NOTES

Synthesis of New Fungicides. 2-(4'-Arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones

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Sulfur compounds have been used as insecticides, fungicides,[1-5] and acaricides[6]. The most important organic sulfur fungicides used have been derivatives of dithiocarbamic acid and its related compounds.[7-13] Horsfall and Rich[14] studied numerous heterocyclic compounds and concluded that a carbonyl group in the ring often confers fungitoxicity on a molecule. A series of benzothiazoles has been extensively studied, resulting in the introduction of 6-(β-diethylaminoethoxy)-2-dimethylamino-benzothiazole in the therapy of superficial fungus infections.[15-20] Some 1, 2, 4-dithiazoles have been also described as fungicides.[21] Rhodamine and a variety of related compounds, including tetraethylthiuram disulfide(disulfiram), have proved to be most active *in vitro*.[22]

Because of the fungitoxic nature of thiazolidones and thiazole derivatives,[23,24] it might be worthwhile to study the evolution of the fungicidal activity of various 2-(4'-arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones and the relationship between their chemical constitution and their fungitoxicity. 2-(4'-Arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones have been prepared by the method of Bhargava,[25] starting from *N*-aryl-*N'*-2-(4-arylthiazolyl)-thioureas,[26] by condensation with monochloroacetic acid in the presence of anhydrous sodium acetate. The compounds have then been tested for fungicidal activity against Aspergillus niger on a Czapeak (dox) agar medium. A number of compounds have been found to be sufficiently active as fungicides. Two compounds, 2-(4'-phenylthiazolyl-2'-imino)-3-*o*-methoxyphenyl-, and -3-*p*-methoxyphenyl-4-thiazolidones, have shown an inhibiting effect on Aspergillus niger and Altenaria tenuis in a dilution ratio of 1 : 10000.

Experimental

***N*-Aryl-*N'*-(4-arylthiazolyl)-thioureas.** Different *N*-aryl-*N'*-2-(4-arylthiazolyl)-thioureas were prepared by condensing 2-amino-4-phenyl-, -4-*p*-bromophenyl-, -4-*p*-methylphenyl-, and -4-*p*-methoxy-phenyl-thiazoles with phenyl-, *m*-, and *p*-chlorophenyl-, *p*-bromophenyl-, *o*-, *m*-, and *p*-methylphenyl-, *o*-, *m*-, and *p*-methoxyphenyl-, and *p*-ethoxyphenyl-isothiocyanates.[26]

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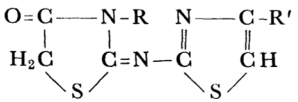
TABLE 1. 2-(4′-ARYLTHIAZOLYL-2′-IMINO)-3-ARYL-4-THIAZOLIDONES AND THEIR FUNGICIDAL ACTIVITY



Diameter of the fungus colony in control plates after 96 hr = 75 mm
Room temperature = 37°C

