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Synthesis and Fungicidal Activity of Some Sulphide Derivatives of O-Ethyl-N-Substituted Phenylcarbamates

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Abstract. Monosulphides of O-ethyl-N-substituted phenylcarbamates were prepared by the reaction between O-ethyl-N-substituted phenylcarbamates and sulphur dichloride, while the corresponding disulphides were prepared by the reaction between O-ethyl-N-substituted phenylcarbamates and sulphur monochloride. The synthesized compounds were characterized by elemental analysis, thin layer chromatography (TLC), Fourier-transform infrared, and ^{1}H and ^{13}C nuclear magnetic resonance spectroscopic techniques. *In vitro* fungicidal assay of these sulphides against *Fusarium oxysporum*, *Aspergillus niger*, *Aspergillus flavus* and *Rhizopus stolonifer* showed that they had greater fungicidal activity than their parent carbamates. The synthesized sulphides were more active towards *A. niger* and *A. flavus*. Unlike the parent carbamates, the type of substituents attached to the aromatic nucleus of these sulphides had little or no effect on their fungicidal activity as there was insignificant variation in the fungicidal activity of the monosulphide and the disulphide derivatives of O-ethyl-N-substituted phenylcarbamates.

Keywords: fungicidal activity, sulphide derivatives, O-ethyl-N-substituted phenylcarbamate, fungicides, organosulphur compounds

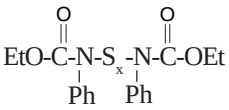
Introduction

Countless sulphur compounds have been tested as fungicides, but only few of these have found worldwide applications (Ayodele, 2005; Lamberth, 2004; Tanaka *et al.*, 1978). Organosulphur compounds are economically important fungicides that play a significant role in the production of agricultural crops and in the preservation of industrial products (Lukens, 1971).

Stability of the metal-chelate formed between heavy metals present in fungal cells and the fungicide sulphur determines the fungicidal activity of these organosulphur compounds (Rich, 1960). Formation of such metal-chelates increases the hydrophobic property of metal ions, which enables them to pass through lipoid layers of cellular membranes to inside the fungus cells, thereby leading to their poisoning (Eyring, 1966).

The toxicity of carbamates lies in their ability to inhibit the nervous system enzyme, acetylcholinesterase. Blockage of this enzyme results in a failure of the nervous system due to accumulation of acetylcholine in the nerve synapse. The inhibition of acetylcholinesterase in mammals (including man) leads to muscular spasm, headaches, diarrhoea, convulsion, respiratory failure and finally cardiac arrest (Kuhr and Dorough, 1976). The substitution of proton on the nitrogen atom of carbamates by a variety of functional groups results in derivatives that have lower anticholinesterase activity and reduced mammalian toxicity when compared to their parent compounds (Fahmy and Fukuto, 1982). The possible attack of carbamates on the nervous system of humans involved in the fungicidal applications is reduced when derivatized carbamates are used in place of N-methylcarbamates (Fahmy *et al.*, 1970).

In continuation of the earlier research efforts (Ayodele *et al.*, 2000; Fahmy *et al.*, 1970) on the synthesis and structure-activity relationships of oligosulphides of the type $PhCH_2$-$S_xCH_2CH_2OH$ (where x = 1-4), a consideration was given to the study of the following types of molecules.



x = 1 and 2 in the presently investigated molecules

Carbamates of this design were likely to cause less health hazards to the operators in particular as reported earlier (Fahmy *et al.*, 1982).

A wide variety of functional groups have been introduced into carbamates, which include sulfenyl, thiono, thiocarbonyl, acyl, sulfinyl, sulfonyl and phosphinothioyl (Szczepanski *et al.*, 1977; Field *et al.*, 1961; Grogan *et al.*, 1955). However, the most widely used functional group for derivatization of carbamates is the sulfenyl group (Black *et al.*, 1973; Kuhle, 1970; Kharasch, 1961; Reid, 1960). Several types of N-sulfenylated

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carbamates have shown lower mammalian toxicity than their corresponding parent compounds (Fahmy *et al*., 1981; 1978; 1974).

