Note

Synthesis and Fungicidal Activity of Diaryl Methylphosphonates†

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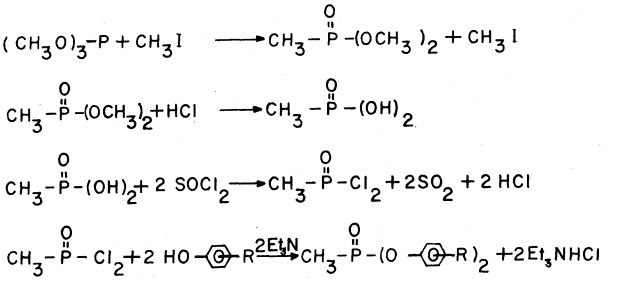
Several phosphorothiolates are known to possess fungicidal activity and are particularly antiblast agents.[1] In earlier papers from this laboratory we have communicated the synthesis of a series of aryl chloromethylphosphonates[2] and aryl chloroethylphosphonates[3] with fungicidal activity. Structure–activity relationships studies of these group of compounds have showed that two aryl groups are essential for fungicidal activity.[4] Our interest was therefore to examine the effects of unsubstitution in the alkyl side chain attached to the phosphorus atom. With this objective the preparation and fungicidal activity of diaryl methylphosphonates were investigated and the results are reported here. Structure–activity relationships of the compounds have also been described.

Synthesis. An attempt was made to synthesize diaryl methylphosphonates by the Michaelis–Arbuzov reaction by refluxing triaryl phosphites with methyl iodide and decomposing the complex with ethanol.[5] The method gave poor yield and many phosphites failed to give the desired phosphonates. The alternate route of synthesis of diaryl methylphosphonates was followed (Scheme 1). In the first step dimethyl methylphosphonate was prepared by reacting trimethylphosphite with methyl iodide[6], bp 138～140°C/110 mm (Y, 79%). Dimethyl methylphosphonate was then hydrolyzed with concentrated HCl to give methylphosphonic acid,[7] mp 105°C (Y, 88%), which was then treated with thionyl chloride to yield methylphosphonic dichloride,[8] mp 35°C (Y, 80%). Methylphosphonic dichloride on condensation with phenols gave diaryl methylphosphonates.

A general procedure for the preparation of diaryl methylphosphonates is given below. Methylphosphonic dichloride (1 mol) in dry benzene (20 ml) was added dropwise to a mixture of phenol (2 mol) in dry benzene (100 ml) containing dry triethylamine (2 mol), with continuous stirring. The reaction mixture maintained at 50～60°C was further stirred for 5～6 hr. After filtering off the triethylamine hydrochloride the solvent was removed by distillation and the product was purified by recrystallization in the case of solids, and distillation or column chromatography over silica gel coated with 1% oxalic acid in the case of liquids. The purity of the compounds was checked by thin layer chromatography on silica gel coated with 1% oxalic acid (250 μm thick) with benzene–acetone (90 : 10 by volume) as the developing solvent, and visualized in an iodine chamber. The physical and analytical data of the synthesized compounds (**1**～**18**) are listed in Table I.

Infrared spectra of the phosphonates recorded on Perkin Elmer 457 spectrophotometer showed maxima at 960～980 cm^{-1} (P–O–C aliphatic), 1180～1200 cm^{-1} (P–O–C aromatic), 1230～1270 cm^{-1} (P=O) and 1300 cm^{-1} (CH_3–P). Nuclear magnetic resonance spectra recorded on a Varian 90 MHz spectrometer exhibited a doublet at δ 1.8～2.0 (J = 18 Hz, P–CH_3) besides the usual signals due to aromatic protons and protons of the substituents like CH_3, OCH_3, and SCH_3 groups at appropriate positions.

Fungicidal studies. The fungicidal activity of the phosphonates (**1**～**18**) against *Pyricularia oryzae* cav., *Helminthosporium oryzae* Auct. *Alternaria alternata Breda* de Haan, *Rhizctonia bataticola* (Tassi) Goid and *Pythium aphanidermatum*, Eds. Fitzp. was determined by the standard poisoned food technique using potato dextrose agar as described by Nene and Thapliyal.[9] ED_{50} values were determined from the data of concentrations and percentage inhibition of fungal growth on a log probit scale, and are presented in Table I.



SCHEME 1.

† Contribution No. 219.

