Synthesis and Fungitoxicity of New Peptidyl 1,3,4-Oxadiazolo[3,2-*a*]pyrimidin-5-ones

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Michael addition of nitrogen nucleophiles 2-amino-5-aryl-1,3,4-oxadiazoles **IIa**,**b** to 4-arylidene-5-oxazolones **Ia**,**b** followed by ring transformation of the resultant Michael adducts **IIIa**−**d** yielded 6-acetamido-2,7-diaryl-6,7-dihydro-5*H*-1,3,4-oxadiazolo[3,2-*a*]pyrimidin-5-ones **IVa**−**d** in a one-pot procedure. The compounds **IVa**−**d** on deacetylation furnished their 6-amino analogues **Va**−**d**, which were converted into their 6-peptidyl (Gly-Gly and Gly-L-Phe) amino derivatives **VIIa**−**h**. The compounds **III**−**V** and **VII** were evaluated in vitro for their fungitoxicities against *Aspergillus niger* and *Fusarium oxysporum*. 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.

Keywords: *Fungicide; peptide transport; nitrogen nucleophiles*

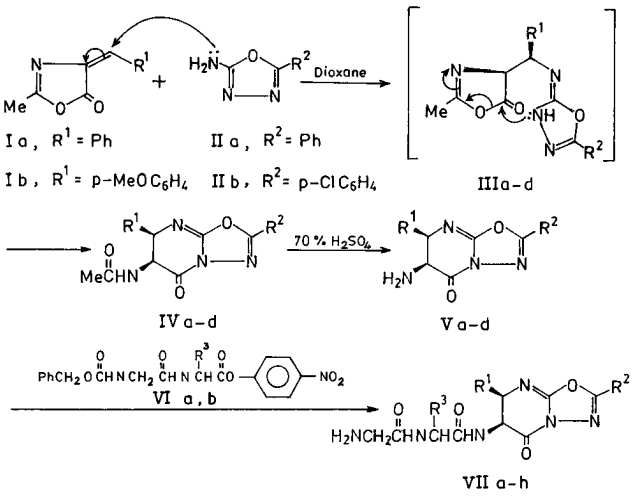
INTRODUCTION

The application of peptides as carriers for toxic agents into cells of pathogenic microorganisms has evoked considerable attention during the past two decades (Ames et al., 1973; Becker and Naider, 1980; Fickel and Gilvarg, 1973; Kingsbury et al., 1983, 1984; McCarthy et al., 1985; Menton et al., 1986). Various bacteria and fungi are now known to have peptide transport systems which translocate di- and oligopeptides against a concentration gradient (Becker and Naider, 1980; Fickel and Gilvarg, 1973; Kingsbury et al., 1983, 1984; McCarthy et al., 1985; Menton et al., 1986). Thus, peptides acting as carriers can deliver toxic agents into the cell, leading to a high intracellular concentration that ultimately causes cell death.

Likewise, owing to its presence in essential biomolecules such as nucleic acids, a pyrimidine nucleus has been widely used for developing various agrochemicals and pharmacological agents. Furthermore, some fused-ring systems derived from the fusion of a 1,3,4-oxadiazole nucleus with other biolabile heterocycles have been reported to display appreciable antifungal activity (Singh et al., 1987, 1989; Yadav et al., 1991, 1994).

The above facts coupled with our desire to develop efficacious agricultural fungicides prompted us to devise a convenient synthesis of the hitherto unknown title compounds **VII** incorporating the biolabile peptidyl, pyrimidine, and 1,3,4-oxadiazole moieties together. The nonpeptidyl compounds **III**−**V** are also new ones. The reaction sequence leading to the formation of **VII** is outlined in Scheme 1. Michael adducts **III** resulting from the Michael addition of nitrogen nucleophiles **II** to 5-oxazolones **I** underwent ring transformation to yield **VI** in a one-pot procedure (Yadav and Saigal, 1995). Compounds **IV** were deacetylated (Vogel, 1984b) to furnish their 6-amino analogues **V**, which were converted into 6-peptidyl(Gly-Gly and Gly-L-Phe)amino derivatives **VII** by coupling with *p*-nitrophenyl esters of *N*-benzyloxycarbonyl-protected peptides followed by deprotection by transfer hydrogenation with palladium black formic acid in methanol (El Amin et al., 1979) in

Scheme 1



III−VII: a,e, R^1 = Ph, R^2 = Ph; b,f, R^1 = Ph, R^2 = p-ClC$_6$H$_4$; c,g, R^1 = p-MeOC$_6$H$_4$, R^2 = Ph; d,h, R^1 = p-MeOC$_6$H$_4$, R^2 = p-ClC$_6$H$_4$; VIa, VII a−d, R^3 = H; VIb, VII e−h, R^3 = PhCH$_2$

72−83% yield. The structural assignments of the synthesized products were based on elemental analyses (C, H, and N) and IR and ^{1}H NMR spectra (Tables 1 and 2).

