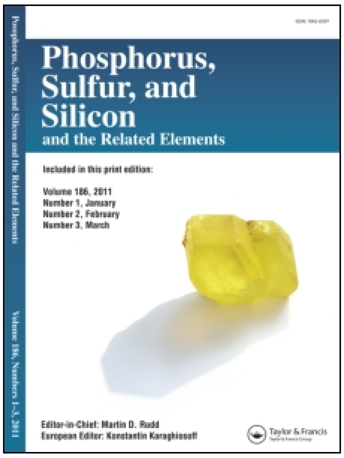

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Synthesis and Bioassay of Phosphorylated and Thiphosphorylated Derivatives of Substituted Benzothiazoles

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Synthesis and Bioassay of Phosphorylated and Thiphosphorylated Derivatives of Substituted Benzothiazoles

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Phosphorylated and thiophosphorylated benzothiazole derivatives have been synthesized by a reaction of phosphorus oxychloride/phosphorus thiochloride with 1,2-bis(2-benzothiazolyl)ethanol in 1:1, 1:2, and 1:3 molar ratios in the presence of triethylamine. Plausible structures have been proposed on the basis of elemental analysis IR, ^{1}H NMR, and ^{31}P NMR spectral studies. The fungicidal activity of these derivatives has been evaluated against pathogenic fungi Aspergillus niger *and* Fusarium oxysporium. *The fungicidal data reveals that these compounds are more fungitoxic than the parent 1,2-bis(2-benzothiazolyl)ethanol compound.*

Keywords Benzothiazole; fungicidal activity; phosphorylated derivatives; phosphorylation

INTRODUCTION

Organophosphorus compounds have been widely studied for their biocidal activity, and their important role as a pesticidal insecticidal, fungicidal, and bactericidal agent is recognized.[1–3] Various phosphorylated compounds of benzothiazole and alcohols are also associated with antifungal activities.[4–6] These observations encouraged us to continue our previous work[7] to synthesize the phosphorylated and thiophosphorylated benzothiazole derivatives, which were screened for antifungal activity. We report herein the synthesis, characterization, and fungicidal activity of some O-phosphorylated/thiophosphorylated benzothiazole derivatives.

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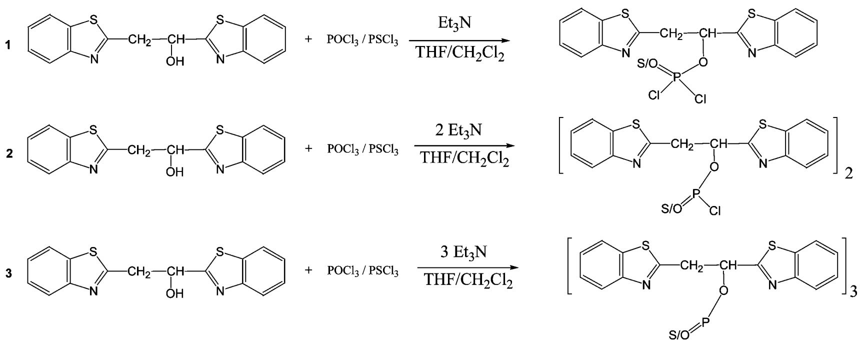

SCHEME 1

RESULTS AND DISCUSSION

1,2-bis(2-benzothiazolyl)ethanol reacted with phosphorus oxychloride/ phosphorus thiochloride (1:1, 2:1, and 3:1 molar ratio) in the presence of a stoichiometric amount of triethylamine in THF/ methylene chloride, which resulted in the formation of corresponding O-phosphorylated/thiophosphorylated benzothiazole derivatives. In this manner, O-1,2-bis (2-benzothiazolyl)ethyl phosphorodichloridate/phosphorodichloridothionate, O,O-di{1,2-bis (2-benzothiazolyl)ethyl)}phosphorochloridate/phosphorochloridothionate, and O,O,O-tri{1,2-bis(2-benzothiazolyl)ethyl}phosphate/phosphorothionate were obtained (Scheme 1). Physical and analytical details of the compounds are given in Table I.

IR Spectra

The formation of O-phosphorylated/thiophosphorylated benzothiazole derivatives was identified by the disappearance of a ν(O–H) absorption band at 3400–3300 cm^{-1} present in 1,2-bis(2-benzothiazolyl)ethanol. In O-(ethyl bis benzothiazolyl-2-)phosphorodichloridate, characteristic stretching vibrations ν(P-O-C)[1], ν(P$=$O)[8], and ν(P-Cl)[1] appeared at 1040–1150 cm^{-1}, 1244–1255 cm^{-1}, 500–530 cm^{-1}, and 600–650 cm^{-1}, and in thiophosphorylated derivatives, absorption bands of ν(P$=$S)[1] appeared at 800–900 cm^{-1} and 650–670 cm^{-1}.

