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Synthesis of Some New Fungicides

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A number of 2-arylimino-3-aryl-4-thiazolidones and their 1,1-dioxides and 5-phenylazo derivatives have been prepared. The structure of these thiazolidones was confirmed by studying their hydrolysis products. Some of these thiazolidones were screened for their fungicidal activity against *Aspergillus niger* by agar-growth method and found to be more appropriately fungistatic and not fungicidal.

Several 4-thiazolidones and their derivatives, especially 1,1-dioxides, have been found therapeutically active as local anaesthetics,¹⁻³ amoebacides⁴) and anticonvulsants.⁵) Rout *et al.*⁶⁻⁸) synthesized 2-arylimino-4-thiazolidones and their 5-substituted

derivatives, and reported them to be active fungicides. Bhargava and coworkers⁹⁻¹¹) have demonstrated that 2-arylimino-3-aryl-4-thiazolidones with the same or different aryl groups, and 3-aryl-2,4-thiazolidones possess considerable fungicidal activity. The acetoxymercuri derivatives of the latter were found to be the most active. Recently it has been reported that the hydrochlorides of 2-arylimino-5-methyl-4-thiazolidones¹²) step the germination of spores of the fungus, *Culvularia lunata* at the concentration of 1 : 500.

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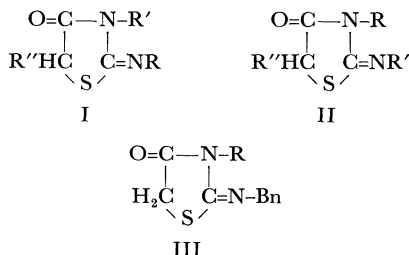
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In view of the significant biological applicability of the 4-thiazolidones and their 1,1-dioxides, it was thought worthwhile to synthesize 2-arylimino-3-aryl-5-substituted-4-thiazolidones (I) and 3-aryl-2-(substituted 2'-benzothiazolyl)imino-4-thiazolidones (III) as fungicides by the methods described earlier.¹³⁻¹⁶



where R=aryl; R'=aryl; R''=H or CH₃
Bn=substituted 2-benzothiazolyl

In this communication asymmetrical *N*-aryl-*N'*-aryl thiocarbamides, needed as starting material,

were prepared by interaction of aromatic primary amines and various aryl isothiocyanates in dry benzene. These thiocarbamides on condensation with monochloroacetic (α -chloropropionic) acid in absolute ethanol in the presence of sufficient anhydrous sodium acetate (which removes HCl *in situ*) yielded the corresponding 2-arylimino-3-aryl-5-substituted-4-thiazolidones. In this case formation of two possible isomeric 4-thiazolidones (I and/or II) may be assumed from the two possible tautomeric forms of thiocarbamides undergoing reaction with monochloroacetic (or α -chloropropionic) acid. The structure of the 2-arylimino-3-aryl-5-substituted-4-thiazolidones, the position of aryl groups, has been confirmed by studying their degradation products^{10,13,17} and characteristic derivatives. Likewise, synthesis of 3-aryl-2-(substituted 2'-benzothiazolyl)imino-4-thiazolidones and their structures have been confirmed. The corresponding 1,1-dioxides of some of these thiazolidones were prepared by oxidizing them with KMnO₄ in glacial acetic acid, and 5-phenylazo derivatives

