# Synthesis and Fungitoxicity of Rationally Designed Thiazolo-1,3-dithiins, -thiazines, and -oxathiins

Lal Dhar S. Yadav,* Sangeeta Sharma, and Anjum Vaish

Department of Chemistry, University of Allahabad, Allahabad 211 002, India

Dithioesters IVa–d obtained by Michael-type addition of *N*-aryldithiocarbamic acids IIIa,b to 3-aryl-5-benzylidenerhodanines IIa,b undergo intramolecular chemoselective heterocyclizations with concentrated $H_2SO_4$, NaOH, and $CH_3I$ to afford 3,7-diaryl-5-(arylimino)-2,3,5,7-tetrahydrothiazolo[4,5-*d*][1,3]dithiin-2-thiones Va–d, 3,4,7-triaryl-2,3,4,5,7-pentahydrothiazolo[4,5-*d*][1,3]thiazine-2,5-dithiones VIa–d, and 3,7-diaryl-5-(arylimino)-2,3,5,7-tetrahydrothiazolo[5,4-*e*][1,3]oxathiin-2-thiones VIIa–d, respectively. Fungitoxicities of the dithioesters and their cyclized products were evaluated in vitro against *Aspergillus niger* and *Fusarium oxysporium*. Some of the compounds displayed activities comparable with that of the commercial fungicide Dithane M-45. Structure–activity relationships for the screened compounds are discussed.

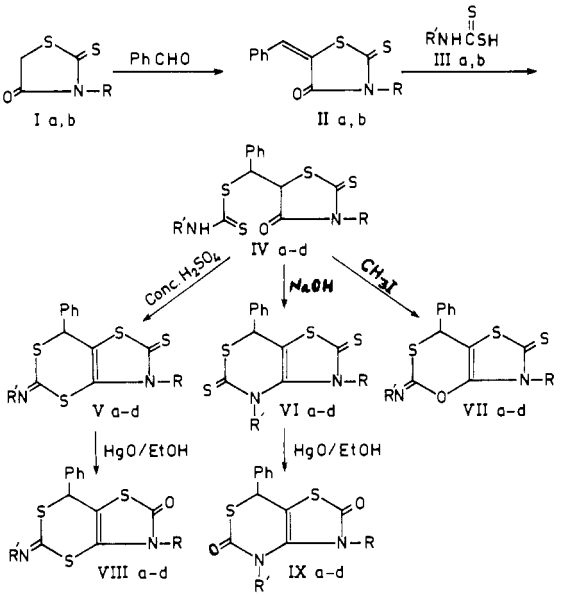
## INTRODUCTION

Dithiocarbamates have been extensively investigated for their fungitoxicity (Spencer, 1963; Thorn and Ludwig, 1962), and many of these, viz. maneb, zineb, Dithane M-45, ziram, thiram, and vapam, have attained major recognition as agricultural fungicides. Compounds bearing the dithiocarbamate grouping as a part of a heterocyclic structure have been relatively less studied, although some of these compounds are known to display useful pesticidal properties. For example, rhodanines are inherently toxic to microorganisms, especially to fungi and bacteria (Brown, 1961), and mylone is used as soil sterilant for controlling soil fungi, nematodes, weeds, and insects. Thus, we have been interested in the investigation of new fungicidal compounds rationally designed, in view of structure–activity relationships, to incorporate the dithiocarbamate grouping as a component of the heterocyclic framework and have already reported some such compounds with appreciable fungicidal activity (Singh et al., 1987; Yadav et al., 1991).

The present paper reports the study on new fungitoxic compounds V–VII which incorporate the toxophorically important dithiocarbamate and 1,3-dithiin, 1,3-thiazine, or 1,3-oxathiin moieties in the same heterocyclic structure. It is noteworthy that the compounds V–VII represent three types of hitherto unreported heterocyclic systems and have been synthesized from the same precursor IV by intramolecular chemoselective heterocyclizations as outlined in Scheme I. The requisite compounds IV were obtained by Michael addition of sulfur nucleophiles III to 5-benzylidenerhodanines II.