The formation of Michael adducts **III** and ring transformation to **IV** were highly diastereoselective. The diastereomeric ratios were checked with the crude isolates to avoid inadvertent alteration of these ratios during subsequent isolation and purification (see Experimental Procedures). Of the tested compounds **III**−**V** and **VII**, compounds **VIIb**−**d** displayed in vitro fungitoxicity 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 oxysporum* (Table 3).

EXPERIMENTAL PROCEDURES

Melting points were determined according to an open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 577 infrared spectrophotometer

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S0021-8561(95)00499-7 CCC: $12.00

Table 1. Analytical Data of Compounds III−V and VII

compd	yield, %	mp, °C	mol formula[a]
IIIa	45	250−253	$C_{19}H_{16}N_4O_3$
b	42	240−242	$C_{19}H_{15}ClN_4O_3$
c	40	236−239	$C_{20}H_{18}N_4O_4$
d	43	205−206	$C_{20}H_{17}ClN_4O_4$
IVa	70	230−232	$C_{19}H_{16}N_4O_3$
b	74	211−213	$C_{19}H_{15}ClN_4O_3$
c	78	236−238	$C_{20}H_{18}N_4O_4$
d	71	224−225	$C_{20}H_{17}ClN_4O_4$
Va	92	238−240	$C_{17}H_{14}N_4O_2$
b	90	188−189	$C_{17}H_{13}ClN_4O_2$
c	85	234−236	$C_{18}H_{16}N_4O_3$
d	88	184−185	$C_{18}H_{15}ClN_4O_3$
VIIa	65	244−246	$C_{21}H_{20}N_6O_4$
b	68	250−253	$C_{21}H_{19}ClN_6O_4$
c	79	254−257	$C_{22}H_{22}N_6O_5$
d	67	259−262	$C_{22}H_{21}ClN_6O_5$
e	62	273−276	$C_{28}H_{26}N_6O_4$
f	69	248−250	$C_{28}H_{25}ClN_6O_4$
g	80	278−281	$C_{28}H_{28}N_6O_5$
h	83	199−201	$C_{28}H_{27}ClN_6O_5$

[a] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.18, N ± 0.24.

(ν_{max} cm^{-1}). ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer in DMSO-d_6 using TMS as an internal reference; chemical shifts are expressed in δ values.

4-Arylidene-5-oxazolones (Ia,b). Following the standard procedure (Vogel, 1984a) acetylglycine was treated with the appropriate aromatic aldehyde in acetic anhydride to furnish **Ia**,**b**, which agreed well with the data already reported in the literature (Vogel, 1984a).

2-Amino-5-aryl-1,3,4-oxadiazoles (IIIa,b). These were prepared by oxidative cyclization of the appropriate aldehyde semicarbazone with bromine in glacial acetic acid in the presence of anhydrous sodium acetate following the method of Gibson (1962). **IIa**,**b** agreed well with their analytical data already reported in the literature (Gibson, 1962).

6-Acetamido-2,7-diaryl-6,7-dihydro-5*H*-1,3,4-oxadiazolo-[3,2-*a*]pyrimidin-5-ones (IVa−d). An equimolar mixture of oxazolone (**I**) and 1,3,4-oxadiazole (**II**) was dissolved in a minimum amount of dioxane, and the solution was refluxed for 20−22 h. The reaction mixture was concentrated, cooled, and poured into water. The yellowish precipitate thus obtained was washed with water to give the crude product, which was recrystallized from ethanol to give a diastereoisomeric mixture (>97:<3 as determined by ^{1}H NMR spectroscopy). The diastereomeric ratios were also checked with crude isolates to avoid inadvertent alteration of these ratios (>94:<6) during subsequent isolation and purification. The products on second recrystallization from ethanol furnished an analytical sample of a single diastereoisomer **IV**. On the basis of ^{1}H NMR spectra and general literature precedent (Booth et al., 1991; Eliel, 1962; Hirayama et al., 1982), *cis* stereochemistry was assigned to **IV**, as the coupling constant ($J_{6,7}$ = 4 Hz) for **IV** was lower than that for the very minor (<3%) diastereoisomer (*trans*) ($J_{6,7}$ = 9 Hz).

