Syntheses of New 1,3,4-Oxadiazolo[3,2-*d*]-1,3,4-dithiazines and 1,3,4-Oxadiazolo[3,2-*d*]thiadiazines with Fungicidal Action

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2-(Chloromethyl)-1,3,4-oxadiazoles (Ia,b) on condensation with ammonium *N*-aryldithiocarbamates (IIa–c) afford (1,3,4-oxadiazol-2-yl)methyl *N*-aryldithiocarbamates (IIIa–f). The dithiocarbamates IIIa–f undergo oxidative cyclization with $SOCl_2$ and I_2 to yield 5-aryl-1,3,4-oxadiazolo[3,2-*d*]-1,3,4-thiadiazine-6(5*H*)-thiones (IVa–f) and 6-(arylimino)-1,3,4-oxadiazolo[3,2-*d*]-1,3,4-dithiazines (Va–f), respectively. The compounds III–V compared with Dithane M-45 for their in vitro antifungal action against *Helminthosporium oryzae* and *Cephalosporium saccharii* showed similar, though lesser, activity.

INTRODUCTION

Dithiocarbamates, maneb, zineb, ziram, and vapam, are among the most used fungicides for controlling plant diseases. Similarly, the 1,3,4-oxadiazole nucleus is associated with a broad spectrum of useful pesticidal activities, for example, bactericidal (Sinnur et al., 1986; Zayed et al., 1986) fungicidal (Dutta et al., 1986; Singh et al., 1987), herbicidal (Dahle and Doyle, 1974; Mitsubishi Chemical Industries, 1985), and insecticidal (Okada, 1970). Perusal of the above papers, in view of achieving new antifungal compounds of high potency prompted us to synthesize IIIa–f to Va–f incorporating the biolabile 1,3,4-oxadiazole and dithiocarbamate moieties. The investigation appeared quite interesting as the 1,3,4-oxadiazolodithia(thiadia)-zines IV and V reported herein are hitherto unknown bicyclic nitrogen-bridged heterocycles.

The reaction sequence leading to the formation of IV and V is outlined in the Scheme I. Acid hydrazides were cyclized with chloroacetyl chloride (Vakula and Srinivasan, 1973) to give 2-(chloromethyl)-1,3,4-oxadiazoles (Ia,b), which condensed with ammonium *N*-aryldithiocarbamates (IIa–c) to furnish IIIa–f. Oxidative cyclization of IIIa–f with thionyl chloride and iodine yielded the isomeric compounds IVa–f and Va–f, respectively.

The structural assignments of the synthesized compounds were based on elemental analyses and IR, ^{1}H NMR, and mass spectra (Table I). The elemental analyses (C, H, and N) of IIIa–f to Va–f were quite compatible with their assigned structures. The isomeric compounds IV and V clearly differ in their IR spectra; V exhibited a strong band around 1690 cm^{-1} (exocyclic C=N), whereas compounds IV were devoid of this band. Of the tested compounds IIIa–f to Va–f, the compounds IVe, Vb, and Ve displayed antifungal activity of the order of Dithane M-45 [a commercial fungicide, a mixed manganous and zinc salt of *N*,*N*′-ethylenebis(dithiocarbamic acid)] at 1000 ppm concentration against *Helminthosporium oryzae* and *Cephalosporium saccharii*.

EXPERIMENTAL PROCEDURES

Melting points were determined by open glass capillary method and are uncorrected. IR spectra, in KBr, were recorded on a Perkin-Elmer 157 infrared spectrophotometer (ν_{max}, cm^{-1}). ^{1}H NMR spectra were recorded on a Varian EM-360L (60 MHz) NMR spectrometer in DMSO-d_6 using TMS as internal reference; chemical shifts are expressed in δ. Mass spectra were recorded on a JEOL JMS-D 300 instrument.

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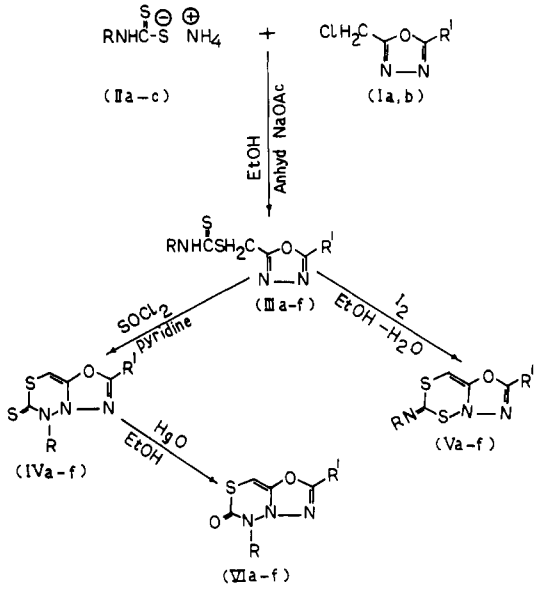
Scheme I



