

Synthesis of *O,O*-diaryl *O-n*-propyl phosphorothionates and their fungitoxicity against *Rhizoctonia solani* and *Sclerotium rolfsii*[†]

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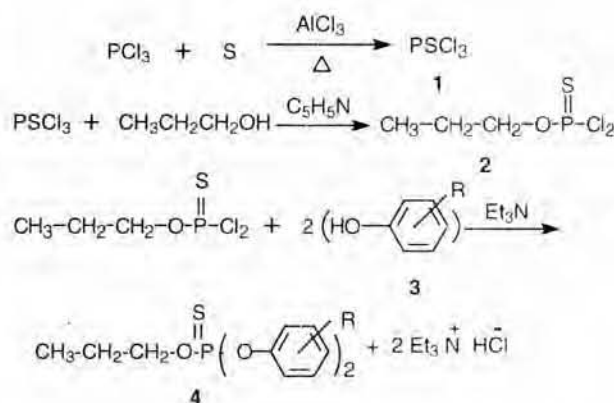
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Twenty new *O,O*-diaryl *O-n*-propyl phosphorothionates **4** have been prepared by condensing *O-n*-propyl phosphorodichloridothioate with substituted phenols and tested *in vitro* for fungitoxicity against *Rhizoctonia solani* and *Sclerotium rolfsii*. The compounds *O,O*-di(3-methylphenyl) *O-n*-propyl phosphorothionate **4c** against *R. solani* ($ED_{50}=0.229$ mg mL⁻¹) and *O,O*-di(2,3-dimethylphenyl) *O-n*-propyl phosphorothionate **4m** against *S. rolfsii* ($ED_{50}=0.275$ mg mL⁻¹) show the highest activity. Important generalisations on structure-activity relationships in this series are being made out based on the fungitoxicity data.

Among organophosphorus compounds, phosphorothionates are known mainly for their insecticidal activity^{1,2}. A report³ leading to the development of tolclofos methyl fungicide for controlling soil borne diseases caused by *Rhizoctonia solani*, and few other recent reports^{4,5} from our laboratory have encouraged us to explore this group further for discovering new fungicide molecules. In this effort, a series of twenty *O,O*-diaryl *O-n*-propyl phosphorothionates were designed, their synthesis and fungicidal activity against *Rhizoctonia solani* and *Sclerotium rolfsii* are reported in this paper.

The sequence of reactions leading to the synthesis of *O,O*-diaryl *O-n*-propyl phosphorothionates **4** is shown in **Scheme I**. The compounds (**Table I**) were prepared by the reaction of *O-n*-propyl phosphorodichloridothioate **2** with respective phenols **3**. Structures of the *O,O*-diaryl *O-n*-propyl phosphorothionates **4** were confirmed by their IR, nuclear magnetic resonance (**Table II**) and mass spectroscopy. The IR spectra⁶ showed the following characteristic peaks: 689.6 to 795.8 and 785.0 to 900.2 cm⁻¹, for P=S, 926.2 to 992.3 and 1000.0 to 1097.6 cm⁻¹ for P-O-C (aliphatic) and 1084.5 to 1235.8 cm⁻¹ for P-O-C (aromatic). A characteristic feature of ¹H NMR spectra was the presence of a triplet at δ 0.90 to 1.20 [P-O-CH₂-CH₂-CH₃^γ, *J*=6-7 Hz], a multiplet at δ 1.60 to 2.00 [P-O-CH₂-CH₂^β-CH₃] and another multiplet (double triplet) at 4.20 to 4.60 [P-O-CH₂^α-CH₂-CH₃], in addition to the usual peaks



Scheme I

corresponding to aromatic protons and protons of the substituents such as -CH₃, -C(CH₃)₃ and -OCH₃. Mass spectra of these phosphorothionates exhibited the molecular ion (M⁺) and M⁺+1 peaks except for the pentachloro analogue which showed (M⁺-Cl) peak showing the loss of one Cl atom.

Fungitoxicity of *O,O*-diaryl *O-n*-propyl phosphorothionates **4** was studied against *Sclerotium rolfsii* and *Rhizoctonia solani*. The ED_{50} (effective dose for 50% inhibition of the fungus growth) values in mg mL⁻¹ are given in **Table I**. The fungitoxicity data show that these compounds exhibit moderate activity against both the test fungi, and are less active than edifenphos and *O,O*-di(2, 4, 6-trichlorophenyl) *O*-methyl phosphorothionate (reference fungicides). Among all the phosphorothionates screened, *O,O*-di(3-methylphenyl) *O-n*-propyl phosphorothionate **4c** against *R.*

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Table I—Physical and fungitoxicity data of *O,O*-diaryl *O*-*n*-propyl phosphorothionates 4