Isolation of the Michael Adducts IIIa−d and Their Conversion into the Corresponding Ring-Transformed Products IVa−d. The procedure followed was the same as described above for the synthesis of **IV** except that the time of reflux in this case was 14−16 h. The Michael adducts were recrystallized from ethanol to give a diastereoisomeric mixture (>95:<5; in the crude products the ratio was >90:<10 as determined by ^{1}H NMR spectroscopy), which was again recrystallized from ethanol to obtain analytical samples. The adducts **IIIa−d** were assigned the *erythro*/*syn* stereochemistry, as the ^{1}H NMR spectra exhibited a lower coupling constant, $J_{\text{cyclic NCH, acyclic NCH}}$ = 4 Hz, than that of the very minor (<5%) diastereoisomer (*threo* or *anti*), $J_{\text{cyclic NCH, acyclic NCH}}$ = 9 Hz (Eliel, 1962; Mukaiyama and Iwasawa, 1984; Tanikaga et al., 1988).

The intermediate compounds **IIIa−d** were refluxed in dioxane for 3−4 h to give the corresponding products **IVa−d** quantitatively.

6-Amino-2,7-diaryl-6,7-dihydro-5*H*-1,3,4-oxadiazolo-[3,2-*a*]pyrimidin-5-ones (Va−d). Compound **IV** (0.01 mol) was refluxed in H_2SO_4−H_2O (60 mL, 4:3, v/v) for 30 min. The reaction mixture was cooled and basified with concentrated NH_4OH (specific gravity 0.88) under ice cooling. The yellowish precipitate thus obtained was washed with water and recrystallized from ethanol to afford light yellow needles of the desired products (**Va−d**).

2,7-Diaryl-6,7-dihydro-6-peptidyl(Gly-Gly and Gly-L-Phe)amino-5*H*-1,3,4-oxadiazolo[3,2-*a*]pyrimidin-5-ones (VIIa−h). To a solution of **V** (0.003 mol) and *p*-nitrophenyl *N*-benzyloxycarbonylglycylglycinate (or *p*-nitrophenyl *N*-benzyloxycarbonylglycyl-L-phenylalaninate) (0.003 mol) in DMF−H_2O (150 ml 1:1, v/v) was added 1-hydroxybenzotriazole (0.003 mol), and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue on trituration with ether yielded a light brown solid which was washed with water and was used for transfer hydrogenation without further purification. Thus, to a solution of the *N*-benzyloxycarbonyl derivative obtained above (0.002 mol) in methanol (60 mL) and DMF (20 mL) were added Pd black (0.55 g) and formic acid (4.5 ml, 88%). After 1.5 h of stirring at room temperature, the catalyst was filtered off, and the filtrate was basified with NH_4OH and evaporated to dryness under reduced pressure. The solid thus obtained was recrystallized from ethanol to give light yellow crystals of the desired products (**VIIa−h**).

Yields, melting points, molecular formulas, and elemental analyses of compounds **III−V** and **VII** are recorded in Table 1 and spectral data in Table 2.

Antifungal Screening. In vitro antifungal activity of compounds **III−VIII** was evaluated against *A. niger* and *F. oxysporum* 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). The number of replicate assays in each case was three, and six replicate controls were used. 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 3.

For the most active compounds **VIIa−d** it was ascertained whether these were fungistatic or fungicidal. Thus, following the procedure of Garber and Houston (1959), compounds **VIIb−d** were added separately to Czapek's agar medium in different Petri dishes to maintain the final concentrations at their respective lethal does (900, 1000, and 800 ppm). The test fungi were inoculated in the center of these Petri dishes and incubated at 28 ± 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 ± 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 compounds **VIIb−d** caused complete inhibition of mycelial growth of the test fingi in treated as well as reinoculated dishes and hence were fungicidal.

RESULTS AND DISCUSSION

The formation of oxadiazolopyrimidinones **IVa−d** involves the Michael addition of nitrogen nucleophiles 2-amino-1,3,4-oxadiazoles **IIa**,**b** to 4-arylidene-5-oxazolones **Ia**,**b** to give the Michael adducts **IIIa−d**, which undergo intramolecular attack of the nitrogen atom of the oxadiazole ring (N-3) at the carbonyl carbon (C-5) of the oxazolone ring to yield **IVa−d** (Scheme 1). This conclusion is based on the observation that the intermediate compounds **IIIa−d** could be isolated in 45−50% yield (see Experimental Procedures) during the reaction and were converted into **IVa−d** quantitatively.

