Studies in Oxadiazoles

Synthesis of Some 2-Mercapto-1,3,4-oxadiazoles and Related Compounds as Potential Fungicides

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Several 2-mercapto-5-substituted-1,3,4-oxadiazoles, alkyl and aralkyl oxadiazolyl sulphides, disulphides and sulphones have been prepared. A representative number of these compounds have been tested against two fungal species.

Although the oxadiazole ring is associated with many types of biological properties such as antifungal,¹⁾ hypoglycemic,²⁾ analgesic³⁾ and herbicidal⁴⁾ etc., the fungicidal properties of the oxadiazole sulphones and related compounds have not been apparently studied. Since a number of aryl and heteroaryl sulphones display pesticidal,^{5~8)} tuberculostatic⁹⁾ and antistreptococcal¹⁰⁾ properties, it was presumed that the sulphones and sulphides derived from biologically versatile oxadiazoles might be the fungicides of choice. Further, the mercapto oxadiazoles from which the above compounds are derived might themselves be useful fungicides since the -SH group attached to the heterocyclic nucleus may induce fungicidal action.¹¹⁾

Keeping above facts in view, we considered it of interest to synthesise these oxadiazoles and study their fungicidal properties. The 2-mercapto-5-substituted oxadiazoles were prepared by reacting acid hydrazides with carbon disulphide in alkaline medium following the method of Young and Wood.¹²⁾ Reaction of mercapto oxadiazole with alkyl and aralkyl halides^{13,14)} in basic medium gave the corresponding sulphides. The oxidation of these sulphide with hydrogen peroxide by a procedure similar to that adopted by Bambas¹⁰⁾ furnished the desired sulphones. The disulphides were obtained by oxidation of the sulphides with bromine.¹⁴⁾

A representative number of each type of oxadiazole was tested against two fungal

species viz. *A. niger* and *A. flavus*. All compounds are toxic to both the species at higher concentrations but their toxicity decreases on dilution. The oxadiazoles with 2-mercapto substituent appear to be more toxic to *A. niger* compared to *A. flavus*. Similarly the sulphides are relatively less toxic than sulphones. In all such compounds the chloro- and nitro-substituents in aryl moiety appear to enhance the fungitoxicity.

EXPERIMENTAL

2-Mercapto-5-substituted-1,3,4-oxadiazoles. These were prepared according to the method of Young and Wood¹²⁾ by reacting acid hydrazides (0.05 M) with carbodisulphide (1 M) in presence of ethanolic KOH. The compounds thus prepared are recorded in Table I.

Methyl-(5-substituted-1,3,4-oxadiazol-2-yl) sulphides. A reaction mixture containing equimolecular amounts of methyl iodide and 2-mercapto-5-substituted oxadiazole in ethanolic KOH was refluxed for 2 hr. This was cooled and poured into water. The precipitated product was filtered, washed and recrystallised from ethanol. The compounds thus prepared are recorded in Table II.

Benzyl-(5-substituted-1,3,4-oxadiazol-2-yl) sulphides. Benzyl chloride (0.02 M) and 2-mercapto-5-substituted-oxadiazole (0.02 M) were taken in benzene (200 ml). To this was added triethylamine (0.02 M) and the mixture was refluxed for 2~3 hr. After cooling, the reaction mixture was poured into water, the benzene layer was separated and concentrated to a small bulk when the required product slowly crystallised out. The sulphides thus prepared are recorded in Table II.

Methyl-(5-phenyl-1,3,4-oxadiazol-2-yl) sulphone.
Methyl-(5-phenyl-1,3,4-oxadiazol-2-yl) sulphide (2 g)

