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Synthesis and Fungitoxicity of Some Oxadiazole Derivatives Derived from Terephthalic Acid

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Some bis-1,4-(5-aryl-1,3,4-oxadiazol-2-yl)benzenes, bis-1,4-(5-thio-1,3,4-oxadiazol-2-yl)benzene and its 5-thioacetic acid and 5-thioethyl-acetate derivatives were synthesised starting from terephthalic acid. These compounds were screened for their antifungal activity against *Aspergillus flavus, Helminthosporium tetramera* and *Penicillium decombens.*

INTRODUCTION

A series of new 2,5-disubstituted-1,3,4-oxadiazoles carrying 1,2-diarylethyl/aryloxyalkyl moieties at 2-position and phenyl, amino, mercapto, thioacetic or ethylthioacetate groups at 5- position were synthesised and evaluated for their pharmacological activity. Some of them exhibited mild to strong antiinflammatory and CNS depressant activity[1]. Recently some bis-1,4-(5-arylamino-1,3,4-oxadiazol-2-yl)benzenes were synthesised starting from terephthalic acid and screened for their antifungal activity in our laboratory[2]. These compounds showed significant fungitoxicity. In view of the above observations, terephthalic acid was converted to its diethyl ester (I) and then to terephthalic acid hydrazide (II), which on cyclisation with substituted benzoic acids in presence of $POCl_3$ gave bis-1,4-(5-aryl-1,3,4-oxadiazol-2-yl)benzene (III). Cyclisation of terephthalic acid hydrazide in presence of KOH and CS_2 gave bis-1,4-(5-thio-1,3,4-oxadiazol-2-yl)benzene (IV), which on further treatment with chloroacetic acid and chloro ethyl acetate yielded its 5-thioacetic acid (V) and 5-thioethyl acetate (VI) derivatives respectively. Various steps involved in the synthesis are shown in Scheme I. Compounds III, IV, V and VI were screened for their antifungal activity against *A. flavus*, *H. tetramera* and *P. decombens.*

EXPERIMENTAL

Melting points were taken in open capillaries in an electric melting point apparatus and are uncorrected. Infrared spectra of the compounds were recorded in KBr pellets, while PMR spectra were recorded on a 60 MHz spectrometer using TMS as an internal standard. Diethylterephthalate (I) and terephthalic acid hydrazide (II) were prepared by the reported procedure[3].

Bis-1,4-(5-aryl-1,3,4-oxadiazol-2-yl)benzenes (III)

A mixture of terephthalic acid hydrazide(II) (0.01 mole) and substituted benzoic acids (0.02 mole) was refluxed in $POCl_3$ (15 mL) for about 5 h. The

reaction mixture was poured in an ice-cold water. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution followed by water, dried and crystallised from dilute acetic acid. Various bis-1,4-(5-aryl-1,3,4-oxadiazol-2-yl)benzenes thus synthesised are recorded in Table-1.

TABLE-1
ANALYTICAL AND SPECTRAL DATA OF BIS-1,4-(5-ARYL-1,3,4-OXADIAZOL-2-YL)BENZENES(III)

Compd. No.	R	m.p. (°C)	Yield (%)	Molecular formula	N (%)	
					Found	Calcd.
IIIa	C_6H_5	235	84.88	$C_{22}H_{14}N_4O_2$	15.45	15.30
IIIb	p-ClC_6H_4	205	73.56	$C_{22}H_{12}N_4O_2Cl_2$	12.99	12.87
IIIc	p-$NH_2C_6H_4$	170	88.38	$C_{22}H_{16}N_6O_2$	21.00	21.21
IIId	p-OHC_6H_4	>250	70.35	$C_{22}H_{14}N_4O_4$	13.93	14.07
IIIe	o-ClC_6H_4	>250	54.47	$C_{22}H_{12}N_4O_2Cl_2$	12.99	12.86
IIIf	o-$NH_2C_6H_4$	235	88.38	$C_{22}H_{16}N_6O_2$	21.01	21.21
IIIg	o-OHC_6H_4	230	80.45	$C_{22}H_{14}N_4O_4$	13.92	14.07
IIIh	p-$CH_3C_6H_4$	180	86.45	$C_{24}H_{18}N_4O_2$	14.35	14.21
IIIi	p-$OCH_3C_6H_4$	170	77.46	$C_{24}H_{18}N_4O_4$	13.28	13.15

