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Synthesis of Aryloxy/Aryl Acetyl Thiosemicarbazides, Substituted 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, 1,2,4-Triazoles and Related Compounds as Potential Fungicides

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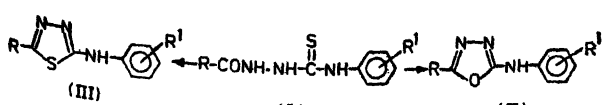
Twelve 1-aryloxy/aryl acetyl-4-aryl thiosemicarbazides, twelve 2-arylamino-5-aryloxy/aryl methyl-1,3,4-oxadiazoles, eleven 2-arylamino-5-aryloxy/aryl methyl-1,3,4-thiadiazoles, twelve 3-aryloxy/aryl methyl-4-aryl-5-mercapto-1,2,4-triazoles, three methyl-(3-aryloxymethyl-4-aryl-1,2,4-triazol-5-yl)-sulphides, three *bis*-(3-aryloxymethyl-4-aryl-1,2,4-triazol-5-yl)-disulphides and six *bis*-(3-aryloxy/aryl methyl-4-aryl-1,2,4-triazol-5-yl)-alkylene disulphides were prepared. Forty nine compounds have been screened against *A. niger* and *H. oryzae* and were found to possess moderate to fairly good antifungal activity.

THIOSEMICARBAZIDES have been reported to possess antifungal[1,2], antibacterial[3] and anticonvulsant[4] properties. 2-Amino-5-substituted-1,3,4-oxadiazoles were prepared as antimitotic[5] and muscle relaxant and tranquilizing agents[6]. Substituted thiadiazoles are known to exhibit fungicidal[7], bactericidal[8], herbicidal[9] and insecticidal[10] activities.

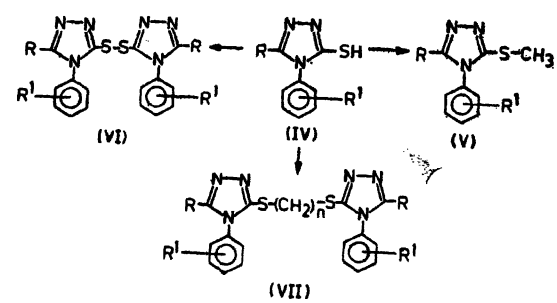
Compounds containing triazole ring have shown good fungicidal[11], bactericidal[12] and pesticidal[13] activities. Anticancer and antifungal activities have been displayed by some heterocyclic sulphides[14]. Further, sulphides have been found to be more active than parent mercapto compounds[15]. In view of these, the title compounds have been synthesised.

1-Aryloxy/aryl acetyl-4-aryl thiosemicarbazides (I) have been prepared by the reaction of aryloxy/aryl acetyl hydrazine[16] and aryl isothiocyanate. I was cyclised into 2-arylamino-5-aryloxy/aryl methyl-1,3,4-oxadiazoles (II) in the presence of mercuric oxide. Reaction of I with sulphuric acid gave 2-arylamino-5-aryloxy/aryl methyl-1,3,4-thiadiazoles (III).



(III) (I) (II)

3-Aryloxy/aryl methyl-4-aryl-5-mercapto-1, 2, 4-triazoles (IV) have been obtained by reacting aryloxy/aryl acetyl hydrazine[16] with aryl isothiocyanate in the presence of alkali. Reaction of IV with methyl iodide gave methyl triazolyl sulphides (V) whereas with bromine, *bis*-triazolyl-disulphides (VI) and with alkylene dihalide, *bis*-triazolyl alkylene disulphides (VII) were produced.



(VI) (IV) (V)

(VII)

The compounds thus prepared are given in Tables 1-5 along with their antifungal data. Satisfactory N and S analyses results were found for all the compounds.

Experimental

. All melting points are uncorrected.

Aryloxy/aryl acetyl hydrazines: These were prepared by the method of Conti[16].

1-Aryloxy/aryl acetyl-4-aryl thiosemicarbazides (I): These were prepared by the method of Paul and Basu[17].