Ia, R′ = 2-ClC$_6$H$_4$; Ib, R′ = 2-ClC$_6$H$_4$OCH$_2$; IIa, R = C$_6$H$_5$; IIb, R = 4-ClC$_6$H$_4$; IIc, R = 4-CH$_3$C$_6$H$_4$; IIIa–c, IVa–c, Va–c, VIa–c, R = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$; R′ = 2-ClC$_6$H$_4$; IIId–f, IVd–f, Vd–f, VId–f R = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$; R′ = 2-ClC$_6$H$_4$OCH$_2$.

2-(Chloromethyl)-5-aryl[and (aryloxy)methyl]-1,3,4-oxadiazoles (Ia,b). These compounds were prepared by heating a mixture of chloroacetyl chloride (0.1 mol) and the appropriate acid hydrazide (0.1 mol) around the melting point of the hydrazide (Vakula and Srinivasan, 1973) until the evolution of HCl had ceased (6 h). The reaction mixture was cooled and the residue was washed with water and recrystallized from ethanol.

Ia: yield 63%; mp 210–11 °C; IR 1625 cm^{-1} (νC=N); ^{1}H NMR δ 4.80 (s, 2 H, CH_2), 6.94–7.86 (m, 4 H, aromatic *H*). Anal. Calcd. for $C_9H_6Cl_2N_2O$: C, 47.16; H, 2.62; N, 12.23. Found: C, 47.24; H, 2.53; N, 12.18.

Ib: yield 60%; mp 179–80 °C; IR 1620 cm^{-1} (νC=N); ^{1}H NMR δ 4.82 (s, 2 H, CH_2), 6.96–7.90 (m, 4 H, aromatic H) 5.22 [s, 2 H, (OCH_2)]. Anal. Calcd. for $C_{10}H_8Cl_2N_2O_2$: C, 46.33; H, 3.09; N, 10.81. Found: C, 46.28; H, 3.14; N, 10.74.

[5-Aryl[and (aryloxy)methyl]-1,3,4-oxadiazol-2-yl]methyl *N*-Aryldithiocarbamates (IIIa–f). A mixture of I (0.1 mol), ammonium *N*-aryldithiocarbamate (II, 0.1 mol), and anhydrous sodium acetate (0.1 mol) was refluxed in 250–300 mL of absolute ethanol for 2 h. The reaction mixture was cooled and poured into water. The desired product thus precipitated was washed with water and recrystallized from ethanol to give yellowish needles. The yields, the melting points, and the spectral data for the products IIIa–f obtained are listed in Table I.

2-Aryl[and (aryloxy)methyl]-5-aryl-1,3,4-oxadiazolo[3,2-*d*]-1,3,4-thiadiazine-6(5*H*)-thiones (IVa–f). Solutions of IIIa–f

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Table I. Yield, Melting Points, and Spectral Data of Compounds IIIa–f to Va–f