The present report is concerned with the sulfenylation of some O-ethyl-N-substituted phenylcarbamates and the potential use of the derivatized products as fungicides.

Materials and Methods

Reagents and solvents. Solid reagents were recrystallized, while the solvents were redistilled. Toluene and diethyl ether were dried over sodium wire. Sulphur monochloride was redistilled over sulphur and collected at 138-139 °C. Similarly, sulphur dichloride was purified by distillation and the fraction was collected at 58-59 °C.

Synthesis of parent compounds. O-ethyl-N-substituted phenylcarbamates were prepared by the reaction between ethyl chloroformate and substituted aniline in the presence of pyridine, which was used for trapping the generated HCl. The general procedure for the synthesis of O-ethyl-N-substituted phenylcarbamates was as reported previously (Adelowo-Imeokparia *et al*., 2005).

Synthesis of O-ethyl-N-(3-nitrophenyl) carbamate. Ethyl chloroformate (3.8 g, 3.3 cm^3, 35 mmol) and 3-nitroaniline (4.8 g, 35 mmol) gave O-ethyl-N-(3-nitrophenyl) carbamate (6.0 g, 82%) as a yellow crystalline solid on recrystallization from methanol (found: C, 51.02; N, 13.08; calculated for $C_9H_{10}N_2O_4$: C, 51.43; N, 13.32%); m.p. 39-40 °C. The TLC (ethanol/DMSO, 3 : 1) gave a single spot, R_f = 0.83; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 3H), 4.1 ($CH_3C\underline{H}_2$, q, 2H), 7.5 (Ar-H, m, 4H), 8.3 (N-H, b.s., 1H); ^{13}C (DMSO): 15 ($\underline{C}H_3CH_2$), 61 ($CH_3\underline{C}H_2$), 112.5 (ArC-6), 117.5 (ArC-5), 124.5 (ArC-4), 130.5 (ArC-2), 141 (ArC-1), 149 (ArC-3), 154 (C=O).

***Synthesis of O-ethyl-N-(4-nitrophenyl) carbamate*.** Ethyl chloroformate (5.4 g, 4.8 cm^3, 50 mmol) and 4-nitroanaline (6.9 g, 50 mmol) gave O-ethyl-N-(4-nitrophenyl) carbamate (8.2 g, 78%) as a light yellow crystalline solid on recrystallization from methanol (found: C, 51.68; N, 13.50; calculated for $C_9H_{10}N_2O_4$: C, 51.43; N, 13.32%); m.p. 129-130 °C. The TLC (ethanol/DMSO, 3 : 1) gave a single spot R_f = 0.75; ^{1}H (C_3D_6O): 1.3 ($C\underline{H}_3CH_2$, t, 3H), 4.2 ($CH_3C\underline{H}_2$, q, 2H), 6.1 (N-H, b.s., 1H), 7.4 (Ar-H, d.d., 4H).

Synthesis of O-ethyl-N-(4-chlorophenyl) carbamate. Ethyl chloroformate (5.4 g, 4.8 cm^3, 50 mmol) and 4-chloroaniline (6.4 g, 50 mmol) gave O-ethyl-N(4-chlorophenyl) carbamate (7.2 g, 72%) as a light brown crystalline solid on recrystallization from methanol (found: C, 54.09; N, 6.92; calculated for $C_9H_{10}ClNO_2$: C, 54.14; N, 7.01%); m.p. 40-41 °C. The TLC (ethanol/DMSO, 3 : 1) gave a single spot, R_f = 0.76; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 3H), 4.1 ($CH_3C\underline{H}_2$, q, 2H), 7.35 (Ar-H, d.d., 4H), 9.7 (N-H, b.s., 1H); ^{13}C (DMSO):15 ($\underline{C}H_3CH_2$), 61 ($CH_3\underline{C}H_2$), 120 (ArC-2,6), 127 (ArC-3,5), 127 (ArC-1), 139 (ArC-4), 154 (C=O).