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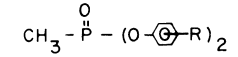
TABLE I. PHYSICAL ANALYTICAL DATA AND FUNGICIDAL ACTIVITY OF DIARYLMETHYLPHOSPHONATES



SCHEME 2.

Series No.	R	mp (°C) bp (°C)/ mm	Yield %	C%		H%		Cl%		ED_{50} (ppm)				
				Found	Calcd.	Found	Calcd.	Found	Calcd.	*P. oryzae*	*H. oryzae*	*A. alternata*	*R. bataticola*	*P. aphanidermatum*
1	H	170/0.4	68	62.1	62.6	5.2	5.2			148	195	94	113	128
2	2-Cl	Liquid*	54	49.6	49.2	3.9	3.5			74	170	84	123	146
3	4-Cl	185/0.4	68	49.7	49.2	3.8	3.5	22.7	22.3	64	123	73	83	25
4	2-Me	142/0.3	62	65.3	65.2	6.0	6.1	22.6	22.3	81	104	96	88	98
5	3-Me	Liquid*	69	64.7	65.2	6.4	6.1			65	114	89	90	93
6	4-Me	145/0.08	56	65.0	65.2	6.5	6.1			170	107	72	87	51
7	2-OMe	Liquid*	52	58.6	58.4	5.7	5.5			227	186	103	93	231
8	4-OMe	Liquid*	54	58.6	58.4	5.7	5.5			133	108	117	92	304
9	4-SMe	94	59	52.6	52.9	5.4	5.0			157	189	112	239	164
10	2,4-Cl_2	Liquid*	60	40.1	40.4	2.7	2.3	36.6	36.7	94	56	97	104	180
11	3-Me, 4-Cl	Liquid*	61	52.6	52.2	4.8	4.4	20.4	20.5	66	50	75	75	107
12	2,3-Me_2	Liquid*	57	67.2	67.1	6.5	6.9			65	46	68	36	90
13	2,4-Me_2	Liquid*	70	67.3	67.1	7.4	6.9			121	121	94	77	117
14	2,6-Me_2	Liquid*	71	67.5	67.1	7.0	6.9			87	126	107	80	375
15	3,4-Me_2	Liquid*	74	67.3	67.1	7.2	6.9			88	99	105	27	285
16	3,5-Me_2	Liquid*	76	67.4	67.1	7.0	6.9			87	118	99	22	55
17	2,4,5-Cl_3	86	74					46.9	46.8	6	14	12	6	9
18	Cl_5	136	58					58.5	58.8	21	24	14	27	23
O,O-Bis(2,4,5-trichlorophenyl)dichloromethylphosphonate (as reference)**										3	20	40	30	50

* Column purified.

** Unpublished data.

Table I shows that the activity does not depend on the electronic nature of the substituents on the phenyl ring. The simple phenyl derivative is only moderately effective against all the test fungi. If the phenyl ring is substituted by a Cl-atom at the *para* position an enhanced activity is observed, especially against *Pythium aphanidermatum*, but the activity falls when the Cl atom is at the *ortho* position. Replacement of the Cl atom by a CH_3 group at the *para* position reduces the degree of activity against *P. oryzae* greatly compared to the *ortho* and *meta* positions. Similarly with *P. aphanidermatum* activity is diminished at the *para* position followed by the *meta* and *ortho* positions as compared to chloro derivatives. No systematic order of activity is exhibited by the other three fungi. The degree of activity is further reduced if the CH_3 group is replaced by OCH_3 and SCH_3 groups.

There is a little enhancement of activity against *P. oryzae* if a second substituent like a Cl atom is introduced on the phenyl ring (**10** and **11**). A similar trend in activity is found with phosphonates having two methyl groups occupying different positions (**12**~**16**) except 2,3-dimethyl substituted phosphonate (**12**) which shows much better activity against all the fungi. The most active compound in this series against all the test fungi is *O,O*-bis-(2,4,5-trichlorophenyl)methylphosphonate (**17**) whose activity is found at par with *O,O*-bis(2,4,5-trichlorophenyl)dichloromethylphosphonate (taken as reference) with the only variation in activity towards *P. oryzae*. The fungicidal activity is not enhanced further even after addition of two more Cl atoms on the phenyl ring (**18**). It can be concluded that the presence of three Cl atoms at positions **2**, **4**, and **5** on the phenyl ring is found to be essential for activity.[3)]

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