

Fungicidal Activity of Phenyl *N*-(4-Substituted-phenyl)thionocarbamates

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Thirteen phenyl *N*-(4-substituted-phenyl)thionocarbamates [(4-X-C₆H₄)NHC(S)OC₆H₅] were synthesized, and their activities as spore germination inhibitors of *Alternaria brassicicola*, *Botrytis cinerea*, *Septoria nodorum*, and *Uromyces viciae-fabae* and as protectants against *Puccinia recondita* on wheat seedlings were determined. High fungicidal activity was found in thionocarbamates substituted with electron-withdrawing groups or the OH group. Results are discussed on the basis of the physicochemical properties of the thionocarbamates.

Keywords: Thionocarbamates; fungicidal activity

INTRODUCTION

Thiocarbamates as fungicides have been extensively studied [see, for example, the review by Ludwig and Thorn (1960)]. However, little attention had been given to phenyl-substituted thionocarbamates until Thorne (1967) studied a wide variety of derivatives of thiocarbamic acid and carbamic acids. He found that phenyl-phenyl carbamates, alkyl-phenyl carbamates, and alkyl thiophenyl carbamates have low fungitoxicity and that some thionocarbamates showed activity. To study the possibility of improving the fungicidal activity of the known thiocarbamates, in the present work a series of phenyl (4-substituted-phenyl)thionocarbamates were synthesized, and their fungitoxic activity was studied in a spore germination test against *Alternaria brassicicola*, *Botrytis cinerea*, *Septoria nodorum*, and *Uromyces viciae-fabae* on agar plates and against brown rust (*Puccinia recondita* sp. *tritici* Eriks and Henn) on wheat seedlings.

MATERIALS AND METHODS

To prepare thionocarbamates, phenyl chlorothionoformate (0.01 mol), obtained according to the method of Thorne (1967) from thiophosgene and phenol, was treated with the corresponding amine (0.02 mol) in 60 mL of dioxane. The temperature was maintained at 10 °C during the addition, and the mixture was stirred continuously at room temperature for 3 h. The reaction product was poured onto crushed ice; the solid was collected by filtration and purified by recrystallization from dichloromethane-hexane. All compounds were identified by their UV, IR (Rao et al., 1964), and PMR spectra.

The method reported by Kunkel (1912) was followed for the condensation of propionyl and butyryl chlorides with acetanilide in the synthesis of 4-aminopropiophenone and 4-aminobutyrophenone. The acetanilide products were hydrolyzed with 20% w/v HCl. 4-Aminobenzaldehyde was synthesized according to the procedure of Campaigne et al. (1951). 4-Bromo-, 4-fluoro-4-methyl, and 4-(dimethylamino)anilines were commercially available.

Biological Methods. Inhibition of germination of conidia of *A. brassicicola* (Schw), *B. cinerea* (Pers), and *S. nodorum* (Berk), and of uredospores of *U. viciae-fabae* (Pers.) (Schrot) was examined using methods described previously (Carter et

Table 1. Melting Points and Yields of 4-Substituted Compounds of General Structure 4-X-C₆H₄NHC(S)OC₆H₅

compd	X	yield	mp (°C)
A	N(CH ₃) ₂	15	130-132
B	OH	69	172-174
C	CH ₃	47	116-117
D	H	35	142-143
E	F	52	136-138
F	SH	72	136-138
G	Br	33	125-126
H	Cl	29	128-129
I	CHO	82	144-145
J	CO ₂ C ₂ H ₅	77	129-130
K	CH ₃ CO	66	161-163
L	C ₂ H ₅ CO	73	150-153
M	<i>n</i> -C ₃ H ₇ CO	78	165-167

al., 1972). The concentration required to inhibit germination completely in each case was measured. The compounds (5-100 ppm) were also incorporated into agar plates, and the concentration for complete inhibition of germination of spores of *A. brassicicola*, *B. cinerea*, and *S. nodorum* spores was recorded.

The activity of the thionocarbamates against infection of wheat seedlings (var. Eclipse) by brown rust (*P. recondita* sp. *tritici* (Eriks and Henn) was also studied (Carter et al., 1972). A 100 ppm solution of the compounds in 50% aqueous acetone was applied to run off as foliar spray to the seedlings, followed immediately after drying by inoculation with the pathogen. The percentage of inhibition of rust development, compared with controls treated with 50% aqueous acetone, was recorded.

RESULTS

Melting points and yields of phenyl *N*-(4-substituted-phenyl)thionocarbamates 4-X-C₆H₄NHC(S)OC₆H₅, obtained from the reaction of 4-substituted anilines with phenyl chlorothionoformate, are shown in Table 1. Assignment of the IR absorption bands was made according to the guidelines of Rao et al. (1964). Nuclear magnetic resonance spectra showed the aromatic protons between 7.2 and 8.1 ppm and the NH amide proton as a wide band between 8 and 9.2 ppm in the different thionocarbamates, in a 9:1 relationship.