No.	R	R′	Yield %	Mp °C	Molecular formula	N, % Found	N, % Calcd	S, % Found	S, % Calcd	Percentage inhibition* Concentrations 1:250	1:500	1:1000	1:10000
1	Phenyl-	Phenyl-	67	299	$C_{18}H_{13}N_3OS_2$	11.92	11.97	18.25	18.23	64.00	60.00	50.67	45.33
2	*m*-Chlorophenyl-	Phenyl-	58	180	$C_{18}H_{12}N_3OS_2Cl$	10.85	10.89	16.57	16.60	72.00	60.00	58.67	57.33
3	*p*-Chlorophenyl-	Phenyl-	69	208	$C_{18}H_{12}N_3OS_2Cl$	10.81	10.89	16.68	16.60	58.67	58.67	53.33	41.33
4	*p*-Bromophenyl-	Phenyl-	68	212	$C_{18}H_{12}N_3OS_2Br$	9.72	9.77	14.96	14.88	55.33	45.33	38.67	33.33
5	*o*-Methylphenyl-	Phenyl-	51	256	$C_{19}H_{15}N_3OS_2$	11.46	11.51	17.49	17.53	42.67	40.00	40.00	38.67
6	*m*-Methylphenyl-	Phenyl-	46	206	$C_{19}H_{15}N_3OS_2$	11.40	11.51	17.56	17.53	42.67	38.67	36.00	32.00
7	*p*-Methylphenyl-	Phenyl-	58	242	$C_{19}H_{15}N_3OS_2$	11.48	11.51	17.51	17.53	96.00	86.67	42.67	38.67
8	*o*-Methoxyphenyl-	Phenyl-	50	140	$C_{19}H_{15}N_3O_2S_2$	11.10	11.02	16.83	16.80	100.00	100.00	100.00	100.00**
9	*m*-Methoxyphenyl-	Phenyl-	54	257	$C_{19}H_{15}N_3O_2S_2$	10.95	11.02	16.74	16.80	66.67	64.00	60.00	58.67
10	*p*-Methoxyphenyl	Phenyl-	61	136	$C_{19}H_{15}N_3O_2S_2$	10.98	11.02	16.85	16.80	100.00	100.00	100.00	100.00**
11	*p*-Ethoxyphenyl-	Phenyl-	64	270	$C_{20}H_{17}N_3O_2S_2$	10.64	10.63	16.32	16.20	48.00	41.33	38.67	33.33
12	Phenyl-	*p*-Bromophenyl-	65	250	$C_{18}H_{12}N_3OS_2Br$	9.71	9.77	14.87	14.88	50.00	49.87	48.67	46.67
13	*m*-Chlorophenyl-	*p*-Bromophenyl-	54	229	$C_{18}H_{11}N_3OS_2BrCl$	9.02	9.04	13.78	13.74	66.67	61.00	58.00	55.20
14	*p*-Chlorophenyl-	*p*-Bromophenyl-	63	234	$C_{18}H_{11}N_3OS_2BrCl$	9.00	9.04	13.75	13.74	59.07	58.67	56.94	55.10
15	*p*-Bromophenyl-	*p*-Bromophenyl-	69	232	$C_{18}H_{11}N_3OS_2Br_2$	8.17	8.25	12.56	12.57	62.67	61.33	60.00	58.27
16	*o*-Methylphenyl-	*p*-Bromophenyl-	48	277	$C_{19}H_{14}N_3OS_2Br$	9.36	9.46	14.38	14.41	59.60	54.27	52.00	51.20
17	*m*-Methylphenyl-	*p*-Bromophenyl-	52	242	$C_{19}H_{14}N_3OS_2Br$	9.41	9.46	14.36	14.41	63.33	62.00	55.20	43.20
18	*p*-Methylphenyl-	*p*-Bromophenyl-	58	260	$C_{19}H_{14}N_3OS_2Br$	9.39	9.46	14.40	14.41	67.33	66.67	61.33	50.67
19	Phenyl-	*p*-Methylphenyl-	61	228	$C_{19}H_{15}N_3OS_2$	11.47	11.51	17.59	17.53	50.67	42.67	40.00	40.00
20	*m*-Chlorophenyl-	*p*-Methylphenyl-	48	210	$C_{19}H_{14}N_3OS_2Cl$	10.46	10.51	16.10	16.02	56.00	44.00	40.00	40.00
21	*p*-Chlorophenyl-	*p*-Methylphenyl-	55	216	$C_{19}H_{14}N_3OS_2Cl$	10.49	10.51	15.95	16.02	36.00	32.00	29.33	21.33
22	*p*-Bromophenyl-	*p*-Methylphenyl-	63	211	$C_{19}H_{14}N_3OS_2Br$	9.43	9.46	14.43	14.41	57.33	53.33	44.00	29.33
23	*o*-Methylphenyl-	*p*-Methylphenyl-	52	241	$C_{20}H_{17}N_3OS_2$	11.01	11.08	16.83	16.89	52.00	46.67	40.00	37.50
24	*m*-Methylphenyl-	*p*-Methylphenyl-	46	219	$C_{20}H_{17}N_3OS_2$	11.07	11.08	16.85	16.89	38.67	38.67	32.00	30.67
25	*p*-Methylphenyl-	*p*-Methylphenyl-	57	234	$C_{20}H_{17}N_3OS_2$	11.05	11.08	16.92	16.89	53.33	52.00	46.00	40.00
26	*o*-Methoxyphenyl-	*p*-Methylphenyl-	42	271	$C_{20}H_{17}N_3O_2S_2$	10.58	10.63	16.13	16.20	53.33	48.00	45.33	38.67
27	*p*-Methoxyphenyl-	*p*-Methylphenyl-	51	232	$C_{20}H_{17}N_3O_2S_2$	10.62	10.63	16.17	16.20	38.67	32.00	30.67	18.67
28	*p*-Ethoxyphenyl-	*p*-Methylphenyl-	59	253	$C_{21}H_{19}N_3O_2S_2$	10.20	10.27	15.59	15.65	57.33	53.33	32.00	28.00
29	Phenyl-	*p*-Methoxyphenyl-	57	225	$C_{19}H_{15}N_3O_2S_2$	10.97	11.02	16.74	16.80	57.87	56.00	49.33	46.67
30	*m*-Chlorophenyl-	*p*-Methoxyphenyl-	49	d.117	$C_{19}H_{14}N_3O_2S_2Cl$	10.03	10.11	15.40	15.40	74.27	71.33	67.20	64.54
31	*p*-Chlorophenyl-	*p*-Methoxyphenyl-	54	223	$C_{19}H_{14}N_3O_2S_2Cl$	10.07	10.11	15.35	15.40	60.54	59.74	59.33	51.07