The infrared spectra of the synthesized carbamates showed strong carbonyl stretching bands between 1700 cm^{-1} and 1705 cm^{-1}, while the secondary amide bands appeared between 3300 cm^{-1} and 3350 cm^{-1} for N-H stretching.

General procedure for the synthesis of monosulphides. ***Synthesis of bis-[N-ethoxycarbonyl-N-(3-nitrophenyl)] monosulphide.*** O-ethyl-N-(3-nitrophenyl) carbamate (1.05 g, 5 mmol) was dissolved in carbon tetrachloride (20 cm^3). To the brown solution was added excess pyridine (10 cm^3). Chilled sulphur dichloride, SCl_2 (0.52 g, 0.4 cm^3, 5 mmol) dissolved in carbon tetrachloride (10 cm^3) was added, dropwise, from a dropping funnel. The whole reaction mixture was set up in a 250 cm^3 three-necked reaction flask fitted with a reflux condenser, a dropping funnel and a magnetic stirrer. The reaction mixture was stirred for 1 h at 20 °C in a fume cupboard. White fumes of hydrogen chloride, which disappeared with time were produced (Fig. 1). An equimolar quantity of O-ethyl-N-(3-nitrophenyl) carbamate (1.05 g, 5 mmol) dissolved in carbon tetrachloride (20 cm^3) was added to the reaction mixture through a dropping funnel. Further evolution of white fumes was observed. The reaction mixture was stirred for another 1 h, and finally left to stir overnight at room temperature. The reaction mixture was washed with 10% hydrochloric acid (100 cm^3) solution in a separatory funnel. The organic layer was separated and washed with distilled water (3 x 100 cm^3). The brown organic layer was separated from the aqueous layer, dried with anhydrous sodium sulphate and filtered under suction. Volatile solvents were removed by means of a rotary evaporator to leave an oily residue, which solidified on cooling. The crude product was recrystallized from methanol to give the desired product, bis-[N-ethoxycarbonyl-N-(3-nitrophenyl)] monosulphide **(I)**; yield: 1.80 g, 80%, brown crystals; m.p. 58-59 °C (found: C, 48.13; N, 12.24; S, 7.51; calculated for $C_8H_{18}N_4O_8S$: C, 47.99; N, 12.44; S, 7.12%). The TLC (ethanol/DMSO, 3 : 1) gave a single spot, R_f = 0.69; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 6H), 4.1 ($CH_3C\underline{H}_2$, q, 4H), 7.5 (Ar-H, m, 8H); ^{13}C (DMSO): 15 ($\underline{C}H_3CH_2$), 61 ($\underline{C}H_3CH_2$), 113 (ArC-6), 118 (ArC-5), 125 (ArC-4), 131 (ArC-2), 142 (ArC-1), 149 (ArC-3), 154 (C=0). The infrared spectrum of the synthesizd compound showed a strong carbonyl absorption at 1715 cm^{-1} and absence of amide band of N-H stretching.

Synthesis of bis-[N-ethoxycarbonyl-N-(4-nitrophenyl] monosulphide. O-ethyl-N-(4-nitrophenyl) carbamate [2 x (1.05

