

Synthesis of Some *O,O*-Dialkyl *N*-[4-(*N*-heteroarylsulfamoyl)-phenyl]phosphoramidothioates as Potential Fungicides

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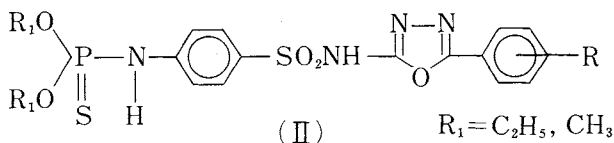
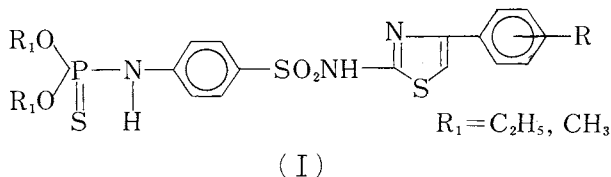
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Fourteen new *O,O*-dialkyl *N*-[4-(*N*-heteroarylsulfamoyl)phenyl]phosphoramidothioate having thiazoles and oxadiazoles as heteroaryl moieties have been synthesised. They have been tested against two species of fungi and their fungicidal activities have been compared with those of two commercial fungicides, viz., Dithane M-45 and Bavistin.

Attachment of a dialkoxyphosphinothioyl moiety at position para to arylsulfonamide structure has furnished a variety of biologically active compounds such as systemic, nematocidal and anthelmintic agents.^{1,2)} Some *N*⁴-phosphorylated sulfanilamides synthesised by us earlier,³⁾ were found to be moderately toxic to fungi. Encouraged by these observations we decided to explore the chemistry and biocidal properties of the sulfanilamide derivatives (I) and (II) having thionophosphoryl moiety at *N*⁴ and a heteroaryl substituent at sulfonamide nitrogen with the hope that incorporation of biologically versatile thiazole and oxadiazole structure would enhance the biocidal spectrum of the title compounds.

The *O,O*-dialkyl phosphorochloridothioates prepared according to method of Fletcher *et al.*,⁴⁾ were refluxed in pyridine with appropriate *N*¹-heteroarylsulfanilamide. The latter compounds were obtained by treating *p*-acetamidobenzenesulfonyl group with amino-heterocycles followed by removal of *N*⁴-acetyl group by mild hydrolysis. The aminothiazoles and oxadiazoles were prepared by known methods.^{5,6)}

Nine such compounds were tested against two species of fungi viz., *Helminthosporium oryzae* and *Aspergillus flavus*. To compare the results, the commercial fungicides, Dithane M-45 and Bavistin were also tested under similar conditions. It has been found that almost all sulfanilamides having thiazole moiety at sulfo-



namide nitrogen were far more active against *H. oryzae* than against *A. flavus*. The oxadiazole compounds in general were weaker fungicides.

EXPERIMENTAL

*N*¹-[4-Aryl-2-thiazolyl]-*N*⁴-acetylsulfanilamides. These compounds were prepared by refluxing an equimolar mixture of *p*-acetamidobenzenesulfonyl chloride with different 2-amino-4-arylthiazoles in pyridine for 1 hr. The reaction mixture was cooled and poured into water. The compound thus obtained was filtered and crystallised from acetone. The compounds are recorded in Table I.

*N*¹-[4-Aryl-2-thiazolyl]sulfanilamides. The *N*¹-[4-aryl-2-thiazolyl]-*N*⁴-acetylsulfanilamides were taken and hydrolysed by boiling with 10% NaOH for 1 hr and allowed to cool. The required compound was precipitated by adding 50% acetic acid solution until the mixture was just acid to litmus. The crude product was filtered and crystallised from acetone. The compounds thus prepared are recorded in Table II.

*N*¹-[5-Aryl-2-oxadiazolyl]-*N*⁴-acetylsulfanilamide. An equimolar mixture of 2-amino-5-aryl-1,3,4-oxadiazole and

p-acetamidobenzenesulfonyl chloride was refluxed in pyridine for 1~1.5 hr. It was cooled and poured into water. The solid compound was filtered washed with water and crystallized from ethanol. The compounds thus obtained are recorded in Table III.