compd	yield, %	mp, °C	IR (KBr), cm^{-1} νC=N (cyclic)	IR (KBr), cm^{-1} νC=S* νC=N (exocyclic)	^{1}H NMR (DMSO-d_6), δ	MS/M$^+$, m/z
IIIa	64	204–5	1630	1090*	9.42 (1 H, br s, NH) 7.00–7.60 (9 H, m, Ar *H*) 4.88 (2 H, s, SC*H*$_2$)	361, 363
IIIb	59	165–66	1635	1100*	9.40 (1 H, br s, NH) 6.96–7.64 (8 H, m, Ar *H*) 4.86 (2 H, s, SC*H*$_2$)	395, 397, 399
IIIc	68	175	1630	1100*	9.36 (1 H, br s, NH) 6.86–7.80 (8 H, m, Ar H) 4.82 (2 H, s, SC*H*$_2$) 2.36 (3 H, s, CH$_3$)	375, 377
IIId	67	110	1630	1090*	9.42 (1 H, br s, NH) 7.02–7.64 (9 H, m, Ar *H*) 5.24 (2 H, s, OCH$_2$)	391, 393
IIIe	61	142–43	1635	1090*	9.38 (1 H, br s, NH) 7.04–7.60 (8 H, m, Ar H) 4.86 (2 H, s, SCH$_2$) 5.26 (2 H, s, OCH$_2$)	425, 427, 429
IIIf	65	198–99	1635	1090*	9.36 (1 H, br s, NH) 6.92–7.84 (8 H, m, Ar H) 4.88 (2 H, s, SCH$_2$) 5.24 (2 H, s, OCH$_2$) 2.24 (3 H, s, CH$_3$)	405, 407
IVa	55	181–82	1625	1080*	7.02–8.00 (10 H, m, Ar H and SCH)	359, 361
IVb	52	223–25	1630	1100*	7.00–8.02 (9 H, m, Ar *H* and SC*H*)	393, 395, 397
IVc	57	193	1625	1090*	7.00–7.98 (9 H, m, Ar H and SC*H*) 2.26 (3 H, s, CH$_3$)	373, 375
IVd	59	205–6	1630	1080*	7.04–8.02 (10 H, m, Ar H and SCH) 5.28 (2 H, s, OCH$_2$)	389, 391
IVe	54	89–90	1630	1090*	7.00–8.02 (9 H, m, Ar H and SCH) 5.26 (2 H, s, OCH$_2$)	423, 425, 427
IVf	60	123–24	1625	1080*	7.06–8.04 (9 H, m, Ar H and SCH) 5.26 (2 H, s, OCH$_2$) 2.24 (3 H, s, CH$_3$)	403, 405
Va	65	224–25	1640	1690	6.96–7.72 (10 H, m, Ar H and SCH)	359, 361
Vb	56	179–81	1640	1685	6.92–7.74 (9 H, m, Ar H and SCH)	393, 395, 397
Vc	58	135–136	1635	1685	6.96–7.74 (9 H, m, Ar H and SCH) 2.30 (3 H, s, CH$_3$)	373, 375
Vd	63	220–21	1640	1690	6.90–7.80 (10 H, m, Ar H and SCH) 5.22 (2 H, s, OCH$_2$)	389, 391
Ve	66	101–2	1635	1680	6.88–7.76 (9 H, m, Ar H and SCH) 5.20 (2 H, s, OCH$_2$)	423, 425, 427
Vf	70	264–65	1640	1690	6.92–7.72 (9 H, m, Ar H and SCH) 5.20 (2 H, s, OCH$_2$) 2.24 (3 H, s, CH$_3$)	403, 405

(0.02 mol) and thionyl chloride (0.025 mol) were refluxed in pyridine (50 mL) for 8 h. Pyridine was distilled under reduced pressure, and the residues were washed with water and recrystallized from ethanol. The yields, the melting points, and the spectral data of compounds IVa–f thus prepared are recorded in Table I.

2-Aryl[and (aryloxy)methyl]-6-(arylimino)-1,3,4-oxadiazolo[3,2-*d*]-1,3,4-dithiazines (Va–f). The compounds IIIa–f (0.02 mol) were treated with a solution of iodine in ethanol–water (80:20 v/v) until decolorization of iodine was no longer observed. On addition of NH_4OH to the reaction mixture, the desired products precipitated. The products were recrystallized from ethanol as light brown needles. The yields, the melting points, and the spectral data for the products Va–f obtained are given in Table I.

2-(2-Chlorophenyl)-5-(4-methylphenyl)-1,3,4-oxadiazolo-[3,2-*d*]-1,3,4-thiadiazin-6(5*H*)-one (VIc). The compound IVc (0.005 mol) and HgO (0.0055 mol) were refluxed in ethanol for 18 h (Silberg and Cosma, 1959). The precipitated HgS was filtered off, and the filtrate was concentrated and cooled to give VIc, which was recrystallized from ethanol.

VIc: yield 56%; mp 110–11 °C; IR 1670 (νC=O) and 1630 cm^{-1} (νC=N); ^{1}H NMR δ 7.02–7.94 (m, 9 H, aromatic *H* and SC*H*), 2.24 (s, 3 H, C*H*$_3$). Anal. Calcd for $C_{17}H_{12}ClN_3O_2S$: C, 57.06; H, 3.36; N, 11.75. Found: C, 57.42; H, 3.28; N, 11.68.

Antifungal Screening. The antifungal activity of compounds IIIa–f to Va–f was evaluated against *H. oryzae* and *C. saccharii*. The pure culture of test fungi, the pathogenicity of which was already verified, were obtained from the Division of Mycology and Plant Pathology, Indian Agricultural Research Institute, Delhi. Agar (bacterological grade) supplied by Sarrabhi M. Chemicals was used as such. Compounds IIIa–f to Va–f were screened by agar plate technique (Horsfall, 1945) at 1000, 100, and 10 ppm concentrations using Czapek's agar medium (Raper and Thom, 1968).