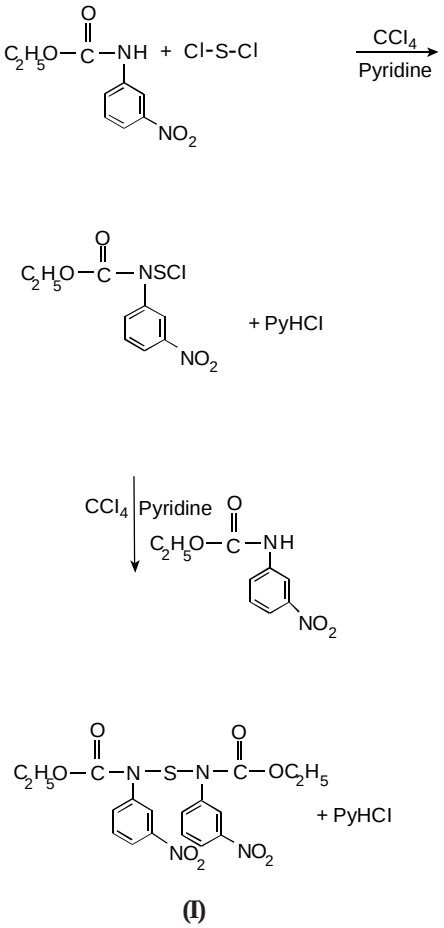

Fig. 1. Synthesis of bis-[N-ethoxycarbonyl-N-(3-nitrophenyl)] monosulphide.

g, 5 mmol)] and sulphur dichloride (0.52 g, 0.4 cm^3, 5 mmol) gave the product bis-[N-ethoxycarbonyl-N-(4-nitrophenyl)] monosulphide; yield: 1.6 g, 71%; brown (shining) crystalline solid on recrystallization from methanol (found: C, 47.91; N, 11.98; S, 6.86; calculated for $C_{18}H_{18}N_4O_8S$: C, 47.99; N, 12.44; S, 7.12%); m.p. 101-102 °C. The TLC (ethanol/DMSO, 3 : 1) gave a single spot, R_f = 0.69; ^{1}H (DMSO): 1.3 ($C\underline{H}_3CH_2$, t, 6H), 4.2 ($CH_3C\underline{H}_2$, q, 4H), 7.4 (Ar-H, m, 8H).

Synthesis of bis-[-N-ethoxycarbonyl-N-(4-chlorophenyl)] monosulphide. O-ethyl-N-(4-chlorophenyl) carbamate [2 x (1.03 g, 5 mmol)] and sulphur dichloride (0.52 g, 0.4 cm^3, 5 mmol) gave the product, bis-[N-ethoxycarbonyl-N-(4-chlorophenyl)] monosulphide; yield: 1.82 g, 85%; brown crystalline solid on recrystallization from methanol (found: C, 49.99; N, 6.57; S, 6.31; calculated for $C_{18}H_{18}Cl_2O_4S$: C, 50.35; N, 6.53; S, 7.47%); m.p. 92-93 °C. The TLC (ethanol/DMSO, 3 : 1) gave a single spot, R_f = 0.68; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 6H), 4.1 ($CH_3C\underline{H}_2$, q, 4H), 7.35 (Ar-H, m, 8H); ^{13}C (DMSO):15 ($\underline{C}H_3CH_2$), 61 ($CH_3\underline{C}H_2$), 121 (ArC-2,6), 127 (ArC-3,5), 129 (ArC-1), 139 (ArC-4), 154 (C=O).

A general procedure for the synthesis of disulphides. ***Synthesis of bis-[N-ethoxycarbonyl-N-(3-nitrophenyl)] disulphide***. To a solution of O-ethyl-N-(3-nitrophenyl) carbamate (1.05 g, 5 mmol) dissolved in carbon tetrachloride (20 cm^3) was added excess triethylamine, Et_3N (10 cm^3). Chilled sulphur monochloride, S_2Cl_2 (0.68 g, 0.4 cm^3, 5 mmol), dissolved in carbon tetrachloride (10 cm^3), was added dropwise from a dropping funnel, whilst the reaction mixture was maintained below 10 °C by the addition of ice to the waterbath in which the reaction vessel stood. White fumes, which disappeared with time, were produced. The reaction mixture was kept stirred for another 30 min after the addition of sulphur monochloride was completed. Another equimolar quantity of O-ethyl-N-(3-nitrophenyl) carbamate, dissolved in carbon tetrachloride (20 cm^3) was added dropwise to the reaction mixture. Further evolution of white fumes was observed. The reaction mixture was allowed to stir at a temperature below 10 °C for an additional 30 min and finally left to stir overnight at room temperature (Fig. 2). The solid, triethylamine hydrochloride was re-

