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Synthesis of Some New Fungicides

V. N. CHOUBEY and H. SINGH

Department of Chemistry, Banaras Hindu University, Varanasi-5, India

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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] amoebacides[4] 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 coworkers[9-11] have demonstrated that 2-arylimino-3-aryl-4-thiazolidones with the same or different aryl groups, and 3-aryl-2,4-thiazolidiones 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-thiazolidones[12] step the germination of spores of the fungus, *Culvularia lunata* at the concentration of 1 : 500.

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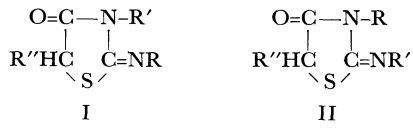
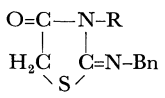
In view of the significant biological applicability of the 4-thiazolidones and their 1,1-dioxides, it was thought worthwhile to synthesize 2-arylimino-3-aryl-5-substituted-4-thiazolidones (I) and 3-aryl-2-(substituted 2′-benzothiazolyl)imino-4-thiazolidones (III) as fungicides by the methods described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



I

II



III

where R=aryl; R′=aryl; R″=H or CH_3
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 $KMnO_4$ 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, % Found	Nitrogen, % Calcd	Percentage-inhibition* at concentrations 1:1000	Percentage-inhibition* at concentrations 1:5000
1	*o*-$OCH_3\cdot C_6H_4$	*o*-$Cl\cdot C_6H_4$	H	149	$C_{16}H_{13}ClN_2O_2S$	8.19	8.42	60	19.25
2	*o*-$OCH_3\cdot C_6H_4$	*m*-$Cl\cdot C_6H_4$	H	143	$C_{16}H_{13}ClN_2O_2S$	8.50	8.42	68	34.65
3	*p*-$Cl\cdot C_6H_4$	*o*-$OCH_3\cdot C_6H_4$	H	135	$C_{16}H_{13}ClN_2O_2S$	8.30	8.42	80	53.90
4	*o*-$OCH_3\cdot C_6H_4$	*p*-$Br\cdot C_6H_4$	H	123	$C_{16}H_{13}BrN_2O_2S$	7.31	7.43	72	50.05
5	*o*-$OCH_3\cdot C_6H_4$	*p*-$I\cdot C_6H_4$	H	190	$C_{16}H_{13}IN_2O_2S$	6.45	6.60	—	—
6	*m*-$OCH_3\cdot C_6H_4$	*o*-$OCH_3\cdot C_6H_4$	H	171	$C_{17}H_{16}N_2O_3S$	8.63	8.54	72	46.20
7	*o*-$OC_2H_5\cdot C_6H_4$	*o*-$OCH_3\cdot C_6H_4$	H	131	$C_{18}H_{18}N_2O_3S$	8.27	8.19	60	30.80
8	*p*-$OC_2H_5\cdot C_6H_4$	*o*-$OCH_3\cdot C_6H_4$	H	122	$C_{18}H_{18}N_2O_3S$	8.35	8.19	—	—
9	*o*-$OCH_3\cdot C_6H_4$	β-Nathphyl	H	125	$C_{20}H_{16}N_2O_2S$	8.14	8.05	68	46.20
10	*o*-$CH_3\cdot C_6H_4$	Ph	CH_3	146	$C_{17}H_{16}N_2OS$	9.13	9.46	—	—
11	*p*-$CH_3\cdot C_6H_4$	Ph	CH_3	165	$C_{17}H_{16}N_2OS$	9.27	9.46	80	57.75
12	*o*-$Cl\cdot C_6H_4$	Ph	CH_3	161	$C_{16}H_{13}ClN_2OS$	8.47	8.84	—	—
13	*p*-$Cl\cdot C_6H_4$	Ph	CH_3	283	$C_{16}H_{13}ClN_2OS$	8.66	8.84	76	42.35
14	*p*-$OCH_3\cdot C_6H_4$	Ph	CH_3	183	$C_{17}H_{16}N_2O_2S$	8.72	8.97	64	34.65
15	*p*-$OC_2H_5\cdot C_6H_4$	Ph	CH_3	131	$C_{18}H_{18}N_2O_2S$	8.38	8.59	68	30.80
16	*p*-$Cl\cdot C_6H_4$	*p*-$CH_3\cdot C_6H_4$	CH_3	130	$C_{17}H_{15}ClN_2OS$	8.27	8.49	—	—
17	*p*-$Br\cdot C_6H_4$	*p*-$CH_3\cdot C_6H_4$	CH_3	159	$C_{17}H_{15}BrN_2OS$	7.31	7.46	80	57.75
18	*p*-$OCH_3\cdot C_6H_4$	*p*-$CH_3\cdot C_6H_4$	CH_3	184	$C_{18}H_{18}N_2O_2S$	8.32	8.59	68	46.20
19	*p*-$OC_2H_5\cdot C_6H_4$	*p*-$CH_3\cdot C_6H_4$	CH_3	161	$C_{19}H_{20}N_2O_2S$	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′-BENZOTHIAZOLYL) IMINO-4-THIAZOLIDONES