TABLE I. 2-MERCAPTO-5-SUBSTITUTED-1,3,4-OXADIAZOLES

S.No.	R	mp °C	Yield %	Molecular formula	N (%)		S (%)	
					Found	Calcd.	Found	Calcd.
1	<i>o</i> -Chlorophenoxymethyl	142	85	C ₉ H ₇ N ₂ O ₂ SCl	11.6	11.6	13.4	13.2
2	<i>m</i> -Chlorophenoxymethyl	161	88	C ₉ H ₇ N ₂ O ₂ SCl	11.8	11.6	13.1	13.2
3	<i>o</i> -Chlorophenyl	176	80	C ₈ H ₅ N ₂ OSCl	13.3	13.2	15.2	15.1
4	<i>p</i> -Chlorophenyl	176~178	90	C ₈ H ₅ N ₂ OSCl	13.1	13.2	15	15.1
5	<i>m</i> -Nitrophenyl	>300	70	C ₈ H ₅ N ₃ O ₃ S	19	18.9	14.1	14.4
6	<i>p</i> -Nitrophenyl	>300	75	C ₈ H ₅ N ₃ O ₃ S	18.6	18.9	14.5	14.4
7	Phenyl	217~219	85	C ₈ H ₆ N ₂ OS	15.9	15.7	18.1	18

TABLE II. METHYL/BENZYL-(5-SUBSTITUTED-1,3,4-OXADIAZOL-2-YL) SULPHIDES

S.No.	R	mp °C	Yield %	Molecular formula	N (%)		S (%)	
					Found	Calcd.	Found	Calcd.
R' = Methyl								
1	<i>o</i> -Chlorophenoxymethyl	32	66	C ₁₀ H ₉ N ₂ O ₂ SCl	11.1	10.9	12.3	12.5
2	<i>m</i> -Chlorophenoxymethyl	58	73	C ₁₀ H ₉ N ₂ O ₂ SCl	10.7	10.9	12.6	12.5
3	<i>o</i> -Chlorophenyl	73	59	C ₉ H ₇ N ₂ OSCl	12.5	12.4	14	14.1
4	<i>p</i> -Chlorophenyl	112	72	C ₉ H ₇ N ₂ OSCl	12.1	12.4	14.2	14.1
5	<i>m</i> -Nitrophenyl	152	65	C ₉ H ₇ N ₃ O ₃ S	17.5	17.7	13.4	13.5
6	<i>p</i> -Nitrophenyl	198	69	C ₉ H ₇ N ₃ O ₃ S	17.4	17.7	13.3	13.5
7	Phenyl	39	68	C ₉ H ₈ N ₂ OS	14.6	14.6	16.5	16.7
R' = Benzyl								
8	<i>o</i> -Chlorophenoxymethyl	108	69	C ₁₆ H ₁₃ N ₂ O ₂ SCl	8.3	8.5	9.9	9.6
9	<i>m</i> -Chlorophenoxymethyl	71	72	C ₁₆ H ₁₃ N ₂ O ₂ SCl	8.7	8.5	9.8	9.6
10	<i>o</i> -Chlorophenyl	58	65	C ₁₅ H ₁₁ N ₂ OSCl	9.1	9.2	10.4	10.6
11	<i>p</i> -Chlorophenyl	118	74	C ₁₅ H ₁₁ N ₂ OSCl	9	9.2	10.7	10.6
12	<i>m</i> -Nitrophenyl	158	64	C ₁₆ H ₁₁ N ₃ O ₃ S	13.1	13.4	10.1	10.2
13	<i>p</i> -Nitrophenyl	201	70	C ₁₆ H ₁₁ N ₃ O ₃ S	13.7	13.4	10.4	10.2
14	Phenyl	98	72	C ₁₆ H ₁₂ N ₂ OS	10.9	10.5	12	11.9

was suspended in glacial acetic acid (40 ml). To this was added 30% hydrogen peroxide (12 ml) and the mixture was refluxed for 45 min. Upon cooling and pouring the reaction mixture into water, a precipitate was obtained. This was filtered, washed with water and recrystallised from ethanol as a colourless solid mp 134°C, yield 70%. Found C, 48.4, H, 3.6; C₉H₈N₂O₃S required C, 48.2, H, 3.6%. Its IR spectrum reveals stretching vibration due to -SO₂- group at 1348~1337 cm⁻¹, a medium band at 1433 and 1481 cm⁻¹ (methyl group) and significant bands in the region 1560 and 1695 cm⁻¹ (aromatic ring).

Other sulphones prepared by exactly the same pro-

cedure are recorded in Table III.

Bis-(5-substituted-1, 3, 4-oxadiazol-2-yl) disulphides. An ethanolic solution of 2-mercapto oxadiazole compound (0.02 M) was stirred with bromine (0.04 M) in ethanol (15 ml). The disulphide compound at once began to separate. It was filtered, washed and recrystallised if necessary. The disulphides thus prepared are recorded in Table IV.