Table 2. Spectral Data of Compounds III−V and VIII

compd	IR(KBr) $\nu_{C=O}$, cm^{-1}	^1H NMR (DMSO-d_6), δ (J, Hz)
IIIa	1795	2.13 (3H, s, Me), 6.68 (1H, d, J = 4, acyclic NCH), 6.80 (1H, d, J = 4, cyclic NCH), 7.10−8.00 (10H, m, ArH), 9.90 (1H, br s, NH)
IIIb	1795	2.12 (3H, s, Me), 6.69 (1H, d, J = 4, acyclic NCH), 6.80 (1H, d, J = 4, cyclic NCH), 7.12−8.03 (9H, m, ArH), 9.93 (1H, br s, NH)
IIIc	1790	2.10 (3H, s, Me), 3.74 (3H, s, OCH3), 6.66 (1H, d, J = 4, acyclic NCH), 6.78 (1H, d, J = 4, cyclic NCH), 7.13−7.98 (9H, m, ArH), 9.89 (1H, br s, NH)
IIId	1790	2.11 (3H, s, Me), 3.76 (3H, s, OCH3), 6.68 (1H, d, J = 4, acyclic NCH), 6.79 (1H, d, J = 4, cyclic NCH), 7.14−8.02 (8H, m, ArH), 9.94 (1H, br s, NH)
IVa	1765, 1635	2.11 (3H, s, Me), 6.64 (1H, d, J = 4, 7-H), 6.75 (1H, dd, J = 4 and 8, 6-H), 7.09−7.98 (10H, m, ArH), 8.60 (1H, br s, NH)
IVb	1765, 1640	2.09 (3H, s, Me), 6.65 (1H, d, J = 4, 7-H), 6.76 (1H, dd, J = 4 and 8, 6-H), 7.13−8.01 (9H, m, ArH), 8.62 (1H, br s, NH)
IVc	1760, 1635	2.08 (3H, s, Me), 3.75 (3H, s, OMe), 6.62 (1H, d, J = 4, 7-H), 6.74 (1H, dd, J = 4 and 8, 6-H), 7.12−7.96 (9H, m, ArH), 8.61 (1H, br s, NH)
IVd	1760, 1640	2.09 (3H, s, Me), 3.76 (3H, s, OMe), 6.63 (1H, d, J = 4, 7-H), 6.75 (1H, dd, J = 4 and 8, 6-H), 7.12−8.01 (8H, m, ArH), 8.64 (1H, br s, NH)
Va	1760	2.90 (2H, s, NH_2), 6.62 (1H, d, J = 4, 7-H), 6.71 (1H, d, J = 4, 6-H), 7.08−7.98 (10H, m, ArH)
Vb	1765	2.93 (2H, s, NH_2), 6.64 (1H, d, J = 4, 7-H), 6.73 (1H, d, J = 4, 6-H), 7.11−8.02 (9H, m, ArH)
Vc	1760	2.91 (2H, s, NH_2), 3.74 (3H, s, OMe), 6.60 (1H, d, J = 4, 7-H), 6.69 (1H, d, J = 4, 6-H), 7.13−7.99 (9H, m, ArH)
Vd	1765	2.93 (2H, s, NH_2), 3.76 (3H, s, OMe), 6.62 (1H, d, J = 4, 7-H), 6.71 (1H, d, J = 4, 6-H), 7.15−8.01 (8H, m, ArH)
VIIa	1765, 1635	2.88 (2H, s, NH_2), 4.54, 4.59 (4H, two s, each CH_2), 6.63 (1H, d, J = 4, 7-H), 6.77 (1H, dd, J = 4 and 8, 6-H), 7.08−7.99 (10H, m, ArH), 8.62 (2H, br s, 2 × NH)
VIIb	1765, 1640	2.86 (2H, s, NH_2), 4.55, 4.58 (4H, two s, each CH_2), 6.65 (1H, d, J = 4, 7-H), 6.78 (1H, dd, J = 4 and 8, 6-H), 7.14−8.02 (9H, m, ArH), 8.64 (2H, br s, 2 × NH)
VIIc	1760, 1635	2.83 (2H, s, NH_2), 3.76 (3H, s, OMe), 6.64 (1H, d, J = 4, 7-H), 6.75 (1H, dd, J = 4 and 8, 6-H), 7.13−7.98 (9H, m, ArH), 8.63 (2H, br s, 2 × NH)
VIId	1760, 1640	2.85 (2H, s, NH_2), 3.77 (3H, s, OMe), 6.65 (1H, dd, J = 4 and 8, 6-H), 7.14−8.03 (8H, m, ArH), 8.65 (2H, br s, 2 × NH)
VIIe	1765, 1635	2.89 (2H, s, NH_2), 3.20 (2H, d, J = 7, CH_2), 4.55 (2H, s, CH_2), 5.05 (1H, t, J = 7, CH), 6.64 (1H, d, J = 4, 7-H), 6.76 (1H, dd, J = 4 and 8, 6-H), 7.08−7.98 (15H, m, ArH), 8.63 (2H, br s, 2 × NH)
VIIf	1765, 1640	2.87 (2H, s, NH_2), 3.22 (2H, d, J = 7, CH_2), 4.56 (2H, s, CH2), 5.07 (1H, t, J = 7, CH), 6.66 (1H, d, J = 4, 7-H), 6.78 (1H, dd, J = 4 and 8, 6-H), 7.12−8.01 (14H, m, ArH), 8.66 (2H, br s, 2 × NH)
VIIg	1760, 1635	2.86 (2H, s, NH_2), 3.20 (2H, d, J = 7, CH_2), 3.77 (3H, s, OMe), 4.54 (2H, s, CH_2), 5.04 (1H, t, J = 7, CH), 6.65 (1H, d, J = 4, 7-H), 6.77 (1H, dd, J = 4 and 8, 6-H), 7.13−7.99 (14H, m, ArH), 8.64 (2H, br s, 2 × NH)
VIIh	1760, 1640	2.84 (2H, s, NH_2), 3.21 (2H, d, J = 7, CH_2), 3.78 (3H, s, OMe), 4.57 (2H, s, CH_2), 5.06 (1H, t, J = 7, CH), 6.66 (1H, d, J = 4, 7-H), 6.78 (1H, dd, J = 4 and 8, 6-H), 7.12−8.04 (13H, m, ArH), 8.66 (2H, br s, 2 × NH)