* Percentage of inhibition $= d_c/(d_c - d_t) \times 100$ where d_c is the diameter of the fungus colony in mm in the control plates after 96 hr; d_t is the diameter of the fungus colony in mm in the treated plates after 96 hr.

** These two compounds, when further tested for fungicidal activity against the organism, Alternaria tenuis, have shown also 100% inhibition at all four concentrations.

2-(4'-Phenylthiazolyl-2'-imino) -3- phenyl -4- thiazolidone. A mixture of *N*-phenyl-*N'*-2-(4-phenylthiazolyl)-thiourea (3.1 g), monochloroacetic acid (1 g), and fused sodium acetate (2.5 g) in absolute ethanol (30 m*l*) was refluxed on a water bath for 6 hr. The ethanol was then removed, and the product was washed with water to remove sodium chloride and any unchanged sodium acetate. Finally the product was crystallised from ethanol, mp 299°C. Yield, 67%.

Found: C, 61.50; H, 3.67; N, 11.92; S, 18.25%. Calcd for $C_{18}H_{13}N_3OS_2$: C, 61.34; H, 3.70; N, 11.97; S, 18.23%.

Similarly, other 2-(4'-arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones were prepared from different thioureas. The properties and analytical data of these compounds are listed in Table 1.

The conversion of *N*-*o*-, -*p*-methoxyphenyl-, and -*p*-ethoxy-phenyl-*N'*-2-(4-*p*-bromophenylthiazolyl)-thioureas and *N*-*p*-methyl-phenyl-, -*p*-bromophenyl-*N'*-2-(4-*p*-methoxyphenylthiazolyl)-thioureas into the corresponding 2-(4'-arylthiazolyl-2'-imino)-3-aryl-4-tihazolidones could not be achieved. The failure of this type of reaction in these compounds may be attributed to an ortho effect and a steric hindrance due to the presence of heavier groups attached as substituents in either of the benzene rings, at the C-4 position in the thiazole nucleus or at the N-3 position in the thiazolidone nucleus.

Fungicidal Activity Screening. The present study was carried out by an agar-growth method.[27,28]

Organism. Aspergillus niger.

Medium. Czapeak (Dox) agar: sodium nitrate (2 g), potassium phosphate (1 g), magnesium sulfate (0.5 g), ferrous sulfate (0.01 g), sucrose (30 g), agar (15 g), and water (1 *l*). Autoclaved for half an hour at 20 psi.

The results of the fungicidal activity are also given in Table 1. The relationships between the observed fungicidal activity and the chemical constitutions of the compounds are as follows:

1) The compounds synthesized from 2-amino-4-*p*-bromophenylthiazoles are found to possess more fungicidal activity than the compounds synthesized from 2-amino -4- phenyl-, - 4 - *p* - methyl-phenyl-, and - 4-*p*-methoxyphenyl-thiazoles.

2) The presence of halogen in either of the benzene rings is found to enhance the fungitoxic nature of the compounds. It may also be concluded that the compounds having chlorine at the meta position in the 3-aryl group in the thiazolidone nucleus possess a much higher activity than the compounds having a para-substituted chlorine atom. The presence of bromine in a compound resulted in a considerable increase in the fungicidal activity.

3) Compounds with a para-substituted methylphenyl group at the C-4 position in the thiazole nucleus have been found to show more inhibitions than the compounds with an ortho or meta methylphenyl group at the same position in the thiazole nucleus.

4) The presence of *o*- and *p*-methoxyphenyl groups at the C-4 position in the thiazole nucleus resulted in exceptionally highest fungitoxicity in all the compounds which have been studied in the present investigation, as is evident from the observed percentage of inhibition in the case of 2-(4'-phenylthiazolyl-2'-imino)-3-*o*-methoxyphenyl- and -3-*p*-methoxyphenyl-4-thiazolidones.

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