Compd	R in structure 4 (Scheme I)	mp °C	Yield (%)	<i>ED</i> ₅₀ (mg mL ⁻¹) against	
				<i>R. solani</i>	<i>S. rolfsii</i>
4a	H	Liquid ^a	75.3	0.796	1.310
4b	2-CH ₃	Liquid ^a	75.2	7.815	1.618
4c	3-CH ₃	Liquid ^a	74.0	0.229	0.552
4d	4-CH ₃	Liquid ^a	74.0	0.566	0.391
4e	4-Cl	Liquid ^a	50.4	0.629	0.345
4f	2-NO ₂	65-67	70.1	0.650	1.816
4g	4-NO ₂	Liquid ^a	73.8	0.685	0.281
4h	2-OCH ₃	Liquid ^a	68.4	0.636	0.327
4i	4-OCH ₃	Liquid ^a	66.6	1.324	1.006
4j	4-C(CH ₃) ₃	Liquid ^a	58.1	0.926	0.904
4k	2,4-Cl ₂	Liquid ^a	77.9	0.438	6.749
4l	2-Cl,4-NO ₂	Liquid ^a	78.1	0.940	0.351
4m	2,3-(CH ₃) ₂	Liquid ^a	73.6	2.126	0.275
4n	2,4-(CH ₃) ₂	Liquid ^a	74.7	0.669	1.023
4o	3,4-(CH ₃) ₂	Liquid ^a	71.4	0.376	0.499
4p	3-CH ₃ ,4-Cl	Liquid ^a	80.5	2.508	0.281
4q	2,3,5-(CH ₃) ₃	Liquid ^a	69.4	0.794	0.331
4r	2,4,5-Cl ₃	105-7	85.5	0.420	1.510
4s	2,4,6-Cl ₃	84-86	87.9	0.915	0.968
4t	Cl ₅	155-57	88.9	0.260	0.319
5 ^b	-	-	-	0.028	0.060
6 ^c	-	-	-	0.0009	0.0025

^aPurified by column chromatography on silica gel.^bEdifenphos.^c*O,O*-di(2,4,6-trichlorophenyl) *O*-methyl phosphorothionate⁴.**Table II**—¹H NMR spectra of *O,O*-diaryl *O*-*n*-propyl phosphorothionates 4

Compd	R	Chemical shifts (δ, ppm)				
		CH ₃ (γ)	CH ₂ (β)	CH ₂ (α)	Ar H	Other protons
4a	H	1.10	1.80	4.40	7.4	-
4b	2-CH ₃	1.00	1.80	4.20	7.3	2.4
4c	3-CH ₃	1.10	1.80	4.30	7.1	2.4
4d	4-CH ₃	1.10	1.80	4.40	7.4	2.4
4e	4-Cl	1.05	1.80	4.30	7.4	-
4f	2-NO ₂	1.10	1.90	4.40	7.7	-
4g	4-NO ₂	0.90	1.70	4.30	7.5, 8.4	-
4h	2-OCH ₃	1.00	1.80	4.30	7.2	3.9
4i	4-OCH ₃	1.00	1.80	4.30	7.0	3.8
4j	4-C(CH ₃) ₃	1.00	1.80	4.30	7.4	1.2
4k	2,4-Cl ₂	1.10	1.80	4.40	7.5	-
4l	2-Cl,4-NO ₂	1.20	2.00	4.60	7.85,8.5	-
4m	2,3-(CH ₃) ₂	1.10	1.80	4.30	7.2	2.3
4n	2,4-(CH ₃) ₂	1.00	1.70	4.20	7.1	2.1
4o	3,4-(CH ₃) ₂	1.10	1.85	4.30	7.15	2.3
4p	3-CH ₃ , 4-Cl	1.00	1.80	4.20	7.2	2.4
4q	2,3,5-(CH ₃) ₃	1.10	1.90	4.35	7.0	2.3
4r	2,4,5-Cl ₃	1.10	1.90	4.40	7.7	-
4s	2,4,6-Cl ₃	0.90	1.60	4.30	7.5	-
4t	Cl ₅	0.90	1.70	4.30	-	-

solani ($ED_{50}=0.229$ mg mL⁻¹) and *O,O*-di(2,3-dimethylphenyl) *O*-*n*-propyl phosphorothionate **4m** against *Sclerotium rolfsii* ($ED_{50}=0.275$ mg mL⁻¹) show the highest activity.

Structure-activity relationships. The fungicidal activity (Table I) of *O,O*-diaryl *O*-*n*-propyl phosphorothionates **4** was independent of the electronic nature of the aromatic substituents but their position in the benzene ring influenced the activity against both fungi, *R. solani* and *S. rolfsii*. The trend in activity against *R. solani* of the methyl and chloro substituted compounds [3-CH₃ > 4-CH₃ > 2-CH₃; 2-CH₃ < 2,3-(CH₃)₂ < 2,3,5-(CH₃)₃ and 2,4-Cl₂ < 2,4,5-Cl₃ < Cl₅] clearly reveals that the presence and progressive introduction of a *meta*-substituent in the benzene ring results in enhanced fungicidal activity of the compounds.