TABLE 1. 2-ARYLIMINO-3-ARYL-5-SUBSTITUTED-4-THIAZOLIDONES AND THEIR FUNGICIDAL ACTIVITY

S. No.	Aryl group R	Aryl group R'	Substituent R''	Mp °C	Molecular formula	Nitrogen, %		Percentage-inhibition* at concentrations	
						Found	Calcd	1: 1000	1: 5000
1	<i>o</i> -OCH ₃ ·C ₆ H ₄	<i>o</i> -Cl·C ₆ H ₄	H	149	C ₁₆ H ₁₃ ClN ₂ O ₂ S	8.19	8.42	60	19.25
2	<i>o</i> -OCH ₃ ·C ₆ H ₄	<i>m</i> -Cl·C ₆ H ₄	H	143	C ₁₆ H ₁₃ ClN ₂ O ₂ S	8.50	8.42	68	34.65
3	<i>p</i> -Cl·C ₆ H ₄	<i>o</i> -OCH ₃ ·C ₆ H ₄	H	135	C ₁₆ H ₁₃ ClN ₂ O ₂ S	8.30	8.42	80	53.90
4	<i>o</i> -OCH ₃ ·C ₆ H ₄	<i>p</i> -Br·C ₆ H ₄	H	123	C ₁₆ H ₁₃ BrN ₂ O ₂ S	7.31	7.43	72	50.05
5	<i>o</i> -OCH ₃ ·C ₆ H ₄	<i>p</i> -I·C ₆ H ₄	H	190	C ₁₆ H ₁₃ IN ₂ O ₂ S	6.45	6.60	—	—
6	<i>m</i> -OCH ₃ ·C ₆ H ₄	<i>o</i> -OCH ₃ ·C ₆ H ₄	H	171	C ₁₇ H ₁₆ N ₂ O ₃ S	8.63	8.54	72	46.20
7	<i>o</i> -OC ₂ H ₅ ·C ₆ H ₄	<i>o</i> -OCH ₃ ·C ₆ H ₄	H	131	C ₁₈ H ₁₈ N ₂ O ₃ S	8.27	8.19	60	30.80
8	<i>p</i> -OC ₂ H ₅ ·C ₆ H ₄	<i>o</i> -OCH ₃ ·C ₆ H ₄	H	122	C ₁₈ H ₁₈ N ₂ O ₃ S	8.35	8.19	—	—
9	<i>o</i> -OCH ₃ ·C ₆ H ₄	β -Nathphyl	H	125	C ₂₀ H ₁₆ N ₂ O ₂ S	8.14	8.05	68	46.20
10	<i>o</i> -CH ₃ ·C ₆ H ₄	Ph	CH ₃	146	C ₁₇ H ₁₆ N ₂ OS	9.13	9.46	—	—
11	<i>p</i> -CH ₃ ·C ₆ H ₄	Ph	CH ₃	165	C ₁₇ H ₁₆ N ₂ OS	9.27	9.46	80	57.75
12	<i>o</i> -Cl·C ₆ H ₄	Ph	CH ₃	161	C ₁₆ H ₁₃ ClN ₂ OS	8.47	8.84	—	—
13	<i>p</i> -Cl·C ₆ H ₄	Ph	CH ₃	283	C ₁₆ H ₁₃ ClN ₂ OS	8.66	8.84	76	42.35
14	<i>p</i> -OCH ₃ ·C ₆ H ₄	Ph	CH ₃	183	C ₁₇ H ₁₆ N ₂ O ₂ S	8.72	8.97	64	34.65
15	<i>p</i> -OC ₂ H ₅ ·C ₆ H ₄	Ph	CH ₃	131	C ₁₈ H ₁₈ N ₂ O ₂ S	8.38	8.59	68	30.80
16	<i>p</i> -Cl·C ₆ H ₄	<i>p</i> -CH ₃ ·C ₆ H ₄	CH ₃	130	C ₁₇ H ₁₅ ClN ₂ OS	8.27	8.49	—	—
17	<i>p</i> -Br·C ₆ H ₄	<i>p</i> -CH ₃ ·C ₆ H ₄	CH ₃	159	C ₁₇ H ₁₅ BrN ₂ OS	7.31	7.46	80	57.75
18	<i>p</i> -OCH ₃ ·C ₆ H ₄	<i>p</i> -CH ₃ ·C ₆ H ₄	CH ₃	184	C ₁₈ H ₁₈ N ₂ O ₂ S	8.32	8.59	68	46.20
19	<i>p</i> -OC ₂ H ₅ ·C ₆ H ₄	<i>p</i> -CH ₃ ·C ₆ H ₄	CH ₃	161	C ₁₉ H ₂₀ N ₂ O ₂ S	8.07	8.23	76	50.05

Diameters of the fungus colonies of control plates in mm., at concentrations 1 : 1000 and 1 : 5000, are 25 and 26 respectively.