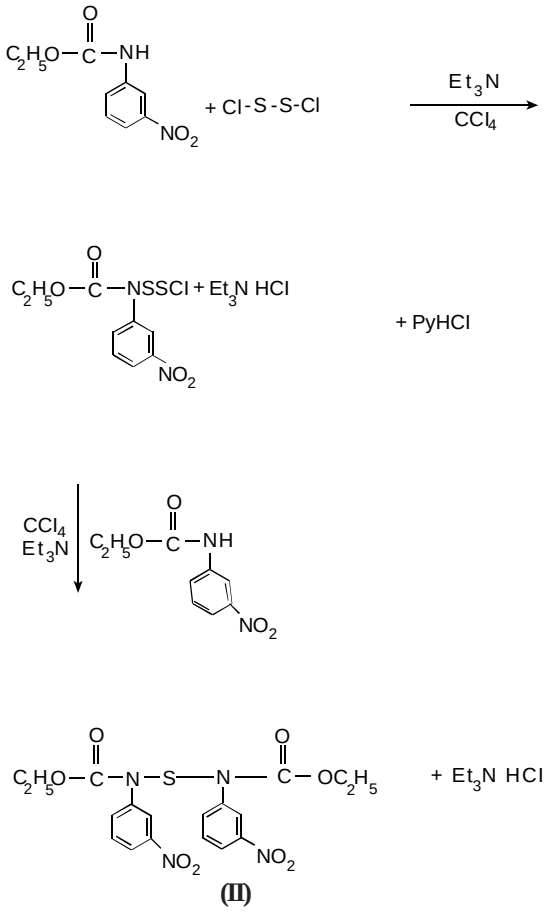

Fig. 2. Synthesis of bis-[N-ethoxycarbonyl-N-(3-nitrophenyl) disulphide.

Table 1. Inhibitory effect of some synthesized compounds (sulphide derivatives of O-ethyl-N-substituted phenylcarbamates) on some fungal species through minimal inhibitory concentration (MIC) and inhibitory concentration at 50% inhibition (IC_{50})

Synthesized compounds	*Aspergillus niger*		*Aspergillus flavus*		*Rhizopus stolonifer*		*Fusarium oxysporum*	
	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
O-ethyl-N-(3-nitrophenyl)carbamate	100	40	100	60	100	60	100	50
O-ethyl-N-(4-nitrophenyl)carbamate	250	80	250	80	250	100	250	100
O-ethyl-N-(4-chlorophenyl)carbamate	200	100	200	100	200	120	200	110
Bis-[(N-ethoxycarbonyl-N-(3-nitrophenyl)] monosulphide	50	10	50	10	50	18	50	21
Bis-[(N-ethoxycarbonyl-N-(4-nitrophenyl)] monosulphide	50	10	50	12	50	20	50	25
Bis-[N-ethoxycarbonyl-N(4-chlorophenyl)] monosulphide	50	11	50	10	50	20	50	22
Bis-[N-ethoxycarbonyl-N(3-nitrophenyl)] disulphide	50	08	50	10	50	20	50	24
Bis-[N-ethoxycarbonyl-N(4-nitrophenyl)] disulphide	50	12	50	15	50	23	50	25
Bis-[N-ethoxycarbonyl-N(4-chlorophenyl)] disulphide	50	10	50	12	50	25	50	25
Phenylmercury acetate (standard)	5	1	5	1	5	2	5	3
DMSO/H_2O (8:2) (control)	0	0	0	0	0	0	0	0

