Synthesis of New Fungicidal Imidazo- and Benzimidazo[2,1-*b*]-1,3-thiazinones Involving Ring Transformation of 5-Oxazolone Derivatives

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Michael-type addition of 2-imidazolidinethione (Ia) and 2-mercaptobenzimidazole (Ib) to 4-benzylidene-5-oxazolones IIa–e followed by ring transformation of the resulting Michael adducts IIIa–j yielded new compounds, 6-acet(and benz)amido-7-aryl-2,3,6,7-tetrahydro-5*H*-imidazo[2,1-*b*]-1,3-thiazin-5-ones IVa–e and 3-acet(and benz)amido-2-aryl-2,3-dihydro-4*H*-benzimidazo[2,1-*b*]-1,3-thiazin-4-ones IVa–j, respectively, in one pot. The compounds IIIa, IIIf, IIIi, and IVa–j were compared with Dithane M-45, a commercial fungicide, for their antifungal activity against *Aspergillus niger* and *Fusarium oxysporium*, and the results were correlated with the structural features of the tested compounds.

INTRODUCTION

The appreciable antifungal activity exhibited by some 1,2,4-triazolo[3,4-*b*]-1,3-thiazinones reported in our earlier papers (Yadav et al., 1988, 1989a) prompted us to design more compounds with certain structural modifications in the framework of this class of heterocyclic system. Among a wide variety of nitrogen heterocycles that have been used for developing useful pharmacological agents and agrochemicals, the imidazoles and benzimidazoles have played an important role. For example, the most used fungicides for controlling a variety of fungal diseases include imidazole derivatives, glyodin, climbazol, and imazalil, and benzimidazole systemic fungicides, benlate, carbendazim, and furidazol. The antifungal compound resulting from the autoxidation of nabam has been shown to be 5,6-dihydroimidazo[2,1-*c*]-1,2,4-dithiazole-3-thione (Beer et al., 1979).

In view of the above facts and our desire to develop agricultural fungicides of high potency, we have fused the biolabile imidazole and benzimidazole rings with 1,3-thiazine structure to probe how far this combination could work for the antifungal efficacy. The investigation was quite interesting because compounds IVa–j are hitherto unreported.

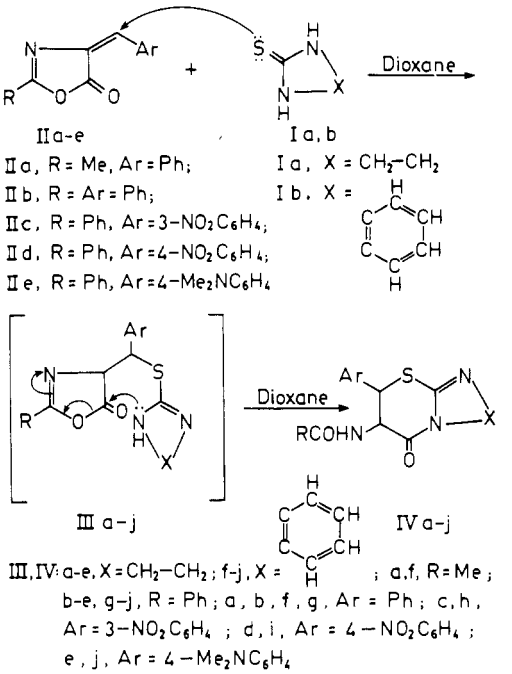
The synthetic route to compounds IVa–j is outlined in Scheme I. Similar to that reported in our earlier papers (Yadav et al., 1988, 1989a), Michael-type addition of Ia,b to IIa–e resulted in the Michael adducts IIIa–j, which underwent ring transformation to afford IVa–j in one pot. Structural assignments of the synthesized compounds were based on their elemental analyses and IR, ^{1}H NMR, and mass spectra (Table I). All of the compounds gave satisfactory microanalyses (C, H, and N). Of the tested compounds IIIa, IIIf, IIIi, and IVa–j, compounds IVa and IVd displayed in vitro fungicidal activity equivalent to that of a 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*.