S. No.	Substituent	Yield %	Mp °C	Molecular formula	Nitrogen, %		Sulphur, %	
					Found	Calcd	Found	Calcd
				Aryl=*p*-Cl·C_6H_4				
1	4′-Methyl	84	246	$C_{17}H_{12}ClN_3OS_2$	11.10	11.24	17.28	17.14
2	5′-Methyl	90	249	$C_{17}H_{12}ClN_3OS_2$	11.39	11.24	17.33	17.14
3	6′-Methyl	95	286	$C_{17}H_{12}ClN_3OS_2$	11.06	11.24	17.29	17.14
4	4′-Chloro	75	218	$C_{16}H_9Cl_2N_3OS_2$	10.54	10.66	16.20	16.25
5	5′-Chloro	78	245	$C_{16}H_9Cl_2N_3OS_2$	10.83	10.66	16.03	16.25
6	6′-Chloro	86	255	$C_{16}H_9Cl_2N_3OS_2$	10.75	10.66	16.38	16.25
7	4′-Methoxy	70	234	$C_{17}H_{12}ClN_3O_2S_2$	10.63	10.78	16.38	16.44
8	6′-Methoxy	82	252	$C_{17}H_{12}ClN_3O_2S_2$	10.58	10.78	16.50	16.44
9	6′-Ethoxy	89	244	$C_{18}H_{14}ClN_3O_2S_2$	10.27	10.41	16.01	15.86
				Aryl=*o*-CH_3·C_6H_4				
10	4′-Methyl	44	157	$C_{18}H_{15}N_3OS_2$	11.72	11.90	17.92	18.13
11	5′-Methyl	41	137	$C_{18}H_{15}N_3OS_2$	11.68	11.90	18.04	18.13
12	6′-Methyl	56	171	$C_{18}H_{15}N_3OS_2$	11.78	11.90	17.83	18.13
13	4′-Chloro	35	143	$C_{17}H_{12}ClN_3OS_2$	11.15	11.24	16.73	17.14
14	5′-Chloro	37	135	$C_{17}H_{12}ClN_3OS_2$	11.07	11.24	16.97	17.14
15	4′-Methoxy	48	165	$C_{18}H_{15}N_3O_2S_2$	10.84	11.39	17.15	17.35
16	6′-Methoxy	57	138	$C_{18}H_{15}N_3O_2S_2$	10.91	11.39	17.21	17.35
17	6′-Ethoxy	53	109	$C_{19}H_{17}N_3O_2S_2$	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 m*l*) 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 m*l*) 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 $C_{20}H_{16}N_2O_2S$: 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 m*l*) 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 m*l*) 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 $C_{16}H_{10}ClN_3OS_2$: 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 m*l*) was treated slowly with $KMnO_4$ (1 g) solution prepared in water (45 m*l*) 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 $C_{16}H_{13}ClN_2O_4S$: 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 m*l* of aniline), cooled in a freezing mixture at 0°C, a solution of the thiazolidone (2 g) in glacial acetic acid (40 m*l*) 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 1) 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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