moved by filtration. The filtrate was washed with 10% hydrochloric acid (100 cm^3) solution in a separatory funnel. The organic layer was washed with distilled water (3 x 100 cm^3), dried with anhydrous sodium sulphate and filtered. Volatile solvents were removed from the filtrate by means of a rotary evaporator to leave oil, which solidified on standing. The crude product was recrystallized from methanol to give the desired product, bis-[N-ethoxycarbonyl-N-(3-nitrophenyl)] disulphide **(II)**; yield: 1.9 g, 79%; brown crystalline solid; m.p. 120-121°C (found: C, 43.98; N, 11.70; S, 10.62; calculated for $C_{18}H_{18}N_4O_8S_2$: C, 44.80; N, 11.61; S, 13.29%). The TLC (ethanol/DMSO 3 : 1) gave a single spot, R_f = 0.51; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 6H), 4.1 ($CH_3C\underline{H}_2$, q, 4H), 7.6 (Ar-H, m, 8H); ^{13}C (DMSO):15 ($\underline{C}H_3CH_2$), 61 ($CH_3\underline{C}H_2$), 112 (ArC-6), 118 (ArC-5), 125 (ArC-4), 130 (ArC-2), 141 (ArC-1), 150 (ArC-3), 154 (C=O). The infrared spectrum of the synthesized compound showed strong carbonyl absorption at 1720 cm^{-1} and absence of amide band of N-H stretching.

Synthesis of bis-[N-ethoxycarbonyl-N-(4-nitrophenyl)] disulphide. O-ethyl-N(4-nitrophenyl) carbamate [2 x (1.05 g, 5 mmol)] and sulphur monochloride (0.68 g, 0.4 cm^3, 5 mmol) gave the product, bis-[N-ethoxycarbonyl-N-(4-nitrophenyl)] disulphide as a brown crystalline solid; yield: 1.9 g, 79%, m.p. 124-125 °C (found: C, 44.33; N, 10.84; S, 10.56; calculated for $C_{18}H_{18}N_4O_8S_2$: C, 44.80; N, 11.61; S, 13.29%). The TLC (ethanol/DMSO 3 : 1) gave a single spot, R_f = 0.54; ^{1}H (DMSO): 1.3 ($C\underline{H}_3CH_2$, t, 6H), 4.2 ($CH_3C\underline{H}_2$, q, 4H), 7.5 (Ar-H, m, 8H).

Synthesis of bis-[N-ethoxycarbonyl-N-(4-chlorophenyl)] disulphide. O-ethyl-N-(4-chlorophenyl carbamate [2 x (0.99 g, 5 mmol)] and sulphur monochloride (0.68 g, 0.4 cm^3, 5 mmol) gave the product,bis-[N-ethoxycarbonyl-N-(4-chlorophenyl)] disulphide as a reddish-wine coloured crystalline solid; yield: 1.6 g, 70%; m.p. 65-66 °C; (found: C, 47.11; N, 5.96; S, 11.64; calculated for $C_{18}H_{18}Cl_2N_2O_4S_2$: C, 46.85; N, 6.07; S, 13.89%). The TLC (ethanol/DMSO 3 : 1) gave a single spot, R_f = 0.54; ^{1}H (DMSO): 1.2 ($C\underline{H}_3CH_2$, t, 6H), 4.1 ($CH_3C\underline{H}_2$, q, 4H), 7.3 (Ar-H, m, 8H); ^{13}C (DMSO):15 ($\underline{C}H_3CH_2$), 61 ($CH_3\underline{C}H_2$), 120 (ArC-2,6), 127 (ArC-3,5), 129 (ArC-1), 139 (ArC-4), 154 (C=O).