IIIb ν cm^{-1} (KBr): 3080, 3000 (aromatic C—H), 1615 (C=N), 1560 (C=C, aromatic), 840 (1,4-disubstituted benzene).

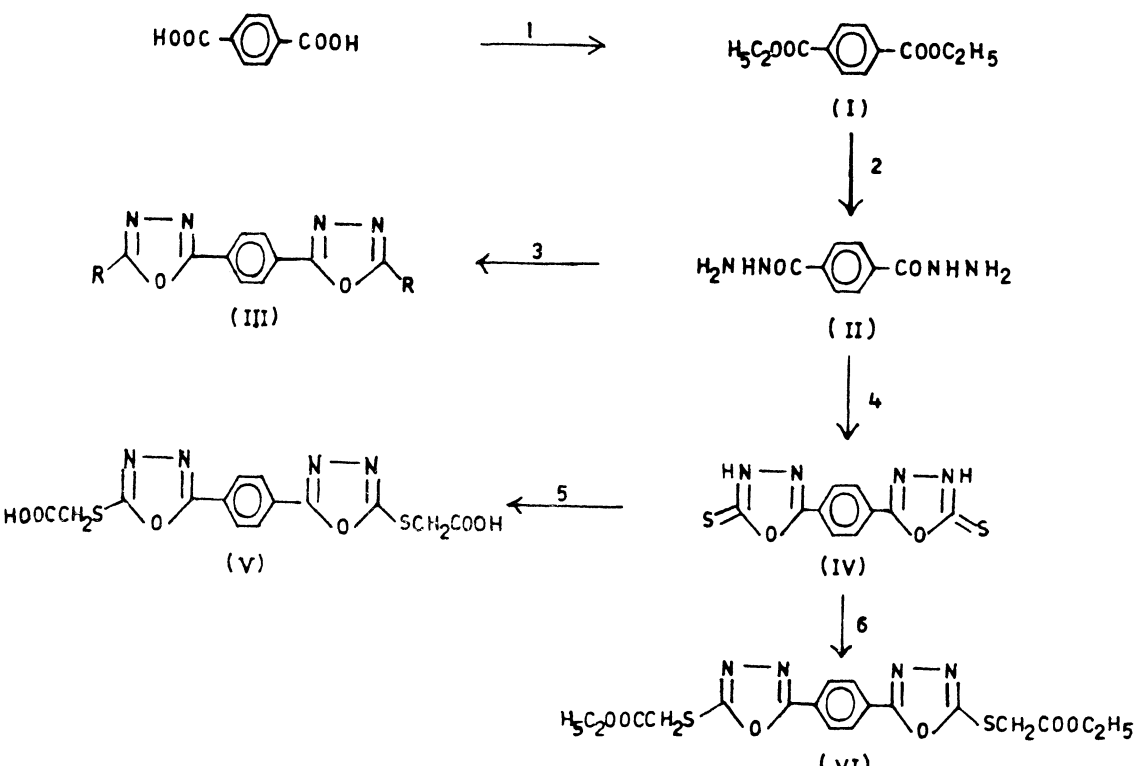
Bis-1,4-(5-thio-1,3,4-oxadiazol-2-yl)benzene (IV)