2-Arylamino-5-aryloxy/aryl methyl-1,3,4-oxadiazoles (II): 1-Aryloxy/aryl acetyl-4-aryl thiosemicarbazide (0.01 *M*) was dissolved/suspended in methanol and mercuric oxide (0.011 *M*) was added to it. The contents were refluxed for 2 hr and the mixture filtered hot. The filtrate was evaporated and the solid obtained was recrystallised from aqueous ethanol.

2-Arylamino-5-aryloxy/aryl methyl-1,3,4-thiadiazoles (III) : 1-Aryloxy/aryl acetyl-4-aryl thiosemicarbazide (0.01 *M*) was dissolved with cooling in conc. sulphuric acid (10 ml). The solution was kept at room temperature for 2 hr, stirred at intervals and then poured over crushed ice. It was stirred well and left as such for 1 hr. The residue was filtered, washed with water and recrystallised.

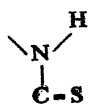
3-Aryloxy/aryl methyl-4-aryl-5-mercapto-1,2,4-triazoles[17] (IV) : A mixture of aryloxy/aryl acetyl hydrazines (0.01 *M*) and aryl isothiocyanate (0.012 *M*) was refluxed in sodium hydroxide solution (20 ml, 8%) for 5 hr, cooled and poured into water. It was stirred and filtered. The filtrate on acidification yielded a solid which was filtered, washed and recrystallised from aqueous ethanol.

Methyl-(3-aryloxymethyl-4-aryl-1,2,4-triazol-5-yl)-sulphides (V) : To a methanolic solution of 3-aryloxy methyl-4-aryl-5-mercapto-1,2,4-triazole (0.01 *M*), fused sodium acetate (2.0 g) and methyl iodide (0.01 *M*) were added. The contents were refluxed for 4 hr, cooled and poured into water. The solid separating out was filtered, washed and recrystallised.

TABLE 1—1-ARYLOXY/ARYL ACETYL-4-ARYL THIOSEMICARBAZIDES (I)

Compd. No.	R	R^1	m.p. °C	Yield %	Fungicidal activity Conc. 10 ppm *A. niger*	*H. oryzae*
1[a]	4-Cl-3-CH_3.C_6H_3-O.CH_2	2-OCH_3	180	94	24.4	25.1
2	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	174	98	18.7	21.3
3	4-Cl-3-CH_3.C_6H_3-O.CH_2	3.4-Cl_2	190	85	27.1	27.9
4	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	164	97	19.2	18.8
5	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	162	99	16.7	14.8
6	2-4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	172	72	21.6	23.4
7	C_6H_5-CH_2	2-OCH_3	105	83	11.9	13.1
8	C_6H_5-CH_2	3,4-$(CH_3)_2$	150	82	–	–
9	C_6H_5-CH_2	3,4-Cl_2	140	76	14.4	16.8
10	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	148	86	18.8	20.5
11	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	200	98	–	–
12[a]	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	150	74	22.4	24.1

IR spectral data ν_{max} in cm^{-1}



	C=S	N-H stretching	-CO.NH-	-C-O-C-	C-Cl	*Ortho*disubstituted benzene
a	1165	3400	1670	1060, 1225	750	760
b	1170	3400	1680	1020, 1270	–	Monosubstituted benzene 730
c	1175	3400	1655	1070, 1225	710	1,2,3,-Trisubstituted benzene 765

NMR spectral data

c Ar-H 2.1-3.2τ, $-CH_2-$ 5.8τ, $-CH_3$ 7.82τ

TABLE 2—2-ARYLAMINO-5-ARYLOXY/ARYL METHYL-1,3,4-OXADIAZOLES (II)