Fungicidal test. The test organisms were *Aspergillus niger* and *Aspergillus flavus*. The antifungal activity was evaluated by agar-growth technique at three different concentrations namely, 1: 1000, 1: 10,000 and

TABLE III. METHYL/BENZYL-(5-SUBSTITUTED-1,3,4-OXADIAZOL-2-YL)SULPHONES

S. No.	R	mp °C	Yield %	Molecular formula	C (%)		H (%)		Significant bands (cm ⁻¹) in IR absorption spectra.
					Found	Calcd.	Found	Calcd.	
R' = Methyl									
1	<i>o</i> -Chlorophenoxymethyl	142	69	C ₁₀ H ₉ N ₂ O ₄ SCl	41.4	41.6	3	3.1	—SO ₂ —, aromatic ring and —CH ₃
2	<i>m</i> -Chlorophenoxymethyl	159	75	C ₁₀ H ₉ N ₂ O ₄ SCl	41.7	41.6	2.9	3.1	—
3	<i>o</i> -Chlorophenyl	165	60	C ₉ H ₇ N ₂ O ₃ SCl	41.5	41.8	2.5	2.7	1326 1587 1468 1412
4	<i>p</i> -Chlorophenyl	221	78	C ₉ H ₇ N ₂ O ₃ SCl	41.6	41.8	2.8	2.7	1348 1608 1484 1397
5	<i>m</i> -Nitrophenyl	279 ^{a)}	66	C ₉ H ₇ N ₃ O ₅ S	40	40.2	2.6	2.6	—
6	<i>p</i> -Nitrophenyl	> 300	72	C ₉ H ₇ N ₃ O ₅ S	40.5	40.2	2.4	2.6	—
R' = Benzyl									
7	<i>o</i> -Chlorophenoxymethyl	134	72	C ₁₆ H ₁₃ N ₂ O ₄ SCl	52.4	52.7	3.8	3.6	—SO ₂ —, aromatic ring and —CH ₂ —
8	<i>m</i> -Chlorophenoxymethyl	163	80	C ₁₆ H ₁₃ N ₂ O ₄ SCl	52.9	52.7	3.4	3.6	1316 1600 1372 1458
9	<i>o</i> -Chlorophenyl	162	68	C ₁₅ H ₁₁ N ₂ O ₃ SCl	53.5	53.8	3.1	3.3	1323 1605 1370 1471
10	<i>p</i> -Chlorophenyl	229	78	C ₁₅ H ₁₁ N ₂ O ₃ SCl	53.4	53.8	3.1	3.3	1326 1585 1410 1466
11	<i>m</i> -Nitrophenyl	253 ^{a)}	68	C ₁₅ H ₁₁ N ₃ O ₅ S	52	52.2	3.2	3.2	1333 1603 1391 1479
12	<i>p</i> -Nitrophenyl	233 ^{a)}	66	C ₁₅ H ₁₁ N ₃ O ₅ S	51.1	52.2	3.1	3.2	—
13	Phenyl	129	70	C ₁₅ H ₁₂ N ₂ O ₃ S	59.7	60	4.1	4	1305 1575 1389 1475
									1340 1431 1481

^{a)} partly melts with decomposition.

TABLE IV. BIS-(5-SUBSTITUTED-1,3,4-OXADIAZOL-2-YL)DISULPHIDES

S.No.	R	mp °C	Yield %	Molecular formula	N (%)		S (%)	
					Found	Calcd.	Found	Calcd.
1	<i>o</i> -Chlorophenoxymethyl	132	75	C ₁₈ H ₁₂ N ₄ O ₄ S ₂ Cl ₂	11.4	11.6	13.1	13.3
2	<i>m</i> -Chlorophenoxymethyl	151	80	C ₁₈ H ₁₂ N ₄ O ₄ S ₂ Cl ₂	11.5	11.6	13.6	13.3
3	<i>o</i> -Chlorophenyl	157	70	C ₁₆ H ₈ N ₄ O ₂ S ₂ Cl ₂	13	13.2	15.4	15.1
4	<i>p</i> -Chlorophenyl	172	82	C ₁₆ H ₈ N ₄ O ₂ S ₂ Cl ₂	13.1	13.2	15	15.1
5	<i>m</i> -Nitrophenyl	278 ^{a)}	72	C ₁₆ H ₈ N ₆ O ₆ S ₂	18.8	18.9	14.7	14.4
6	<i>p</i> -Nitrophenyl	292 ^{a)}	74	C ₁₆ H ₈ N ₆ O ₆ S ₂	19.1	18.9	14	14.4
7	Phenyl	193 ~ 195	82	C ₁₆ H ₁₀ N ₄ O ₂ S ₂	16	15.8	18.4	18.1

^{a)} Partly melts with decomposition.