Results obtained in the spore germination test with compounds synthesized in this work are summarized in Table 2 on a scale ranging from 6 (high activity) to 0 (no activity). Compounds were ordered according to their Hammett constant, which broadly measures the capacity of the substituent to withdraw or to release electrons from the aromatic ring (Hine, 1962). Table 2

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Table 2. Fungitoxic Activity of Thionocarbamates As Given by the Concentration Required To Completely Inhibit Germination of Spores of Four Fungi According to the Following Scale: 1, 500–1000 ppm; 2, 100–200 ppm; 3, 50–100 ppm; 4, 10–50 ppm; 5, 5–10 ppm; 6, <5 ppm

compd ^a	Hammett constant	A. <i>brassicicola</i>	S. <i>nodorum</i>	B. <i>cinerea</i>	U. <i>fabae</i>
A	-0.83	2		4	1
B	-0.37	4	4	6	5
C	-0.17			2	
D	0.00		1	2	
E	0.06	2	2	4	3
F	0.10	3	3	4	4
G	0.23	2	2	5	6
H	0.23	3	4	5	5
I		3	4	6	4
J	0.45	4	4	6	6
K	0.50	4	4	6	6
L	0.50	4	5	6	6
M	0.50	5	5	6	6

^a Aryl substituents as in Table 1.

Table 3. Concentration (Parts per Million) of Compounds Incorporated into Agar Necessary To Inhibit 100% Spore Germination of Three Fungi Compared to Controls

compd	A. <i>brassicicola</i>	B. <i>cinerea</i>	S. <i>nodorum</i>
B	<5	<5	<5
F	50	50	50
I	20	20	20
J	50	50	50
K	<5	<5	<5
L	20	20	10
M	20	20	20

shows that the fungi differ in their sensitivity to the fungicides and that the hydroxy compound **B** and thionocarbamates with electron-withdrawing substituent groups are highly active.

Seven of the 13 compounds required less than 50 ppm to fully inhibit spore germination on agar plates. These are listed in Table 3. A similar response to the fungicides was found with all three fungi used in this experiment. Thionocarbamates having acyl or hydroxyl groups were the most active in this test.

Compounds **B**, **H**, **I**, **K**, and **L** showed the best activity when applied as a protectant spray against brown rust (*P. recondita*) on wheat seedlings (Table 1).

The thionocarbamates were generally unstable in solution, especially on heating and when chromatographed on silica gel. The major products were the corresponding isothiocyanate and phenol. Thin layer silica gel plates of 5 mg samples of thionocarbamates were developed with hexane/acetone 3:1 and sprayed with *Cladosporium cucumerinum*; the resulting inhibition zones produced by thiocarbamates and their decomposition products on the plate were measured. None of the degradation products had greater fungicidal activity than the parent thionocarbamate, and phenol was inactive.

DISCUSSION

Results presented in this paper reveal high fungicidal activity of certain thionocarbamates (Table 2) against *A. brassicicola* (Schw), *B. cinerea* (Pers), *S. nodorum* (Berk), and uredospores of *U. viciae-fabae* (Pers) (Schrot). Thionocarbamates with a ketone, ester, or OH substituent (**K**, **L**, **M**, **J**, **B**) showed the highest activity.

Thionocarbamates substituted with electron-withdrawing groups or OH showed also the best fungicidal activities when incorporated into agar (Table 3).

During the attempted recrystallization of phenyl *N*-(4 acetylphenyl)thionocarbamate, a less polar compound was isolated which was identified as the corresponding isothiocyanate, and a further experiment showed that the same conversion occurred on heating. It was found that purification of compounds was achieved with less decomposition when the thionocarbamates did not possess electron-attracting groups. Schultz and Gleizner (1962) found that the biocidal properties of aliphatic thionocarbamates are higher when they can liberate the isothiocyanate [see also Hill et al. (1983)]. Both ketone and ester are electron attracting compounds which make the NH hydrogen relatively acid and promote the transformation of the thionocarbamates to the corresponding isothiocyanates; the phenolic OH, however, is an electron-releasing group, and the isothiocyanate is not easily formed (Hill et al., 1983). On the other hand, our experiments with *Clamidosporium cucumerinum* showed that isothiocyanates do not have higher activity than the thionocarbamates. The fungicidal activity of these compounds is probably due to the thiocarbamate molecule as a whole and not to their transformation to the isothiocyanate. The presence of an acidic hydrogen in both OH and electron-attracting substituted thiocarbamates is to be noted.

Good activity was also shown by thionocarbamates substituted with electron-withdrawing groups or OH against brown rust on wheat seedlings when applied as protective foliage sprays. The results of this test were in good agreement with those obtained in the spore germination test (Tables 2 and 3). Potential agricultural applications of these compounds are under study.

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