^{1}H NMR Spectra

^{1}H NMR spectra of bis(1-hydroxyethyl)benzothiazole showed an OH proton signal at δ3.74 ppm, and aromatic protons were observed at δ7.7–8.1 ppm. The OH proton signal at δ3.74 ppm disappeared in O-phosphorylated/thiophosphorylated benzothiazole derivatives.

TABLE I Analytical Data of 2-Substituted Benzothiazole and Phosphorylated and Thiophosphorylated Compounds of 2-Substituted Benzothiazole

Compounds	Yield %	M.P. °C	Analysis % Found (Calcd.) C	H	N	S	P	Cl	Mol. Wt. Found (Calcd.)
($C_{16}H_{12}N_2S_2O$)	65	125–127	61.51 (61.39)	3.87 (3.82)	8.96 (8.76)	21.18 (20.52)	—	—	312.41 (300)
($C_{16}H_{11}N_2S_2O$)P(O)(Cl_2)	57	90–95	44.70 (44.01)	2.58 (2.49)	6.53 (6.40)	14.93 (14.61)	7.22 (6.99)	16.52 (16.11)	429.28 (420.21)
($C_{16}H_{11}N_2S_2O$)$_2$P(O)(Cl)	54	90–91	53.29 (52.47)	3.07 (2.76)	7.94 (7.65)	18.18 (18.01)	4.39 (4.13)	4.39 (4.25)	705.24 (698.27)
($C_{16}H_{11}N_2S_2O$)$_3$P(O)	58	79–80	58.81 (57.85)	3.33 (3.19)	8.57 (8.23)	19.60 (18.57)	3.16 (2.93)	—	981.19 (975.23)
($C_{16}H_{11}N_2S_2O$)P(S)(Cl_2)	51	70–71	43.15 (42.92)	2.57 (2.45)	6.38 (6.12)	21.60 (21.51)	6.95 (6.86)	15.92 (15.01)	445.35 (439.27)
($C_{16}H_{11}N_2S_2O$)$_2$P(S)(Cl)	50	65–66	53.28 (53.01)	3.07 (2.86)	7.77 (6.94)	22.22 (22.73)	4.29 (4.18)	4.29 (4.10)	721.31 (715.34)
($C_{16}H_{11}N_2S_2O$)$_3$P(S)	49	90–95	57.81 (56.65)	3.33 (2.75)	8.43 (8.12)	22.51 (21.97)	3.10 (2.95)	—	977.26 (960.05)

TABLE II The Assignment of the Main IR Bands (cm^{-1}) of Phosphorylated and Thiophosphorylated Benzothiazole Derivatives

Compounds	ν(P═S)	ν(P—Cl)	ν(P═O)	ν(P—O—C)
$(C_{16}H_{11}N_2S_2O)P(O)(Cl_2)$	—	520 (sym) 600 (asym)	1240	1040 (I) 980 (II)
$(C_{16}H_{11}N_2S_2O)_2P(O)(Cl)$	—	525 (sym) 600 (asym)	1250	1100 (I) 970 (II)
$(C_{16}H_{11}N_2S_2O)_3P(O)$	—	—	1255	1150 (I) 965 (II)
$(C_{16}H_{11}N_2S_2O)P(S)(Cl_2)$	800 (I) 650 (II)	525 (sym) 610 (asym)		1010 (I) 980 (II)
$(C_{16}H_{11}N_2S_2O)_2P(S)(Cl)$	850 (I) 690 (II)	530 (sym) 640 (asym)	—	1050 (I) 975 (II)
$(C_{16}H_{11}N_2S_2O)_3P(S)$	890 (I) 710 (II)	—	—	1075 (I) 970 (II)

^{31}P NMR Spectra

All the O-phosphorylated and thiophosphrylated benzothiazole derivatives were characterized by the downfield ^{31}P NMR signal at δ 70–98 ppm.[9]

Antifungal Activity

Results of the fungicidal screening of the synthesized phosphorylated and thiophosphorylated benzothiazole derivatives against *Aspergillus niger* and *Fusarium oxysporium* are summarized in Table III. The

TABLE III Fungitoxic Screening Data of Organophosphorus Derivatives Containing 2-Substituted Benzothiazoles

	Percent Mycelial Inhibition					
	Aspergillus niger Compound Dose (ppm)			*Fusarium oxysporium* Compound Dose (ppm)		
Compounds	**50**	**100**	**200**	**50**	**100**	**200**
$(C_{16}H_{11}N_2S_2O)P(O)(Cl_2)$	18.9	59.3	78.1	20.8	49.2	65.5
$(C_{16}H_{11}N_2S_2O)_2P(O)(Cl)$	38.8	64.7	79.2	41.2	55.5	76.8
$(C_{16}H_{11}N_2S_2O)_3P(O)$	48.2	71.4	88.5	50.7	67.1	80.1
$(C_{16}H_{11}N_2S_2O)P(S)(Cl_2)$	25.3	62.5	80.5	39.5	59.8	70.3
$(C_{16}H_{11}N_2S_2O)_2P(S)(Cl)$	52.3	75.8	82.1	46.7	76.7	82.4
$(C_{16}H_{11}N_2S_2O)_3P(S)$	70.1	83.9	94.3	71.4	89.6	95.2
Dithane M-45	75	90	100	73	92	100

antifungal activity of phosphorylated and thiophosphorylated benzothiazole derivatives was found to be greater than that of the corresponding starting material. These compounds were compared with commercial fungicides Dithane M-45.