Although the trend in activity among the monomethyl substituted compounds is, 4-CH₃ > 3-CH₃ > 2-CH₃ but the contribution of *meta*-position towards imparting more activity is also evident from the fungitoxicity results against *S. rolfsii*. Among all the dimethyl substituted compounds, the 2,3-dimethyl analogue **4m** showed the highest activity which considerably increased in comparison to the monomethyl substitution at *ortho*-position **4b** and also from the better activity shown by the 3-CH₃, 4-Cl analogue **4p** compared to the 4-Cl analogue **4e**. The 2, 3, 5-trimethyl substituted compound **4q** showed less activity than the 2,3-dimethyl analogue **4m**. This shows that further introduction of another methyl group in the other *meta*-position is not favouring fungitoxicity in case of *S. rolfsii*.

Experimental Section

General. For synthesis, all solvents and reagents used were dried and purified by either distillation (liquids) or recrystallisation (solids). Thin layer chromatography (on pre-activated silica gel G plates) was used to monitor reaction and check the purity of the compounds. Melting points (°C) were determined in sulphuric acid-bath and are uncorrected. Characterisation of the products was done by spectroscopic methods. ¹H NMR (chemical shifts in δ , ppm) spectra were recorded on a Varian EM 360L, 60 MHz spectrometer in CCl₄ using TMS as internal standard, IR (ν_{max} in cm⁻¹) spectra on a Nicolet FT-IR, Model Impact 400 spectrophotometer (liquids as thin films and solids as KBr pellets), and EI mass

spectra on a Fisons Trio 1000 ion trap mass spectrometer at ionisation potential 70 eV.

Thiophosphoryl trichloride **1** was prepared as described⁷, by the reaction of phosphorus trichloride with sulphur in the presence of anhydrous aluminium chloride, bp 118-20°C, yield 90%.

***O*-*n*-propyl phosphorodichloridothioate 2.** *n*-Propanol (60 g, 1 mole) was added to thiophosphoryl trichloride **1** (204 g, 1.2 moles) with continuous stirring for about 10 min. To this mixture, pyridine (79 g, 1 mole) was added dropwise with stirring at 25-30°C. Pyridine was added slowly, in about 2 hr and the reaction mixture further stirred for 30 min at this temperature and then dissolved in *n*-hexane (250-300 mL). The contents were transferred to a separatory funnel, washed with cold water (2-3 times) followed by saturated solution of sodium chloride and then dried over anhydrous sodium sulphate. The solvent was removed by distillation and the residual liquid distilled under reduced pressure. The fraction which boiled at 80-82°C/20 mm Hg was collected (yield 80%) (reported⁸ bp 80°C/20 mm Hg). The structure of *O*-*n*-propyl phosphorodichloridothioate **2** was confirmed by ¹H NMR and IR spectroscopy; ¹H NMR: δ 1.10 (3H, t, $J=6-7$ Hz, >P-O-CH₂-CH₂-CH₃), 1.80 (2H, m, >P-O-CH₂-CH₂-CH₃), 4.40 (2H, m, >P-O-CH₂-CH₂-CH₃), IR (Neat): 1012 (P-O-C aliphatic), 758 (P=S), 495 and 544 (P-Cl₂).

***O,O*-Diaryl *O*-*n*-propyl phosphorothionates 4.** A solution of *O*-*n*-propyl phosphorodichloridothioate **2** (1.2 moles) in dry benzene was added dropwise with stirring to a cooled (0-5°C) solution of the respective phenol **3** (2 moles) in dry benzene containing dry triethylamine (2 moles). The reaction mixture was further stirred for 3-4 hr at room temperature. After filtering off the triethylamine hydrochloride, the filtrate was washed with 2% cold sodium hydroxide solution followed by distilled water. The benzene layer was then dried over anhydrous sodium sulphate and the solvent removed by distillation. The residue was purified by column chromatography (on silica gel 60-80 mesh) and recrystallized from hexane in case of solid compounds. The purity of the compounds was checked by thin layer chromatography on pre-activated silica gel G plates, using hexane + benzene (9+1 by volume) as developing solvent and iodine vapour as visualising agent.

Fungitoxicity testing. Fungitoxicity testing of *O,O*-diaryl *O*-*n*-propyl phosphorothionates **4** was carried out against *Rhizoctonia solani* Kühn and

Sclerotium rolfsii Saccardo by the poisoned food technique using standard potato-dextrose-agar (PDA) as described by Nene and Thapliyal⁹. The ED_{50} (effective dose for 50% inhibition of fungus growth) values in mg mL^{-1} were determined from the growth inhibition data by means of a BASIC LD_{50} programme version 1.1¹⁰ and are given in **Table I**.

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