Table 3. Antifungal Screening Results of Compounds III−V and VII

	av % inhibition after 96 h against					
	A. niger at			*F. oxysporum* at		
compd	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IIIa	36	24	11	38	27	14
IIIb	40	33	19	43	35	20
IIIc	38	27	14	40	30	17
IIId	45	32	22	48	34	25
IVa	61	48	35	64	52	40
IVb	66	52	41	69	55	43
IVc	63	50	38	67	54	42
IVd	69	58	46	72	60	48
Va	55	43	31	58	46	35
Vb	61	48	35	64	49	38
Vc	58	45	32	61	47	37
Vd	61	52	38	65	54	40
VIa	42	33	26	46	36	29
VIb	38	27	16	41	31	19
Gly-Gly	36	30	19	38	31	21
Gly-L-Phe	33	25	15	35	28	17
VIIa	84	61	47	87	67	49
VIIb	100	72	52	100	74	53
VIIc	98	68	50	100	71	51
VIId	100	75	55	100	78	57
VIIe	78	62	41	82	65	45
VIIf	90	62	46	93	68	48
VIIg	85	68	44	88	66	47
VIIh	92	72	48	94	75	49
Dithane M-45	100	83	66	100	86	67

It is obvious from the antifungal screening data (Table 3) that most of the screened compounds have significant fungitoxicity at higher concentration (1000 ppm) against both test fungi, but their toxicity considerably decreased on dilution (100 and 10 ppm).

Of the tested compounds, the most active dipeptidyl compounds **VIIb−d** displayed fungicidal action comparable with that of Dithane M-45 at 1000 ppm and inhibited 52−57% mycelial growth of both fungal species even at 10 ppm concentration.

Although compounds **IVa−d** containing the pyrimidine nucleus are the structural isomers of their precursors **IIIa−d**, the former are by far more potent than the latter. This demonstrates that the presence of the pyrimidine nucleus plays a key role in the fungitoxicity of these compounds. Likewise, 6-amino compounds **Va−d** are less active than the 6-acetamido derivatives **IVa−d**. It is noteworthy that the conversion of compounds **Va−d** into their dipeptidyl derivatives **VIIa−h** resulted in the appreciable enhancement of fungitoxicity.

The present study indicates that the 1,3,4-oxadiazolo-[3,2-*a*]pyrimidin-5-one framework reported herein might be useful for developing efficacious fungicides by achieving a suitable combination of the peptidyl moiety and substituents present on this fused ring bicyclic system.

ACKNOWLEDGMENT

We sincerely thank Professor H. P. Tiwari, Head, Department of Chemistry, University of Allahabad, for providing laboratory facilities and RSIC, Lucknow, for microanalyses and spectra. R.Y. sincerely thanks UGC, New Delhi, for the award of a Project Assistantship.

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Received for review July 27, 1995. Revised manuscript received February 29, 1996. Accepted March 18, 1996.[⊗]

JF950499U

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1996.