Compd. No.	R	R^1	m.p. °C	Yield %	Fungicidal activity Conc. 10 ppm *A. niger*	*H. oryzae*
13[a]	4-Cl-3-CH_3-C_6H_3-O-CH_2	2-OCH_3	171	54	33.9	35.7
14	4-Cl-3-CH_3.C_6H_3-O.CH_2	3-4-$(CH_3)_2$	194	70	22.8	27.8
15	4-Cl-3-CH_3.C_6H_3-O.CH_2	3-4-Cl_2	145	51	36.7	39.1
16	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	82	44	31.1	33.2
17	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	130	94	27.1	29.8
18	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	179	76	32.0	35.1
19	C_6H_5-CH_2	2-OCH_3	196	84	13.9	14.1
20	C_6H_5-CH_2	3-4-$(CH_3)_2$	116	93	–	–
21[a]	C_6H_5-CH_2	3,4-Cl_2	125	83	16.8	16.9
22	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	145	60	–	–
23	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	194	51	29.0	32.4
24	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	155	54	35.2	38.0

IR spectral data ν_{max} in cm^{-1}

	-C-O-C, C-O stretching	-NH	Conjugated cyclic -C=N	-C-O-C-	C-Cl	*Ortho*disubstituted benzene
d	1115	3480	1570	1020, 1235	790	740
e	1110	3360	1570	1030, 1250	730	Monosubstituted benzene 720

TABLE 3—2-ARYLAMINO-5-ARYLOXY/ARYL METHYL-1,3,4-THIADIAZOLES (III)

Compd. No.	R	R^1	m.p. °C	Yield %	Fungicidal activity Conc. 10 ppm *A. niger*	*H. oryzae*
25	4-Cl-3-CH_3.C_6H_3-O.CH_2	2-OCH_3	190[d]	75	40.1	44.5
26	4-Cl-3-CH_3.C_6H_3 O.CH_2	3,4-$(CH_3)_2$	210	97	32.0	36.5
27[f]	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-Cl_2	218[d]	98	45.8	48.2
28	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	200[d]	90	30.5	34.1
29	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	199[d]	87	36.7	40.0
30	C_6H_5-CH_2	2-OCH_3	252	97	15.2	16.1
31	C_6H_5-CH_2	3,4-$(CH_3)_2$	200	95	—	—
32[g]	C_6H_5-CH_2	3,4-Cl_2	151	98	19.9	21.5
33	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	208[d]	57	—	—
34[h]	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	221	95	32.2	35.0
35	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	234[d]	81	41.4	45.0

IR spectral data ν_{max} in cm^{-1}

	-NH	Conjugated cyclic -C=N-	-C-O-C-	C-Cl	1,2,3-Trisubstituted benzene
f	3470	1605	1030, 1250	750	–
h	3440	1625	1035, 1275	–	745

NMR spectral data

g Ar-H 2.6-2.8τ, -CH_2- 5.8τ

TABLE 4—3-ARYLOXY/ARYL METHYL-4-ARYL-5-MERCAPTO-1,2,4-TRIAZOLES (IV)

Compd. No.	R	R^1	m.p. °C	Yield %	Fungicidal activity Conc. 10 ppm *A. niger*	*H. oryzae*
36[i]	4-Cl-3-CH_3.C_6H_3-O.CH_2	2-OCH_3	160	88	41.0	48.7
37	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	175	75	36.5	42.0
38	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-Cl_2	161	71	44.3	52.7
39	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	168	97	34.0	40.6
40[j]	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	123	94	31.7	32.0
41	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	189	76	38.5	45.8
42	C_6H_5-CH_2	2-OCH_3	182	79	26.2	28.6
43	C_6H_5-CH_2	3-4-$(CH_3)_2$	110	78	—	—
44[k]	C_6H_5-CH_2	3,4-Cl_2	154	67	28.7	36.0
45	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	202	88	—	—
46	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	228	90	30.4	32.9
47	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	222	67	37.8	44.2

IR spectral data ν_{max} in cm^{-1}

	Secondary -NH	Conjugated cyclic -C=N-	-C=S	-C-O-C-	-SH	C-Cl	*Ortho*disubstituted benzene
i	3100	1600	1160	1040, 1235	2580	690	750
j	3150	1500	1130	1035, 1250	–	–	–

NMR spectral data

k Ar-H 2.6-3.0τ, -CH_2 5.8τ, -SH 8.75τ

Bis-(3-aryloxymethyl-4-aryl-1, 2, 4-triazol-5-yl)-disulphides (**VI**) : To an ice cold methanolic solution of 3-aryloxymethyl-4-aryl-5-mercapto-1,2,4-triazole (0.01 *M*), a cold methanolic solution of bromine (0.005 *M*) was added dropwise with swirling. It was kept as such for 2 hr and then evaporated. The residue obtained was washed successively with water, dilute sodium hydroxide and water and recrystallised.