Among phosphorylated and thiophosphorylated derivatives, O,O,O-tri1,2-bis(2-benzothiazolyl)ethyl}phosphate/phosphorothionate showed stronger fungitoxic activity against both fungi.

EXPERIMENTAL

All commercial reagents and solvents were dried and distilled by common methods before use. $POCl_3$/$PSCl_3$ was purchased from Fluka.

Melting points were determined by the capillary method and are uncorrected. All operations involving phosphorus compounds were carried out in dry equipment under a nitrogen atmosphere. IR spectra were recorded on a Perkin-Elmer 577 grating spectrometer in KBr discs in the region 4000–200 cm^{-1}. NMR spectra were recorded on JEOL FX-90Q spectrophotometer using $CDCl_3$ as a solvent. Nitrogen was estimated by Kjeldahl's method. Phosphorus was estimated as ammonium phosphomolybdate. Chlorine was estimated volumetrically by Volhard's method.

The Synthesis of the Ligand

The ligand 1,2-bis(2-benzothiazolyl)ethanol was synthesized on the basis of a previously reported method.[10]

The Synthesis of O-1,2-Bis(2-benzothiazolyl)ethyl Phosphorodichloridate/phosphorodichloridothionate

In a fast-stirring solution of 1,2-bis(2-benzothiazolyl)ethanol (0.001 mole) and Et_3N (0.001 mole) in dry THF/CH_2Cl_2, a solution of $POCl_3$/$PSCl_3$ (0.001 mole) in dry THF was added dropwise. The reaction mixture was then filtered through a closed sintered funnel in another round-bottom flask and then refluxed under a nitrogen atmosphere for 14–15 h. Then it was cooled and filtered through closed sintered funnel. The filtrate was then concentrated to one fourth of its volume and kept for crystallization in a vaccum for 2 days. It was recrystallized from dry ethanol.

TABLE IV ^{1}H NMR and ^{31}P NMR Spectral Data of Phosphorylated and Thiophosrylated Derivatives

Cpd	^{31}P-NMR ($CDCl_3$)	^{1}H-NMR (δ ppm)
$(C_{16}H_{11}N_2S_2O)P(O)(Cl_2)$	76.1	2.7(d, 2H, C-CH_2); 3.8(t, 1H, O-CH); 7.77(m, 4H, C_6H_4)
$(C_{16}H_{11}N_2S_2O)_2P(O)(Cl)$	72.3	2.9(d, 2H, C-CH_2); 4.1(t, 1H, O-CH); 7.82(m, 4H, C_6H_4)
$(C_{16}H_{11}N_2S_2O)_3P(O)$	68.5	3.0(d, 2H, C-CH_2); 4.3(t, 1H, O-CH); 8.01(m, 4H, C_6H_4)
$(C_{16}H_{11}N_2S_2O)P(S)(Cl_2)$	79.5	2.5(d, 2H, C-CH_2); 3.7(t, 1H, O-CH); 7.68(m, 4H, C_6H_4)
$(C_{16}H_{11}N_2S_2O)_2P(S)(Cl)$	74.4	2.6(d, 2H, C-CH_2); 3.9(t, 1H, O-CH); 7.75(m, 4H, C_6H_4)
$(C_{16}H_{11}N_2S_2O)_3P(S)$	70.5	2.8(d, 2H, C-CH_2); 4.2(t, 1H, O-CH); 7.93(m, 4H, C_6H_4)

The Synthesis of O,O-di{1,2-Bis(2-benzothiazolyl)ethyl} Phosphorochloridate/phosphorochloridothionate

In a fast-stirring solution of 1,2-bis(2-benzothiazolyl)ethanol (0.002 mole) and Et_3N (0.002 mole) in dry THF/CH_2Cl_2, a solution of $POCl_3/PSCl_3$ (0.001 mole) in dry THF was added dropwise. Then the reaction was carried out in a manner similar to what was previously described. The product was filtered, concentrated, and recrystallized from dry ethanol.

The Synthesis of O,O,O-tri{1,2-Bis(2-benzothiazolyl)ethyl} Phosphate/phosphorothionate

In a fast-stirring solution of 1,2-bis(2-benzothiazolyl)ethanol (0.003 mole) and Et_3N (0.003 mole) in dry THF/CH_2Cl_2, a solution of $POCl_3$ (0.001 mole) in dry THF was added dropwise by a droping funnel. Then the reaction was carried out in a manner similar to what was previously described. The product was recrystallized from dry ethanol.

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