EXPERIMENTAL PROCEDURES

Melting points were determined in open glass capillaries and are uncorrected. IR in KBr were recorded on a Perkin-Elmer 577 infrared spectrophotometer (ν_{max} cm^{-1}). ^{1}H NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer in $CDCl_3$ using TMS as an internal reference; chemical shifts are expressed in δ values. Mass spectra were recorded on a JEOL D-300 mass spectrometer.

Commercially available (Aldrich) 2-imidazolidinethione (Ia) and 2-mercaptobenzimidazole (Ib) were used without further purification.

Scheme I



4-Benzylidene-5-oxazolones IIa–e. Following the standard procedure (Vogel, 1978), *N*-acylglycines were treated with aromatic aldehydes in acetic anhydride to furnish IIa–e, which have already been reported in the literature (Vogel, 1978; Blatzzi and Davis, 1962; Meyer et al., 1975; Acheson et al., 1960).

6-Acet(and benz)amido-7-aryl-2,3,6,7-tetrahydro-5*H*-imidazo[2,1-*b*]-1,3-thiazin-5-ones IVa–e. Solutions of IIa–e (0.01 mol) and 2-imidazolidinethione (Ia, 0.01 mol) in dioxane (40 mL) were refluxed for 4 h and then concentrated to half of their volumes, cooled, and poured into water. The desired products thus precipitated were recrystallized from benzene as white needles.

According to the same procedure as described for IVa–e, compounds IVf–j were synthesized using 2-mercaptobenzimidazole (Ib) in place of Ia and recrystallized from benzene as light yellow needles.

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Table I. Yields, Melting Points, and Spectral Data of Compounds IVa–j

compd	yield, %	mp, °C	IR ($\nu_{C=O}$), cm^{-1}, thiazinone; amido	^1H NMR ($CDCl_3$), δ (J, Hz)	MS/M^+, m/z
IVa	86	133–134	1760; 1635	2.08 (3 H, s, COMe), 3.94 (4 H, s, CH_2CH_2), 6.60 (1 H, d, J = 5, 7-H), 6.71 (1 H, dd, J = 8, 6-H), 7.20–8.21 (5 H, m, Ar H), 8.60 (1 H, br s, NH)	289
IVb	88	151–152	1765; 1640	3.96 (4 H, s, CH_2CH_2), 6.61 (1 H, d, J = 5, 7-H), 6.72 (1 H, dd, J = 8, 6-H), 7.22–8.24 (10 H, m, Ar H), 8.62 (1 H, br s, NH)	351
IVc	83	165–166	1765; 1642	3.98 (4 H, s, CH_2CH_2), 6.64 (1 H, d, J = 5, 7-H), 6.73 (1 H, dd, J = 8, 6-H), 7.21–8.26 (9 H, m, Ar H), 8.63 (1 H, br s, NH)	396
IVd	84	222–224	1765; 1645	3.98 (4 H, s, CH_2CH_2), 6.66 (1 H, d, J = 5, 7-H), 6.74 (1 H, dd, J = 8, 6-H), 7.22–8.26 (9 H, m, Ar H), 8.64 (1 H, br s, NH)	396
IVe	80	207–208	1765; 1640	3.04 (6 H, s, Me_2N), 3.93 (4 H, s, CH_2CH_2), 6.60 (1 H, d, J = 5, 7-H), 6.71 (1 H, dd, J = 8, 6-H), 7.21–8.22 (9 H, m, Ar H), 8.61 (1 H, br s, NH)	394
IVf	83	117–118	1765; 1635	2.05 (3 H, s, COMe), 6.59 (1 H, d, J = 5, 2-H), 6.70 (1 H, dd, J = 8, 3-H), 7.22–8.20 (9 H, m, Ar H), 8.59 (1 H, br s, NH)	337
IVg	84	133–134	1760; 1638	6.60 (1 H, d, J = 5, 2-H), 6.72 (1 H, dd, J = 8, 3-H), 7.20–8.21 (14 H, m, Ar H), 8.60 (1 H, br s, NH)	399
IVh	79	141–142	1760; 1640	6.62 (1 H, d, J = 5, 2-H), 6.72 (1 H, dd, J = 8, 3-H), 7.20–8.24 (13 H, m, Ar H), 8.62 (1 H, br s, NH)	444
IVi	78	172–174	1760; 1640	6.63 (1 H, d, J = 5, 2-H), 6.73 (1 H, dd, J = 8, 3-H), 7.22–8.23 (13 H, m, Ar H), 8.63 (1 H, br s, NH)	444
IVj	76	167–168	1760; 1635	3.03 (6 H, s, Me_2N), 6.57 (1 H, d, J = 5, 2-H), 6.69 (1 H, dd, J = 8, 3-H), 7.22–8.20 (13 H, m, Ar H), 8.60 (1 H, br s, NH)	442

