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SYNTHESIS OF NEW 5,3/5 AND 2-SUBSTITUTED (1,3,4)-OXADIAZOLES AND THEIR RELATED PRODUCTS AS POTENTIAL ANTIFUNGAL AND ANTIVIRAL AGENTS

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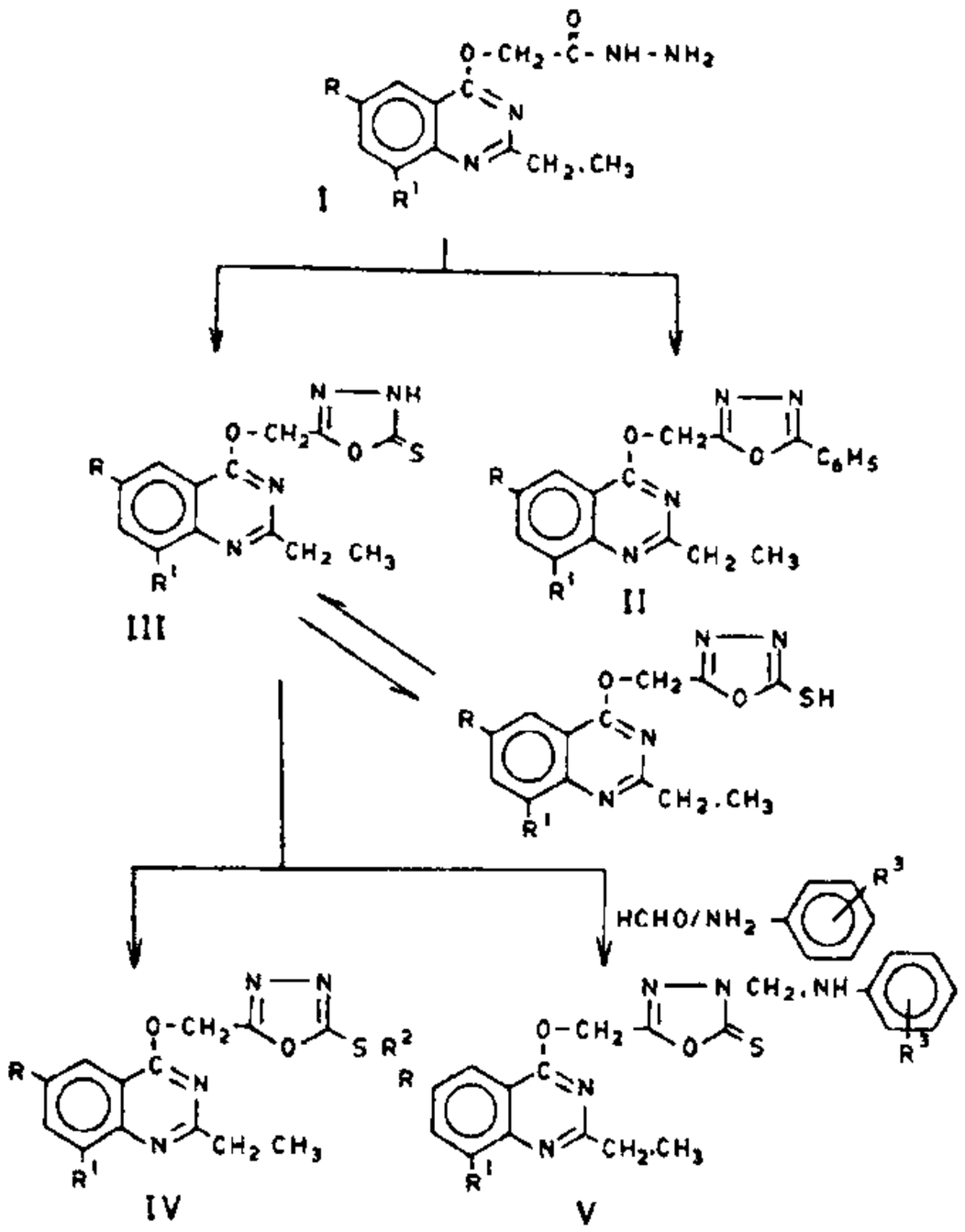
ABSTRACT

Three 5-(6′,8′-disubstituted-2′-ethyl-quinazolin-4'-oxymethyl)-2-mercapto-1,3,4-oxadiazoles (III) were synthesised by the cyclisation of N-(6′,8′-disubstituted-2′-ethyl-quinazolin-4′-oxy-acetyl) hydrazines (I) and two 5-(6′,8′-disubstituted-2′-ethyl-quinazolin-4′-oxy-methyl)-2-pheryl-1,3,4-oxadiazoles (II) were prepared by the compound (I) in the presence of $POCl_3$ and benzoic acid. III undergoes condensation with chloro compounds at position-2 to give IV in the presence of dryacetone and anhyd. potassium carbonate. III also undergoes Mannich condensation at position-3 in the presence of formaldehyde and 3/4-(2′-benzimidazolyl)-anilines and furnished V. All the synthesised compounds were screened against plant virus SRV both *in vivo* and *in vitro* for their antiviral action at a conc. 1 mg/ml and found to inhibit 4–48% *in vivo* and 6–53% *in vitro*. Four compounds (III 1, IV 3, V 1 and V 2) were screened for their antifungal action against *Fusarium* sp. and *A. niger* and three compounds caused a very significant inhibition at a conc. 1:1000.