* Percentage inhibition = $(d_c - d_t)/d_c \times 100$ where d_c , the diameter of the fungus colony in mm in the control plates after 90 hr; d_t the diameter of the fungus colony in mm in the treated plates after 90 hr.

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TABLE 2. 3-ARYL-2-(SUBSTITUTED 2'-BENZOTHAZOLYL) IMINO-4-THIAZOLIDONES

S. No.	Substituent	Yield %	Mp °C	Molecular formula	Nitrogen, %		Sulphur, %	
					Found	Calcd	Found	Calcd
Aryl= <i>p</i> -Cl·C ₆ H ₄								
1	4'-Methyl	84	246	C ₁₇ H ₁₂ ClN ₃ OS ₂	11.10	11.24	17.28	17.14
2	5'-Methyl	90	249	C ₁₇ H ₁₂ ClN ₃ OS ₂	11.39	11.24	17.33	17.14
3	6'-Methyl	95	286	C ₁₇ H ₁₂ ClN ₃ OS ₂	11.06	11.24	17.29	17.14
4	4'-Chloro	75	218	C ₁₆ H ₉ Cl ₂ N ₃ OS ₂	10.54	10.66	16.20	16.25
5	5'-Chloro	78	245	C ₁₆ H ₉ Cl ₂ N ₃ OS ₂	10.83	10.66	16.03	16.25
6	6'-Chloro	86	255	C ₁₆ H ₉ Cl ₂ N ₃ OS ₂	10.75	10.66	16.38	16.25
7	4'-Methoxy	70	234	C ₁₇ H ₁₂ ClN ₃ O ₂ S ₂	10.63	10.78	16.38	16.44
8	6'-Methoxy	82	252	C ₁₇ H ₁₂ ClN ₃ O ₂ S ₂	10.58	10.78	16.50	16.44
9	6'-Ethoxy	89	244	C ₁₈ H ₁₄ ClN ₃ O ₂ S ₂	10.27	10.41	16.01	15.86
Aryl= <i>o</i> -CH ₃ ·C ₆ H ₄								
10	4'-Methyl	44	157	C ₁₈ H ₁₅ N ₃ OS ₂	11.72	11.90	17.92	18.13
11	5'-Methyl	41	137	C ₁₈ H ₁₅ N ₃ OS ₂	11.68	11.90	18.04	18.13
12	6'-Methyl	56	171	C ₁₈ H ₁₅ N ₃ OS ₂	11.78	11.90	17.83	18.13
13	4'-Chloro	35	143	C ₁₇ H ₁₂ ClN ₃ OS ₂	11.15	11.24	16.73	17.14
14	5'-Chloro	37	135	C ₁₇ H ₁₂ ClN ₃ OS ₂	11.07	11.24	16.97	17.14
15	4'-Methoxy	48	165	C ₁₈ H ₁₅ N ₃ O ₂ S ₂	10.84	11.39	17.15	17.35
16	6'-Methoxy	57	138	C ₁₈ H ₁₅ N ₃ O ₂ S ₂	10.91	11.39	17.21	17.35
17	6'-Ethoxy	53	109	C ₁₉ H ₁₇ N ₃ O ₂ S ₂	10.71	10.96	16.47	16.71

by coupling with benzenediazonium chloride in which coupling occurs at the active methylene group.

Experimental

Asymmetrical *N*-Aryl-*N'*-aryl Thiocarbamides.

A mixture of arylamine (0.1 mol) and aryl isothiocyanate (0.1 mol) in dry benzene (25 ml) was refluxed on a water-bath for 1–2 hr during which a solid mass was obtained. Unreacted amine and isothiocyanate were removed by washing the crude product with dil. HCl and ether respectively. It was crystallized from 95% ethanol.