The structural assignments of the synthesized compounds were based on their IR, $^1$H NMR, and mass spectra (Table I) and elemental analyses (C, H, and N), which were quite compatible with those of the assigned structures. Of the tested compounds, IVa–d—VIIa–d, VIIId, and IXd, the compounds Vd, VId, and VIId exhibited in vitro fungicidal activity comparable with that of the commercial fungicide Dithane M-45 [a mixed manganous and zinc salt of *N*,*N*′-ethylenebis(dithiocarbamic acid)] at 1000 ppm concentration against *Aspergillus niger* and *Fusarium oxysporium*.

**Scheme I**




I–III : a, R = Ph; b, R = o-$MeC_6H_4$

IV–IX: a, R = R′ = Ph; b, R = Ph, R′ = o-$MeC_6H_4$;

c, R = o-$MeC_6H_4$, R′ = Ph; d, R = R′ = o-$MeC_6H_4$

## EXPERIMENTAL PROCEDURES

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 577 infrared spectrophotometer ($\nu_{max}$, $cm^{-1}$). $^1$H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer in $CDCl_3$ plus DMSO-$d_6$ using TMS as internal reference; chemical shifts are expressed in $\delta$. Mass spectra were recorded on a JEOL 300 mass spectrometer.

**3-Arylrhodanines (Ia,b).** These were prepared according to the method of Brown et al. (1956), and their analytical data agreed well with that already reported in the literature (Brown et al., 1956).

**3-Aryl-5-benzylidenerhodanines (IIa,b).** Condensation of an equimolar mixture of appropriate I and benzaldehyde furnished the benzylidene derivatives IIa,b as already reported in the literature (Zapadnyuk, 1962).

**(3-Arylperhydro-4-oxo-2-thioxothiazol-5-yl)phenylmethyl *N*-Aryldithiocarbamates (IVa–d).** These were prepared by Michael-type addition of *N*-aryldithiocarbamic acids IIIa,b, generated in situ, to IIa,b. Thus, the suspension of ammonium *N*-phenyldithiocarbamic acid (0.05 mol) in dioxane (250 mL)

* Author to whom correspondence should be addressed.

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**Table I. Yields, Melting Points, and Spectral Data of Compounds IV–IX**