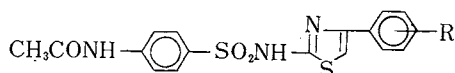
*N*¹-[5-Aryl-2-oxadiazolyl]sulfanilamides. The *N*¹-[5-aryl-2-oxadiazolyl]sulfanilamides were taken and hydrolysed by boiling with 10% sodium hydroxide solution. The reaction mixture was cooled and poured into cold water, boiled and filtered. The filtrate upon neutralisation with 50% acetic acid gave the desired product. The compounds were crystallised from ethanol. The compounds are recorded in Table IV.

O,O-Diethyl phosphorochloridothioate, bp 67~71°C/4~6 mm, was prepared according to method of Fletcher *et al.*⁴

O,O-Dimethyl phosphorochloridothioate, bp 70~72°C/20 mm, was prepared according to above method.

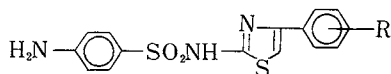
O,O-Dialkyl *N*-[*p*-(*N*-4-arylthiazol-2-yl sulfamoyl)-phenyl]phosphoramidothioates. A mixture of *N*¹-[4-aryl-2-thiazolyl]sulfanilamide (0.1 M) and *O,O*-dialkyl phosphorochloridothioate (0.1 M) was refluxed in pyridine for 3~4 hr. The reaction mixture was cooled and poured

TABLE I.



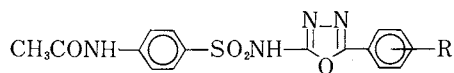
Sample No.	R	Molecular formula	mp (°C)	Yield (%)	%N		%S	
					Found	Calcd.	Found	Calcd.
1	H	C ₁₇ H ₁₅ N ₃ S ₂ O ₃	124	70	11.21	11.26	17.02	17.16
2	4-Cl	C ₁₇ H ₁₄ N ₃ S ₂ O ₃ Cl	154	75	10.34	10.31	15.70	15.71
3	4-Br	C ₁₇ H ₁₄ N ₃ S ₂ O ₃ Br	181	75	9.18	9.29	14.02	14.16
4	4-OCH ₃	C ₁₈ H ₁₇ N ₃ S ₂ O ₄	174-6(d)	70	10.23	10.42	15.72	15.88

TABLE II.



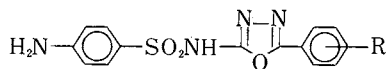
Sample No.	R	Molecular formula	mp (°C)	Yield (%)	%N		%S	
					Found	Calcd.	Found	Calcd.
1	H	C ₁₅ H ₁₃ N ₃ S ₂ O ₂	145(d)	56	12.63	12.69	19.33	19.34
2	4-Cl	C ₁₅ H ₁₂ N ₃ S ₂ O ₂ Cl	144	50	11.28	11.49	17.46	17.51
3	4-Br	C ₁₅ H ₁₂ N ₃ S ₂ O ₂ Br	167	52	10.01	10.24	15.50	15.61
4	4-OCH ₃	C ₁₆ H ₁₅ N ₃ S ₂ O ₃ Cl	190	53	11.65	11.63	17.62	17.73

TABLE III.



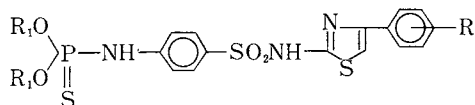
Sample No.	R	Molecular formula	mp (°C)	Yield (%)	%N		%S	
					Found	Calcd.	Found	Calcd.
1	H	C ₁₆ H ₁₄ N ₄ SO ₄	237	55	15.58	15.64	8.46	8.94
2	4-OCH ₃	C ₁₇ H ₁₆ N ₄ SO ₅	243-4	77	14.28	14.43	8.37	8.25
3	4-Cl	C ₁₆ H ₁₃ N ₄ SO ₄ Cl	249	73	14.03	14.27	8.00	8.15

TABLE IV.