2-*o*-Methoxyphenylimino-3- α -naphthyl-4-thiazolidone. *N*-*o*-Methoxyphenyl-*N'*- α -naphthylthiocarbamide (15.4 g), monochloroacetic acid (5 g) and anhydrous sodium acetate (8 g) in absolute ethanol (60 ml) were refluxed on a water-bath for 7–10 hr with occasional shaking. After distilling ethanol, the gummy product was washed with hot water which solidified on being kept overnight in contact with ice-cold water. It was crystallized from ethanol, yield 72%, mp 172°C.

Found: N, 7.92; S, 9.23%. Calcd for C₂₀H₁₆N₂O₂S: N, 8.05; S, 9.19%.

Similarly, other 2-arylimino-3-aryl-4-thiazolidones were synthesized. Their yields, melting points and analytical data are recorded in Table 1.

2-Arylimino-3-aryl-5-methyl-4-thiazolidones.

These were prepared in a similar manner as described above, using requisite amount of α -chloropropionic acid instead of monochloroacetic acid. These were crystallized from ethanol and are reported in Table 1.

***N*-Aryl-*N'*-substituted 2-Benzothiazolylthiocarbamides.** 2-Amino-(substituted)benzothiazole (0.1 mol) and arylisothiocyanate (0.1 mol) in dry benzene (110 ml)

were heated under reflux condenser on a water-bath for 4–20 hr. The rest of the procedure for its isolation and purification was the same as above. These thiocarbamides were crystallized from glacial acetic acid.

3-*p*-Chlorophenyl-2-(2'-benzothiazolyl)imino-4-thiazolidone. A mixture of *N*-*p*-chlorophenyl-*N'*-2-benzothiazolylthiocarbamide (3 g), monochloroacetic acid (1 g) and anhydrous sodium acetate (2 g) in absolute ethanol (60 ml) was refluxed on a water-bath for 8–10 hr. Excess ethanol was removed by distillation and the crude product was washed with hot water to remove unchanged reactants. It was crystallized from ethanol-acetone mixture (1 : 1), yield 80%, mp 254°C. Found: N, 11.93; S, 17.89%. Calcd for C₁₆H₁₀ClN₃O₂S₂: N, 11.68; S, 17.80%.

Following the same procedure, various 3-*p*-chlorophenyl (or *o*-tolyl)-2-(substituted 2'-benzothiazolyl)imino-4-thiazolidones were synthesized (Table 2).

2-(*o*-Methoxyphenyl)imino-3-*m*-chlorophenyl-4-thiazolidone-1,1-dioxide. 2-*o*-Methoxyphenylimino-3-*m*-chlorophenyl-4-thiazolidone (1 g) dissolved in glacial acetic acid (20 ml) was treated slowly with KMnO₄ (1 g) solution prepared in water (45 ml) at 0°C. The resulting mixture was allowed to stand for some time and then sodium bisulphite solution was added to discharge the colour of potassium permanganate. The residue was washed with ice-cold water, dried and crystallized from ethanol, yield 69%, mp 148°C.

Found: N, 7.53; S, 8.94%. Calcd for C₁₆H₁₃ClN₂O₅S: N, 7.68; S, 8.78%.

5-Phenylazo-2-*o*-ethoxyphenylimino-3-*o*-methoxyphenyl-4-thiazolidone. To a solution of benzenediazonium chloride (prepared from 2 ml of aniline), cooled in a freezing mixture at 0°C, a solution of the thiazolidone (2 g) in glacial acetic acid (40 ml) was added in small portions with continuous stirring. The resulting reaction mixture was kept for about an hour

at 0—3°C. The precipitate formed was filtered, washed with ice-cold water and, crystallized, yield 73%, mp 77°C. Found: N, 12.44; S, 7.01%. Calcd for $C_{24}H_{22}N_4O_3S$: N, 12.56; S, 7.17%.

Fungicidal Screening. Compounds 1, 2, 3, 4, 6, 7, 9, 11, 13, 14, 15, 17, 18 and 19 (Table I) were screened for fungicidal activity against *Aspergillus niger* by agar-growth method, incubated for 90 hr at 25°C, at concn. 1 : 1000 and 1 : 5000. It is evident from the fungicidal screening results of tested compounds that these are

more appropriately fungistatic and not fungicidal.

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