| compd | yield, % | mp, °C | IR $\nu_{max}$, $cm^{-1}$ | $^1H$ NMR, $\delta$ | MS/M+, m/z |
|---|---|---|---|---|---|
| IVa | 88 | 156 | 3160 (NH), 1705 (C=O) | 6.52 (1 H, d, $J$ = 4 Hz, COCH), 6.63 (1 H, d, $J$ = 4 Hz, PhCH), 7.26–7.74 (15 H, m, Ar H), 9.38 (1 H, br s, NH) | 466 |
| IVb | 83 | 158–160 | 3150 (NH), 1705 (C=O) | 2.26 (3 H, s, Me), 6.50 (1 H, d, $J$ = 4 Hz, COCH), 6.63 (1 H, d, $J$ = 4 Hz, PhCH), 7.29–7.73 (14 H, m, Ar H), 9.36 (1 H, br s, NH) | 480 |
| IVc | 80 | 148 | 3160 (NH), 1700 (C=O) | 2.24 (3 H, s, Me), 6.52 (1 H, d, $J$ = 4 Hz, COCH), 6.60 (1 H, d, $J$ = 4 Hz, PhCH), 7.30–7.70 (14 H, m, Ar H), 9.38 (1 H, br s, NH) | 480 |
| IVd | 76 | 168–170 | 3150 (NH), 1700 (C=O) | 2.25 (6 H, s, 2 × Me), 6.49 (1 H, d, $J$ = 4 Hz, COCH), 6.60 (1 H, d, $J$ = 4 Hz, PhCH), 7.39–7.74 (13 H, m, Ar H), 9.35 (1 H, br s, NH) | 494 |
| Va | 86 | 144 | 1680 (C=N) | 6.76 (1 H, s, PhCH), 7.27–7.76 (15 H, m, Ar H) | 448 |
| Vb | 81 | 148–149 | 1685 (C=N) | 2.24 (3 H, s, Me), 6.74 (1 H, s, PhCH), 7.28–7.77 (14 H, m, Ar H) | 462 |
| Vc | 84 | 161 | 1680 (C=N) | 2.22 (3 H, s, Me), 6.75 (1 H, s, PhCH), 7.27–7.74 (14 H, m, Ar H) | 462 |
| Vd | 74 | 145 | 1685 (C=N) | 2.23 (6 H, s, 2 × Me), 6.74 (1 H, s, PhCH), 7.40–7.76 (13 H, m, Ar H) | 476 |
| VIa | 77 | 166 | [a] | 6.73 (1 H, s, PhCH), 7.27–7.74 (15 H, m, Ar H) | 448 |
| VIb | 80 | 173–175 | [a] | 2.23 (3 H, s, Me), 6.70 (1 H, s, PhCH), 7.26–7.75 (14 H, m, Ar H) | 462 |
| VIc | 76 | 194–196 | [a] | 2.22 (3 H, s, Me), 6.72 (1 H, s, PhCH), 7.25–7.76 (14 H, m, Ar H) | 462 |
| VId | 73 | 179–181 | [a] | 2.22 (6 H, s, 2 × Me), 6.70 (1 H, s, PhCH), 7.37–7.74 (13 H, m, Ar H) | 476 |
| VIIa | 82 | 177 | 1685 (C=N) | 6.79 (1 H, s, PhCH), 7.28–7.78 (15 H, m, Ar H) | 432 |
| VIIb | 80 | 114 | 1690 (C=N) | 2.26 (3 H, s, Me), 6.76 (1 H, s, PhCH), 7.28–7.78 (14 H, m, Ar H) | 446 |
| VIIc | 75 | 155 | 1685 (C=N) | 2.24 (3 H, s, Me), 6.72 (1 H, s, PhCH), 7.28–7.75 (14 H, m, Ar H) | 446 |
| VIId | 72 | 148–149 | 1690 (C=N) | 2.25 (6 H, s, 2 × Me), 6.71 (1 H, s, PhCH), 7.41–7.76 (13 H, m, Ar H) | 460 |
| VIIId | 66 | 163–164 | 1700 (C=O) 1685 (C=N) | 2.24 (6 H, s, 2 × Me), 6.75 (1 H, s, PhCH), 7.39–7.78 (13 H, m, Ar H) | 460 |
| IXd | 62 | 198–200 | 1700, 1670 (C=O) | 2.23 (6 H, s, 2 × Me), 6.73 (1 H, s, PhCH), 7.38–7.76 (13 H, m, Ar H) | 444 |

[a] No significant IR band above 1605 $cm^{-1}$.

was acidified with 5 N HCl (11 mL) to generate IIIa as a clear solution. To this solution was added compound IIa (0.05 mol), and the homogeneous mixture thus obtained was refluxed for 3 h and then concentrated to half of its volume, cooled, and poured into water to give the desired product IVa, which was recrystallized from ethanol as shining white needles. Following the same procedure, compounds IVb–d were also synthesized and recrystallized from ethanol. Yields, melting points, and spectral data of compounds IVa–d are recorded in Table I.

**3,7-Diaryl-5-(arylimino)-2,3,5,7-tetrahydrothiazolo[4,5-*d*][1,3]dithiin-2-thiones (Va–d).** The cyclodehydration of IVa–d furnished the corresponding Va–d. Thus, the neat compounds IVa–d (0.01 mol) were separately treated dropwise with concentrated $H_2SO_4$ (8 mL). The mixture in each case was cooled and poured into ice–water after 30 min. On neutralization with ammonia the desired precipitated products Va–d were recrystallized from ethanol. Yields, melting points, and spectral data of Va–d are recorded in Table I.

**3,4,7-Triaryl-2,3,4,5,7-pentahydrothiazolo[4,5-*d*][1,3]thiazine-2,5-dithiones (VIa–d).** A reaction mixture containing IVa (0.01 mol), 4% aqueous NaOH (33 mL), and ethanol (20 mL) was refluxed for 2 h, cooled, poured into water, and brought to pH 5–6 with 5 N HCl. The precipitate was filtered and recrystallized from ethanol to give VIa. Similarly, compounds VIb–d were prepared and recrystallized from ethanol. Yields, melting points, and spectral data of VIa–d are recorded in Table I.