Suspensions of different concentrations of each compound viz. 10 000, 1000, and 100 ppm, were prepared in an acetone–water (20:80 v/v) mixture. One milliliter of each concentration of the test compounds was added separately to presterilized Petri dishes containing 9 mL of sterilized Czapek's agar medium to maintain the final concentration of 1000, 100, and 10 ppm. The compounds were thoroughly mixed with the medium by rotating the plates on table top, thus swirling the contents. A fungal disk of 5-mm diameter, cut out with the help of sterilized cork borer from the periphery of 1-week-old culture of the test fungus already planted on the Czapek's medium, was inoculated in the center of each plate in an inverted position to bring the mycelia in direct contact with the medium. Petri dishes containing 9 mL of Czapek's medium and 1 mL of acetone water (20:80 v/v) mixture served as controls. The number of replicate assays in each case was three, whereas six replications of controls were provided. The plates were incubated at 28 °C (±1 °C) for 96 h. No remarkable morphological change was observed in developing fungi. After 96 h, four diameters of the fungal colony, intersecting one another at about 45°, were measured with the help of a millimeter scale and percent inhibition of mycelial growth was calculated by

$$\% \text{ inhibition} = [(C - T) \times 100]/C$$

where C is the average diameter of the fungal colony (millimeter)

Table II. Antifungal Screening Results of Compounds IIIa–f to Va–f

compd	av % inhibition after 96 h against *H. oryzae* 1000 ppm	100 ppm	10 ppm	*C. saccharii* 1000 ppm	100 ppm	10 ppm
IIIa	42	27	14	43	23	12
IIIb	47	29	15	46	29	15
IIIc	44	28	14	44	28	14
IIId	58	36	16	61	42	19
IIIe	65	38	20	64	44	22
IIIf	63	37	18	61	34	18
IVa	68	49	24	67	46	22
IVb	94	68	47	92	66	47
IVc	77	53	29	77	55	25
IVd	74	50	26	72	47	24
IVe	98	70	51	99	69	51
IVf	83	61	48	84	60	41
Va	71	53	32	71	53	29
Vb	96	69	50	94	68	48
Vc	84	62	32	77	58	32
Vd	78	55	37	76	57	38
Ve	100	72	54	99	72	53
Vf	87	68	46	85	65	45
Dithane M-45[a]	100	85	72	100	83	70

[a] Commercial fungicide.

in control plates and T the average diameter of the fungal colony (millimeter) in treated plates.

Dithane M-45, a standard commercial fungicide, was also tested under similar conditions for comparing the results. The antifungal activity displayed by the tested compounds IIIa–f to Va–f is summarized in Table II.

RESULTS AND DISCUSSION

Chemoselectivity in the oxidative cyclization of III to IV and V may be rationalized by the "hard and soft acids and bases, *HSAB*, principle". The cyclization of III to IV with $SOCl_2$ involves the attack of hard N of the dithiocarbamate chain and that of the oxadiazole ring (N-3) on the hard S of $SOCl_2$, followed by the extrusion of SO (Barluenga et al., 1979). On the other hand, I_2, a soft Lewis acid, is attacked by the soft thionic S of the dithiocarbamate function, followed by the cyclization to V with elimination of HI. Further, the representative compound IVc was converted into their 6-one analogues VIc on treatment with HgO (see Experimental Procedures). This conversion, involving desulfurization of the exocyclic sulfur, provides chemical evidence for the assigned structure of IV.

From the antifungal screening data it is obvious that compounds IVa–f and Va–f inhibited more than 65% of growth of both the test fungi at 1000 ppm concentration and hence are antifungal. The most active of these compounds, viz. IVe, Vb, and Ve, exhibited antifungal action almost equivalent but not better than that of Dithane M-45 at 1000 ppm concentration and inhibited 48–54% of growth of both the fungal species even at 10 ppm. In spite of the fact that dithiocarbamates IIIa–f have a preformed open-chain skeleton of the 1,3,4-thiadiazine and 1,3,4-dithiazine rings, these were less toxic than their cyclized products IVa–f and Va–f, where the chain is closed, resulting in more planar and compact systems. This is in conformity with earlier observations that compact size and planarity of a molecule often enhances its pesticidal activities (Fischer and Summers, 1976; Chatt et al., 1956; Rothwell and Wain, 1964). The order of antifungal activity was found to be V > IV > III. It was noted that the introduction of a chloro group in the aryl moiety tended to augment the antifungal activity significantly over the introduction of a methyl group. Presumably, this is due to greater lipophilic character of the chloro group relative to that of methyl, which favors the permeation of the compound through lipoid layers of the fungal cell wall. The antifungal activity varied marginally with the fungal species.

Although some of the screened compounds, IVe, Vb, and Ve, were highly toxic to *H. oryzae* and *C. saccharii* at higher concentration (1000 ppm), the overall results are not so encouraging as one would expect from the combined performance of two biolabile dithiocarbamate and oxadiazole nuclei. This might be attributed to the partial saturation in the oxadiazolodithia(thiadia)zine ring systems resulting in the loss of planarity.

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