A mixture of terephthalic acid hydrazide (0.1 mole), KOH (0.2 mole), carbon disulphide (60 mL) was heated under reflux until the evolution of H_2S ceased. The reaction mixture was concentrated, dissolved in water and acidified with dil. HCl. The precipitate thus obtained was filtered, washed with water, dried and crystallised from dilute acetic acid, mol. formula $C_{10}H_6N_4O_2S_2$, m.p. 250°C, yield 62.95% (found: N 20.34, S 20.82%; calcd.: N 20.14, S 23.02%), IR (KBr, ν_{max} cm^{-1}): 3100 (NH, stretch), 2940 (C—H, aromatic), 1645 (C=N), 1570 (C=C, aromatic), 815 (1,4-disubstituted benzene), PMR (DMSO-d_6, δ ppm): 6.7–7.9 (m, 4H, ArH).

Bis-1,4-(5-thioacetic acid-1,3,4-oxadiazol-2-yl)benzene (V)

A mixture of bis-1,4-(5-thio-1,3,4-oxadiazol-2-yl)benzene (IV) (0.05 mole), NaOH (8%, 10 mL) and monochloroacetic acid (0.1 mole) was heated under reflux for 5–6 h. The reaction mixture was poured into cold water. The precipitate thus obtained was filtered, washed with water, dried and crystallised from ethanol, mol. formula: $C_{14}H_{10}N_4O_6S_2$, m.p. > 250°C, yield 63.45% (found: N 14.31, S 17.86%; calcd.: N 14.21, S 16.24%), IR (KBr, ν cm^{-1}): 1770 (C=O), 1610 (C=C,

SCHEME I



1. PCl_5, C_2H_5OH 2. $NH_2NH_2.H_2O$. 3. $RCOOH/POCl_3$ 4. CS_2/KOH 5. $ClCH_2COOH$ 6. $ClCH_2COOC_2H_5$

aromatic, C=N stretch), 770 (1,4-disubstituted benzene), PMR (DMSO-d_6, δ ppm): 3.85 (s, 4H, $2CH_3$), 7.5–8.0 (m, 4H, ArH).

Bis-1,4-(5-thioethylacetate-1,3,4-oxadiazol-2-yl)benzene(VI)

A mixture of bis-1,4-(5-thio-1,3,4-oxadiazol-2-yl)benzene (0.05 mole), NaOH (8%, 10 mL) and chloroethyl acetate (0.1 mole) was heated under reflux for 5–6 h. The reaction mixture was cooled and poured into cold water. The precipitate thus obtained was filtered, dried and crystallised from ethanol, mol. formula: $C_{18}H_{18}N_4O_6S_2$, m.p. > 250°C, yield 51.11% (found: N 13.68, S 15.64%; Calcd.: N 12.44, S 14.22%), IR (KBr, ν cm^{-1}): 3080 (C—H), 1760 (C=O), 1680 (C=N), 1600 (C=C, aromatic). PMR spectra could not be determined due to the poor solubility of the compound in DMSO-d_6 and other solvents.

Screening for antifungal activity

Compounds III, IV, V and VI were screened for their antifungal activity against *A. flavus*, *H. tetramera* and *P. decombens* as the test fungi by paper-disc plate method[4] at concentration levels 2.0 and 0.2% (w/v) in dimethylsulphoxide. Standard PDA medium was used. Filter paper discs of 12 mm diameter were used and the diameters of zones of inhibition formed around each disc after incubating for a period of 48 h at 25–30°C were recorded. Results are compared with reference fungicides, Dithane Z-78 and Thiram 75W. Antifungal activity results of compounds (III) indicate that the compounds having phenyl nucleus showed moderate antifungal activity against *P. decombens* and *H. tetramera* at both the test concentrations, while it was inactive against *A. flavus*. Introduction of chloro and hydroxy substituents at *o*- and *p*- position of the phenyl nucleus resulted in an increase in the fungicidal activity. Highest fungicidal activity was shown by the compound (IIIg) which was comparable to that of the reference fungicides. Compounds IV, V and VI did not exhibit any significant antifungal activity against the test fungi.

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