Biological screening. Potato dextrose agar (PDA) plates were flooded with spore suspension of each fungus. About 6 mm

dia filter paper discs were sterilized in petri dishes at 160 ^{o}C for 2 h. With the aid of a sterilized pair of forceps, filter paper discs that had been soaked in solutions of various concentrations of each synthesized compound were put on the surface of inoculated PDA plates. Filter paper discs were also soaked in the standard (phenylmercury acetate) and the control (CDMSO/H_2O; 8 : 2), and then placed on the surface of the inoculated PDA plates. All the PDA plates were incubated at room temperature. The growth dia of the fungus colony was measured after every 24 h interral, until the control plate was complete covered with the growth of fungus. The minimum concentration of each synthesized compound, that gave 100% inhibition of fungus growth, was taken as the 'minimal inhibitory concentration (MIC) of the compound (Adelowo-Imeokparia *et al*., 2005). The IC_{50} (inhibitory concentration of the synthesized compound at 50% inhibition of the fungus colony) was extrapolated from the graph of percentage inhibition (1%) of fungus against concentration of the synthesized compound (Adelowo-Imeokparia *et al*., 2005; Tabakova *et al*., 1995).

Results and Discussion

A strongly basic tertiary amine was used in the synthesis of disulphides of O-ethyl-N-substituted phenylcarbamate so as to prevent any formation of their corresponding monosulphides (Fahmy *et al.*, 1974; Kuhle, 1970).

The values of the minimal inhibitory concentration (MIC) and the 50% inhibitory concentration (IC_{50}) of the synthesized compounds are presented in Table 1. The MIC value of the parent compounds (carbamates) were between 100 and 250 ppm, while their sulphides were 2- to 5-folds lower (50 ppm). Organic sulphur compounds move into the fungus cells and are able to take part in chemical reactions, such as chelation, oxidation-reduction and nucleophilic displacement (Lukens, 1971). Dithiocarbamates (disulphides of carbamate), such as thiram and ziram owe their fungicidal activity to their ability to chelate with heavy metals present in the cells of fungi (Metcalf, 1971). Ethylenebisdithiocarbamates (nabam, maneb and zineb), on the other hand, undergo oxidative decomposition. The ethylene diisothiocyanate so produced reacts with thiol compound within the fungal cell. This is responsible for the fungicidal activity of ethylenebisdithiocarbamates (Lukens, 1971). N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide (a monosulphide) owe its fungicidal action to its involvement in nucleophilic displacement reaction with cellular thiols to produce thiophosgene as the toxicant (Cremlyn, 1979). It seems very appropriate, therefore, that the observed increase in fungicidal activity of the synthesized monosulphides and disulphides of O-ethyl-N-substituted phenylcarbamates (as shown by their MIC and IC_{50} values), when compared with their parent compounds, could be ascribed to their involvement in any of the earlier mentioned reactions within the fungal cells.

The results of the MIC and IC_{50} of the synthesized compounds showed that the monosulphides were as good as their disulphide analogues for the control of the four fungal species. The IC_{50} values of the synthesized monosulphides and disulphides were about two-folds lower when tested against *Aspergillus* species. This shows that *Aspergillus* species were more susceptible to the synthesized mono- and disulphides than the remaining two fungal species. There was no evidence of dependence of activity on the benzene ring substituents since only electron withdrawing substituents were involved in this work.

The IC_{50} of the standard, pheylmercury acetate (a well known fungicide), was about 4- to 12-folds lower than that for the monosulphides and disulphides, while it was about 20- to 60-folds lower than the carbamates. Since the level of activity of the monosulphides and disulphides was almost comparable to that of the standard, it may be concluded that the studied derivatives showed good promise as potential fungicides.

Conclusion

This work has demonstrated that the synthesized compounds have shown promising fungicidal activities against the selected fungi. The sulphide derivatives of phenylcarbamate precursors can probably improve on their fungicidal activity by the introduction of more sulphur atoms, replacing ethoxy group with phenoxy or naphthoxy group, and the use of electron donating substituents in the benzene ring.

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