TABLE V. ANTIFUNGAL ACTIVITY

S. No.	Compounds	Average percentage inhibition after 96 hr					
		Organism— <i>A. niger</i> Concentrations used			Organism— <i>A. flavus</i> Concentrations used		
		1: 1000	1: 10,000	1: 100,000	1: 1000	1: 10,000	1: 100,000
1	Methyl-[5-(<i>o</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]sulphone	68.2	62.4	50.1	65.3	59.2	40.6
2	Benzyl-[5-(<i>o</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]sulphone	62.4	56.1	41	56.2	49	32.4
3	Benzyl-[5-(<i>m</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]sulphone	89.6	76.8	42.2	88.4	70.2	38.7
4	Methyl-[5-(<i>o</i> -chlorophenyl)-1,3,4-oxadiazol-2-yl]sulphone	78	69.2	50.5	62	50.2	42
5	Benzyl-[5-(<i>o</i> -chlorophenyl)-1,3,4-oxadiazol-2-yl]sulphone	66.4	60	49.2	67.4	51	39.4
6	Benzyl-[5-(<i>p</i> -chlorophenyl)-1,3,4-oxadiazol-2-yl]sulphone	71	62.6	52.4	68.5	51.2	42
7	Methyl-[5-(<i>m</i> -nitrophenyl)-1,3,4-oxadiazol-2-yl]sulphone	63.2	58.1	41.9	66.6	65.4	43.4
8	Benzyl-[5-(<i>p</i> -nitrophenyl)-1,3,4-oxadiazol-2-yl]sulphone	66.5	57	42.6	64.2	58	41
9	5-(<i>p</i> -chlorophenyl)-2-mercapto-1,3,4-oxadiazole	70	66.8	50	68.4	59	38.4
10	5-(<i>o</i> -chlorophenyl)-2-mercapto-1,3,4-oxadiazole	65.6	59.3	39	69.4	58.4	32.3
11	5-(<i>m</i> -chlorophenoxymethyl)-2-mercapto-1,3,4-oxadiazole	80	60.6	40.4	79	62.5	38.7
12	Methyl-[5-(<i>m</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]sulphide	70.2	56.2	35	60.4	51	31.5
13	Benzyl-[5-(<i>p</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]sulphide	70.2	56.2	35	60.4	51	31.5
14	Bis-[5-(<i>p</i> -chlorophenyl)-1,3,4-oxadiazol-2-yl]disulphide	67.3	52.3	43.4	68.2	55	41.6
15	Bis-[5-(<i>o</i> -chlorophenoxymethyl)-1,3,4-oxadiazol-2-yl]disulphide	72.4	51.6	46.6	70.9	50.3	36.2

1: 100,000 and number of replications in each case was three. The average percentage inhibition by various compounds is recorded in Table V.

RESULTS AND DISCUSSION

In view of the reported pesticidal properties of a variety of sulphones.^{5~8)} it was considered worthwhile to study the fungicidal properties of oxadiazolyl sulphones and sulphides. Obviously these compounds are fungitoxic at higher concentration but their toxicity decreases upon dilution. Further, their activity varies with the species of fungus as well.

The mercapto oxadiazole (compound No. 9) having a *o*-chlorophenyl substituent is more active against *A. niger* than *A. flavus*. The compound Nos. 1, 4, 5, 6, 7, 8 and 14 which are representatives of sulphides and sulphones appear to be promising fungicides. It is noteworthy that all of them have either a chlorophenyl or nitrophenyl substituent.

These results are in conformity with earlier observations that heterocyclic rings with aryl or other lipophilic substituents are usually fungitoxic.

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