**3,7-Diaryl-5-(arylimino)-2,3,5,7-tetrahydrothiazolo[5,4-*e*][1,3]oxathiin-2-thiones (VIIa–d).** An equimolar mixture of IV and methyl iodide was refluxed for 6 h in methanol. The progress of the reaction was indicated by the evolution of methanethiol. After completion of the reaction, the excess of solvent was evaporated, the residue was treated with 5% aqueous NaOH to remove HI, present as the salt of VII, and the product thus obtained was washed with water and recrystallized from ethanol to yield VII. Yields, melting points, and spectral data of compounds VIIa–d thus synthesized are given in Table I.

**Conversion of Vd and VId into Their -2-One and -2,5-Dione Analogs VIIId and IXd, Respectively.** Compound Vd (0.005 mol) and HgO (0.011 mol) were refluxed in ethanol (50 mL) for 13 h (Silberg and Cosma, 1959). The precipitated HgS was filtered off, and the filtrate was concentrated and cooled to furnish VIIId, which was recrystallized from ethanol as white needles. IXd was similarly prepared from VId and recrystallized from ethanol. Yields, melting points, and spectral data of VIIId and IXd are given in Table I.

**Antifungal Screening.** In vitro antifungal activity of compounds IVa–d—VIIa–d, VIIId, and IXd was evaluated against *A. niger* and *F. oxysporium* by poisoned food technique (Horsfall, 1945) at 1000, 100, and 10 ppm concentrations using Czapek's agar medium as described earlier (Yadav et al., 1989, 1991). A standard commercial fungicide, Dithane M-45, was also tested under similar conditions for comparison. No remarkable morphological change was observed in developing fungi. The antifungal screening results are summarized in Table II.

**Table II. Antifungal Screening Results of Compounds IV–IX**

| | av % inhibition after 96 h against | | | | | |
|---|---|---|---|---|---|---|
| | *A. niger* at | | | *F. oxysporium* at | | |
| compd | 1000 ppm | 100 ppm | 10 ppm | 1000 ppm | 100 ppm | 10 ppm |
| IVa | 48 | 26 | 8 | 51 | 28 | 10 |
| IVb | 50 | 29 | 10 | 53 | 32 | 12 |
| IVc | 52 | 31 | 12 | 55 | 35 | 16 |
| IVd | 55 | 33 | 13 | 59 | 37 | 18 |
| Va | 69 | 46 | 22 | 74 | 49 | 27 |
| Vb | 74 | 51 | 26 | 77 | 55 | 30 |
| Vc | 87 | 65 | 40 | 90 | 69 | 44 |
| Vd | 100 | 76 | 52 | 100 | 79 | 54 |
| VIa | 65 | 44 | 18 | 71 | 47 | 20 |
| VIb | 70 | 49 | 24 | 73 | 52 | 27 |
| VIc | 84 | 62 | 38 | 86 | 65 | 41 |
| VId | 97 | 73 | 50 | 99 | 76 | 51 |
| VIIa | 73 | 48 | 25 | 77 | 52 | 31 |
| VIIb | 78 | 54 | 30 | 80 | 57 | 33 |
| VIIc | 90 | 67 | 43 | 93 | 71 | 47 |
| VIId | 100 | 78 | 54 | 100 | 81 | 56 |
| VIIId | 74 | 56 | 39 | 77 | 61 | 42 |
| IXd | 63 | 50 | 36 | 72 | 56 | 38 |
| Dithane M-45 | 100 | 82 | 67 | 100 | 85 | 68 |

For the most active compounds Vd, VId, and VIId, it was ascertained whether these were fungistatic or fungicidal. Thus, following the procedure of Garber and Houston (1959), compounds Vd, VId, and VIId were added separately to Czapek's agar medium in different Petri dishes to maintain the final concentrations at their respective lethal doses (900, 950, and 825 ppm, respectively). The test fungi were inoculated in the center of these Petri dishes and incubated at 28 °C (±1 °C) for 96 h, after which time the percent inhibition of mycelial growth compared with that in the control dishes was recorded. Then the fungal disks were taken out from the treated as well as the control dishes, washed with sterilized double-distilled water, and reinoculated in fresh Petri dishes containing Czapek's agar medium only. The plates were incubated for 96 h at 28 °C (±1 °C), and percent inhibition compared with the dishes containing

the fungal disks taken from the control dishes was recorded. The number of replicate assays in each case was three, and six replicate controls were used. It was found that compounds Vd, VId, and VIId caused complete inhibition of mycelial growth of the test fungi and that there was no growth in the reinoculated fungal disks taken from the treated dishes. This shows that compounds Vd, VId, and VIId are fungicidal.