Yields, melting points, and spectral data of compounds IVa–j are recorded in Table I.

Isolation of Michael Adducts IIIa, IIIf, and IIIi. As representatives of the intermediates IIIa–j, the Michael adducts IIIa, IIIf, and IIIi were isolated. The procedure followed was the same as described above for the synthesis of IVa–j except the time of reflux, which was 1.5 h in this case instead of 4 h for IVa–j.

IIIa: yield 45%, mp 118–119 °C (from benzene); IR 1800 cm^{-1} ($\nu_{C=O}$); ^1H NMR δ 2.10 (3 H, s, Me), 3.28–4.22 (4 H, m, CH_2CH_2), 6.69 (1 H, d, J = 5, SCH), 6.78 (1 H, d, J = 5, 4-H oxazolone ring), 7.21–8.22 (5 H, m, Ar H), 9.22 (1 H, br s, NH); m/z 289 (M^+).

IIIf: yield 42%; mp 129–130 °C (from benzene); IR 1795 cm^{-1} ($\nu_{C=O}$); ^1H NMR δ 2.09 (3 H, s, Me), 6.69 (1 H, d, J = 5, SCH), 6.76 (1 H, d, J = 5, 4-H oxazolone ring), 7.20–8.21 (9 H, m, Ar H), 9.18 (1 H, br s, NH); m/z 337 (M^+).

IIIi: yield 41%; mp 144–145 °C (from benzene); IR 1805 cm^{-1} ($\nu_{C=O}$); ^1H NMR δ 6.71 (1 H, d, J = 5, SCH), 6.79 (1 H, d, J = 5, 4-H oxazolone ring), 7.23–8.24 (13 H, m, Ar H), 9.26 (1 H, br s, NH); m/z 444 (M^+).

Compounds IIIa, IIIf, and IIIi were converted into IVa, IVf, and IVi, respectively, in quantitative yield by refluxing in dioxane for 2.5 h.

Antifungal Screening. In vitro antifungal activity of compounds IIIa, IIIf, IIIi, and IVa–j 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., 1988, 1989b). A standard commercial fungicide, Dithane M-45, was also tested under similar conditions for comparison. No remarkable morphological change was observed in the developing fungi. The antifungal screening results are summarized in Table II.

For the most active compounds, IVa and IVd, it was ascertained whether these were fungistatic or fungicidal. Thus, following the procedure of Garber and Houston (1959), compounds IVa and IVd were added separately to Czapek's agar medium in different Petri dishes to maintain the final concentrations at their respective lethal doses (800 and 1000 ppm). 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 control dishes was recorded. Then the fungal disks were taken from the treated and 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 the percent inhibition was recorded. The number of replicate assays in each case was three, and six replicate controls were used. It was found that both compounds IVa and IVd caused complete inhibition of mycelial growth of the test fungi in treated as well as reinoculated dishes. This showed that compounds IVa and IVd were fungicidal.