Bis-(3-aryloxy/aryl methyl-4-aryl-1,2,4-triazol-5-yl)-alkylene disulphides (**VII**) : A methanolic solution of 3-aryloxy/aryl-4-aryl-5-mercapto-1, 2, 4 - triazole (0.01 *M*), methylene/ethylene dihalide (0.005 *M*) and fused sodium acetate (2.0 g) was refluxed gently for 4 hr, cooled and poured into water. The solid obtained was filtered, washed and recrystallised from aqueous ethanol.

Fungicidal screening: The compounds were evaluated for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* by agar plate technique[18,19] at three different concentrations viz., 1000, 100 and 10 ppm. Two commercial fungicides, BLITOX 50 WP and MEMCGE, were also tested under parallel conditions to compare the result. The number of replications in each case was three.

Results and Discussion

The compounds screened possess moderate to fairly good antifungal activity against both the

TABLE 5—METHYL-(3-ARYLOXYMETHYL-4-ARYL-1,2,4-TRIAZOL-5-YL)-SULPHIDES (V)

Compd. No.	R	R^1	m.p. °C	Yield %	Fungicidal activity Conc. 10 ppm *A. niger*	*H. oryzae*
48	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	63	86	39.8	42.7
49[l]	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	Viscous liquid	67	–	–
50	2,6-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	99	76	39.0	44.7
	Bis-(3-Aryloxymethyl-4-aryl-1,2,4-Triazol-5-yl)-Disulphides (VI)					
51	4-Cl-3-CH_3.C_6H_3-O.CH_2	2-OCH_3	121	71	47.8	54.6
52[m]	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	157	46	41.3	45.2
53	4-Cl-3-CH_3.C_6H_3-O.CH_2	3,4-Cl_2	160	50	50.6	56.9
	Bis-(3-Aryloxy/Aryl Methyl-4-Aryl-1,2,5-Triazol-5-yl)-Alkylene Disulphides (VII)					
	n = 1					
54[n]	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	2-OCH_3	169	91	44.0	46.8
55	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-$(CH_3)_2$	109	91	36.5	38.7
56	2,4-$(CH_3)_2$.C_6H_3-O.CH_2	3,4-Cl_2	205	85	48.5	53.3
	n = 2					
57	C_6H_5-CH_2	2-OCH_3	Semi solid	60	–	–
58	C_6H_5-CH_2	3,4-$(CH_3)_2$	70	70	20.0	21.6
59	C_6H_5-CH_2	3,4-Cl_2	81	71	30.6	31.8
	MEMEGE				83.4	75.8
	BLITOX 50 WP				73.4	80.0
	(Commercial fungicides)					
	IR spectral data ν_{max} in cm^{-1}					
	Conjugated cyclic -C = N-	= C-O-C-	1,2,3-Trisubstituted benzene			C-Cl
l	1480	1035, 1265	750			715
m	1480	1040, 1250	–			–
n	1490	1040, 1250	*Ortho*disubstituted benzene 755			

fungi. In general, the presence of chlorine and/or methoxy group increases the antifungal activity of the compound. The thiadiazoles (III) are more active than the corresponding oxadiazoles (II) which are relatively more potent than the corresponding thiosemicarbazides (I). Further, the alkyl sulphides display nearly the same level of fungicidal activity as their parent triazoles whereas *bis*-triazolyl disulphides and *bis*-triazolyl methylene disulphides are better than their corresponding triazoles. The highest level of activity in each Table has been shown by compounds Nos. 3, 15, 27, 38, 53 which contain 4-chloro-3-methylphenoxy and 3,4-dichlorophenyl moieties.

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