## RESULTS AND DISCUSSION

Chemoselectivity in the intramolecular cyclizations of the dithioesters IVa–d to the corresponding Va–d, VIa–d, and VIIa–d may be rationalized on the basis of the "hard and soft acids and bases (HSAB) principle". In the case of cyclization of IVa–d with concentrated $H_2SO_4$, the hard proton protonates the hard carbonyl oxygen, leading to the formation of Va–d via intramolecular nucleophilic attack by thionic S of the dithiocarbamate moiety (Ueno and Okawara, 1979). The soft Lewis acid methyl iodide methylates the thionic S of the dithiocarbamate moiety of IVa–d followed by cyclization to VIIa–d with the elimination of methanethiol, which could be easily detected (Ueno and Okawara, 1979). The reaction of NaOH with the dithioesters IVa–d furnishes N,S-ambident anion, the terminal nitrogen of which attacks the carbonyl carbon to yield the corresponding VIa–d [cf. Postovskii and Vereshchagina (1956)].

The isomeric compounds V and VI clearly differ in their IR spectra; V exhibited a strong band attributable to $\nu_{C=N}$ around 1680 $cm^{-1}$, whereas VI was devoid of this band. Further, the representative compounds Vd and VId were converted into their -6-one and -2,5-dione analogs VIIId and IXd, respectively, on treatment with HgO (see Experimental Procedures). This conversion involving desulfurization of the exocyclic sulfur provides chemical evidence for the assigned structures of the isomeric V and VI, as their desulfurated products VIII and IX are not isomeric.

It is obvious from the antifungal screening data (Table II) that the compounds V–IX significantly inhibited (65–100%) mycelial growth of the test fungi at higher concentration (1000 ppm) but their antifungal activity decreased markedly at lower concentrations (100 and 10 ppm). The most active of these compounds, Vd, VId, and VIId, displayed fungicidal action of the order of Dithane M-45 at 1000 ppm concentration and inhibited the growth of both test fungi by 50–56% even at 10 ppm concentration.

Although the dithioesters IVa–d have a preformed open-chain skeleton of -1,3-dithiin, -thiazine, and -oxathiin rings, these were less toxic than their cyclized products Va–d, VIa–d, and VIIa–d, where ring closure has resulted in more planar and compact systems. This is in conformity with the earlier observations that compact size and planarity of a molecule often enhance its pesticidal activities (Fischer and Summers, 1976; Singh et al., 1987; Yadav et al., 1989, 1991). In general, the order of fungitoxicity was found to be VII > V > VI > VIII > IX > IV. It was noted that the introduction of a methyl group in the aryl moiety of these compounds tended to augment the antifungal action. Presumably, this is due to the lipophilic character of the methyl group, which favors the permeation of the compound through lipoid barriers in the fungal cell membranes. However, besides the lipophilicity of the *o*-methyl group, the role of a steric factor is also possible in the fungitoxicity of the herein reported compounds. Comparison of the fungitoxicity of compounds Vd and VId with that of VIIId and IXd, respectively, clearly indicates that the replacement of the thionic sulfur by oxygen tends to reduce the antifungal activity considerably.

In conclusion, the new types of ring-fused heterocycles V–VII reported herein might be useful for developing efficacious, potentially commercially useful fungicides by optimizing the electronic and lipophilic properties of these compounds.

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**Registry No.** Ia, 1457-46-1; Ib, 23522-37-4; IIa, 13037-56-4; IIb, 126750-95-6; IIIa, 40231-24-1; IVa, 141344-13-0; IVb, 141344-14-1; IVc, 141344-15-2; IVd, 141344-16-3; Va, 141344-17-4; Vb, 141344-18-5; Vc, 141344-19-6; Vd, 141344-20-9; VIa, 141344-21-0; VIb, 141344-22-1; VIc, 141344-23-2; VId, 141344-24-3; VIIa, 141344-25-4; VIIb, 141344-26-5; VIIc, 141344-27-6; VIId, 141344-28-7; VIIId, 141344-29-8; IXd, 141344-30-1; $PhNHC(S)SH{\cdot}NH_3$, 1074-52-8.