Table II. Antifungal Screening Results of Compounds IIIa, IIIf, IIIi, and IVa–j

	av % inhibition against					
	A. niger at			*F. oxysporium* at		
compd	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IIIa	64	54	30	66	58	35
IIIf	61	49	21	65	52	26
IIIi	60	47	16	63	50	20
IVa	100	76	54	100	79	56
IVb	76	55	33	78	58	36
IVc	92	67	45	94	70	46
IVd	100	73	51	100	77	54
IVe	73	50	31	76	55	34
IVf	91	69	47	93	72	49
IVg	70	50	31	74	53	34
IVh	87	61	40	89	66	43
IVi	90	67	45	93	71	48
IVj	68	46	29	71	48	30
Dithane M-45	100	82	67	100	85	68

RESULTS AND DISCUSSION

Michael adducts IIIa–j resulting from the Michael-type addition of 2-imidazolidinethione (Ia) and 2-mercaptobenzimidazole (Ib) to 4-benzylidene-5-oxazolones IIa–e underwent intramolecular nucleophilic attack of the nitrogen atom of the imidazoline (and benzimidazole) ring at the carbonyl carbon (C-5) of the oxazolone nucleus with simultaneous cleavage of the oxazolone ring to yield IVa–j in one pot (Scheme I). This conclusion is based on the observation that the representative intermediate compounds IIIa, IIIf, and IIIi were isolated in 41–45% yield and that these could be converted into the respective final products IVa, IVf, and IVi quantitatively by refluxing in dioxane for 2.5 h (see Experimental Procedures).

It is obvious from the antifungal screening data (Table II) that compounds IVa–j significantly inhibited (68–100%) the mycelial growth of both test fungi at 1000 ppm concentration and hence are antifungal. Of these, the most active compounds, IVa and IVd, displayed fungicidal action equivalent to that of Dithane M-45 at 1000 ppm concentration and inhibited the growth of both test fungi by 51–56% even at 10 ppm concentration.

Although compounds IVa, IVf, and IVi containing the 1,3-thiazine ring are structural isomers of their precursors IIIa, IIIf, and IIIi, the former are by far more potent than the latter. This demonstrates that the presence of the 1,3-thiazine ring plays a key role in the fungitoxicity of these compounds. Likewise, the compounds bearing an acetamido and/or imidazo moiety are more fungitoxic than their benzamido and/or benzimidazo analogues. It was, however, noteworthy that (i) nitration of the phenyl nucleus augmented the antifungal activity appreciably, (ii) introduction of the nitro group at the para position was more effective than that at the meta position, (iii) introduction of a dimethylamino group reduced the fungitoxicity, and (iv) all of the tested compounds were marginally more potent against *F. oxysporium* than against *A. niger*.

The present study suggests that the fusion of imidazoline and 1,3-thiazine nuclei might result in fungicides of high potency if the substituents on the imidazo[2,1-*b*]-1,3-thiazine framework are optimized for the toxophoric requirements for fungi. Thus, the fungicidal compounds reported herein should be an excellent foundation for the development of efficacious fungicides of this class.

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Registry No. Ia, 96-45-7; Ib, 583-39-1; IIa, 881-90-3; IIb, 842-74-0; IIc, 15601-45-3; IId, 7152-75-2; IIe, 1564-29-0; IIIa, 137918-82-2; IIIf, 137918-83-3; IIIi, 137918-84-4; IVa, 137918-85-5; IVb, 137918-86-6; IVc, 137918-87-7; IVd, 137918-88-8; IVe, 137918-89-9; IVf, 137918-90-2; IVg, 137918-91-3; IVh, 137918-92-4; IVi, 137918-93-5; IVj, 137918-94-6; benzaldehyde, 100-52-7; 3-nitrobenzaldehyde, 99-61-6; 4-nitrobenzaldehyde, 555-16-8; 4-(dimethylamino)benzaldehyde, 100-10-7.