50	0	0	0	50	100	72	50	46	268
3147	Dibenzoyl N,N′-dimethyl-ethylenebis(dithiocarbamate)	R&H	100	69	11	4	184	100	63	28	33	224
3148	Dicarbophenoxyethylenebis (dithiocarbamate)	R&H	100	100	100	97	397	100	100	100	60	360
4442	Ethylenebis(dimethylthio-carbamyl) sulfide	R&H	100	100	100	0	300	100	100	100	75	375
4579	Ethylenebis(thiocarbamyl) trisulfide	R&H	100	100	100	59	359	100	100	100	100	400
5345	Ethylenebis(thiocarbamyl) disulfide	RTV	100	100	100	0	300	100	100	100	23	323
5346	Ethylenebis(thiocarbamyl) sulfide	N. Chem.	100	100	100	100	400	100	100	100	100	400

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[1] See Sources of Compounds following Table 3.

Table 3. Fungitoxicity of nabam esters, sulfides and isothiocyanates (continued)

Code No.	Name	Source[1]	*Stemphylium* 10.0	1.0	0.10	0.01	Index	*Monilinia* 10.0	1.0	0.10	0.01	Index
5361	Piperazinebis(thiocarbamyl) tetrasulfide	R&H	100	0	0	0	100	100	100	100	100	400
5362	Propylenebis(thiocarbamyl) tetrasulfide	R&H	100	100	80	0	280	100	100	100	95	395
5363	Ethylenebis(thiocarbamyl) tetrasulfide	R&H	100	100	100	28	328	100	100	100	77	377

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[1] See Sources of Compounds following Table 3.

Tables

C & C	Union Carbide and Carbon Corp.
CBCC	Chemical Biological Coordination Center, National Research Council.
Co.S.	Columbia-Southern Chemical Corp.
EK	Eastman Kodak Co.
Monsanto	Monsanto Chem. Co.
N. Chem.	Naugatuck Chem. Co.
R&H	Rohm & Haas Co.
RTV	R. T. Vanderbilt Co.
SRI	Southern Research Institute
Spencer	Spencer Chem. Co.
Stauffer	Stauffer Chem. Co.
UCB	Union Chim. Belge.
USDA	United States Dept. Agr.
USIC	U. S. Industrial Chemicals Co.

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