Sample No.	R	Molecular formula	mp (°C)	Yield (%)	%N		%S	
					Found	Calcd.	Found	Calcd.
1	H	C ₁₄ H ₁₂ N ₄ SO ₃	206	48	17.61	17.72	9.98	10.13
2	4-OCH ₃	C ₁₅ H ₁₄ N ₄ SO ₄	209	58	16.22	16.18	9.26	9.25
3	4-Cl	C ₁₄ H ₁₁ N ₄ SO ₃ Cl	207-9	57	15.73	15.98	9.02	9.13

TABLE V.

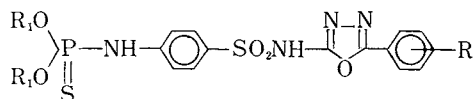


Sample No.	R	R ₁	Molecular formula	mp (°C)	Yield (%)	%N		%P		%S	
						Found	Calcd.	Found	Calcd.	Found	Calcd.
1	H	C ₂ H ₅	C ₁₉ H ₂₂ N ₃ PO ₄ S ₃	140	58	8.58	8.70	6.38	6.42	19.72	19.88
2	4-Cl	C ₂ H ₅	C ₁₉ H ₂₁ N ₃ PO ₄ S ₃ Cl	170	74	8.03	8.12	5.88	5.99	18.43	18.55
3	4-Br	C ₂ H ₅	C ₁₉ H ₂₁ N ₃ PO ₄ S ₃ Br	148	76	7.52	7.47	5.46	5.52	17.00	17.08
4	4-OCH ₃	C ₂ H ₅	C ₂₀ H ₂₃ N ₃ PO ₅ S ₃	174	73	8.27	8.19	5.92	6.05	18.82	18.71
5	H	CH ₃	C ₁₇ H ₁₈ N ₃ PO ₄ S ₃	139	57	9.12	9.23	6.73	6.81	21.25	21.01
6	4-Cl	CH ₃	C ₁₇ H ₁₇ N ₃ PO ₄ S ₃ Cl	172	74	8.70	8.58	6.32	6.33	19.39	19.61
7	4-Br	CH ₃	C ₁₇ H ₁₇ N ₃ PO ₄ S ₃ Br	157	77	7.82	7.87	5.80	5.81	18.02	17.98
8	4-OCH ₃	CH ₃	C ₁₈ H ₁₉ N ₃ PO ₅ S ₃	169	70	8.49	8.66	6.28	6.39	19.67	17.79

Significant bands in IR absorption spectra KBr (disc) cm⁻¹

Compound No.	-SO ₂ -NH-	C=N	P-O-C (alkyl)	P=S
2	1340 1180	1635	1020	720
4	1320 1170	1610	1025	735
6	1325 1180	1625	1030	725
8	1320 1178	1610	1035	740

TABLE VI.



Sample No.	R	R ₁	Molecular formula	mp (°C)	Yield (%)	%N		%P		%S	
						Found	Calcd.	Found	Calcd.	Found	Calcd.
9	H	C ₂ H ₅	C ₁₈ H ₂₁ N ₄ PO ₅ S ₂	262 (d)	46	11.72	11.97	6.45	6.62	13.54	13.68
10	4-OCH ₃	C ₂ H ₅	C ₁₉ H ₂₃ N ₄ PO ₅ S ₂	175	52	11.43	11.25	6.24	6.22	12.73	12.85
11	4-Cl	C ₂ H ₅	C ₁₈ H ₂₀ N ₄ PO ₅ S ₂ Cl	above 265	54	11.02	11.14	6.04	6.17	12.64	12.74
12	H	CH ₃	C ₁₆ H ₁₇ N ₄ PO ₅ S ₂	175 (d)	45	12.51	12.73	7.12	7.05	14.53	14.55
13	4-OCH ₃	CH ₃	C ₁₇ H ₁₉ N ₄ PO ₅ S ₂	165	51	11.69	11.91	6.48	6.60	13.67	13.62
14	4-Cl	CH ₃	C ₁₆ H ₁₆ N ₄ PO ₅ S ₂ Cl	above 270	54	11.81	11.82	6.46	6.53	13.38	13.41

Significant bands in IR absorption spectra KBr (discs) cm⁻¹

Compound No.	-SO ₂ -NH-	C=N	P-O-C (alkyl)	P=S
9	1300 1160	1720	1040	730
10	1310 1180	1720	1020	740
14	1300 1160	1675	1025	740

TABLE VII.

Compound No.	R	R ₁	Average % inhibition after 86 hr					
			Organism <i>A. flavus</i>			Organism <i>H. oryzae</i>		
			1:100	1:1000	1:10,000	1:100	1:1000	1:10,000
1	C ₂ H ₅	H	100	57.1	15.0	100	100	65.7
2	C ₂ H ₅	4-Cl	85.7	71.4	11.4	100	100	100
4	C ₂ H ₅	4-OCH ₃	42.9	31.4	28.6	100	100	57.1
6	CH ₃	4-Cl	71.4	65.7	26.0	100	100	77.1
8	CH ₃	4-OCH ₃	57.1	42.9	31.4	85.7	77.1	51.4
10	C ₂ H ₅	4-Cl	60.0	28.6	15.0	80.0	54.3	40.0
11	C ₂ H ₅	4-OCH ₃	100	69.0	51.4	100	40.0	28.6
13	CH ₃	4-Cl	65.7	38.6	28.6	48.6	42.9	20.0
14	CH ₃	4-OCH ₃	100	71.4	40.0	80.0	68.6	25.7
Dithane M-45			100	63.0	54.3	100	100	100
Bavistin			100	100	100	100	65.7	57.1

into cold water and the product separating was isolated as usual. The compounds were crystallised from acetone. The compounds thus synthesized are recorded in Table V.

O,O-Dialkyl *N*-[*p*-(*N*-5-aryl-1,3,4-oxadiazol-2-ylsulfamoyl)phenyl]-phosphoramidithioates. These compounds were prepared by refluxing *N*¹-[5-aryl-2-oxadiazolyl]-sulfanilamide (0.1M) in pyridine for 5~6 hr. The reaction mixture was cooled and poured into cold water. It was filtered and crystallised from ethanol. The compounds are recorded in Table VI.

Fungicidal test The antifungal activity of nine compounds was evaluated by agar growth technique⁷⁾ on two different organisms viz. *Aspergillus flavus* and *Helminthosporium oryzae* at three different concentrations and number of replication in each case was three. Dithane M-45 and Bavistin, the two commercial fungicides were also tested under similar conditions with a view to compare the results. These results are recorded in the Table VII. The numbering is taken from the Table V and VI. Dithane M-45 is a mixture containing 70% Zineb and 10% Maneb. The chemical name of Zineb is zinc ethylene bisdithiocarbamate and of Maneb is man-

ganese ethylene bisdithiocarbamate and also Bavistin is 2-(methoxycarbamoyl)benzimidazole.

RESULTS AND DISCUSSION

As is evident from toxicity data, almost all compounds are fairly toxic to both the organisms. Compound No. 1 and 11 completely inhibited the growth of *A. flavus* at 1:100. The commercial fungicide Bavistin has shown 100% inhibitions at all the three concentrations. At lower concentration % inhibitions by Dithane M-45 was higher in comparison to the other compounds.

Compound No. 1, 2, 4, 6 have shown 100% inhibition against *H. oryzae* at 1:100 and 1:1000. These compounds have shown even more fungitoxicity at 1:1000, than commercial fungicide Bavistin. Compound No. 2 showing 100% inhibition at the lowest concentration was found to be the best antifungal agent among all compounds against *H. oryzae*. It can be concluded that the compounds having thiazole nucleus at N^1 , are more toxic to *H. oryzae* in comparison to the compounds having oxadiazole nucleus at N^1 and also except compound No. 13, most of these

compounds have shown better fungitoxicity at 1:1000 against *H. oryzae* in comparison to *A. flavus*.

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