INTRODUCTION

OUR earlier work on the synthesis of N-(6′, 8′-disubstituted -2′ -ethyl-quinazolin-4′- oxy-acetyl)-substituted hydrazines[1] as intermediate for the title compounds revealed that they possessed antimicrobial activity and since oxadiazole has been reported to exhibit significant biological activities[2,3], it was considered worthwhile to incorporate this moiety in the parent nucleus (I) and to evaluate them as fungicides and virucides. Further substituents such as phenyl mercapto, 2-methyl-1-benzimidazolyl, *N*-phenyl-*N*′-acetyl-ureido at position-2 in II and III were introduced to evaluate them for their antifungal and antiviral action. The tautomer of III, which has a labile hydrogen at position-3, was made to undergo Mannich condensation with different benzimidazolyl anilines as benzimidazole and Mannich bases are also well known for their antimicrobial activities[4–7].

2,5-Disubstituted 1,3,4-oxadiazoles (II) have been synthesised by the cyclisation of compound (I) in the presence of phosphorous oxychloride and benzoic acid and I, when cyclised in the presence of carbon disulphide and potassium hydroxide, furnished 5-substituted 2-mercapto-1,3,4-oxadiazoles (III). III undergoes condensation at position-2 with chloro compounds like *N*-phenyl-*N*′-chloroacetyl ureas and 2-chloro methyl-benzimidazole in the presence of dry acetone and anhyd. potassium carbonate and resulted in the formation of IV. III also undergoes Mannich condensation at position-3 in the presence of formaldehyde and benzimidazolyl anilines to give V. Various steps involved in the synthesis of the titled compounds are shown in scheme 1. Structural charac-



SCHEME - 1

terisation is based on elemental analyses, IR and PMR spectra.

EXPERIMENTAL

Spectra were recorded on Perkin-Elmer 137G spectrophotometer in KBr (υ max cm^{-1}) and PMR spectra in DMSO-d_6 on a Varian A-90D instrument using TMS as internal standard (chemical shift in δ ppm). Purity of the compounds was checked on TLC.

N(6,8'-Disubstituted-2'-ethyl-quinazolin-4'-oxyacetyl)-substituted hydrazines (I) were prepared according to previously reported method[1].

5-(6,8'-Disubstituted-2'-ethyl-quinazolin-4-oxymethyl)-2-phenyl 1,3,4-oxidiazole (II) (R=Br, R'=H).

In a typical reaction, a mixture of I (4.2 g, 0.015 mol) and benzoic acid (1.2 g, 0.01 mol) in $POCl_3$ (15 ml) was refluxed for 5 hr on a wire gauze. The cooled reaction mixture was poured in ice cooled water, made basic by the addition of sodium bicarbonate solution and the resulting solid was filtered the dried solid was recrystallised from methanol/chloroform yield = 2.5 g (50 %) m.p. 140°. Other II were also synthesised by the same procedure and given in table 1.

5-(6',8'-Disubstituted-2'-ethyl-quinazolin-4'-oxymethyl)-2-mercapto-1,3,4-oxadiazole (III) (R=R'=Br).

A suspension of I (4.0 g, 0.01 mol), potassium hydroxide (0.56 g, 0.01 mol) and CS_2 (0.6 ml, 0.011 mol) in 50 ml of methanol was refluxed on a water bath for 8 hr. After the reaction the solvent is distilled off and the residue after dissolving in water was acidified with dilute HCl. The precipitated solid was filtered, dried and recrystallised from methanol/acetone. Yield = 3.5 g (80 %) m.p. 236°C. Other III were prepared by following the same method and are given in table 2.

5-(6',8'-Disubstituted-2'-ethyl-quinazolin-4'-oxymethyl)-2-methyl-2''-benzimidazolyl)/N-phenyl-N'-acetyl-ureido mercapto-1,3,4-oxadiazoles (IV).

A mixture of compound (III) (0.01 mol), anhydrous potassium carbonate (0.015 mol) and chloromethyl-2''-benzimidazol/N-phenyl-N'-chloroacetylurea (0.01 mol) in dry acetone (50 ml) was refluxed on water bath for 24 hr. Thereafter the excess of solvent was distilled off, the reaction mixture cooled and ice-cooled water added to it. The solid which separated out was filtered,

Table 1 5-(6',8'-*Disubstituted-2'-ethylquinazolin-4'-oxy-methyl*)-2-*phenyl*-1,3,4-*oxadiazoles* (*II*) *and their antiviral activity*

R	R^1	M.P.°C	Molecular formula	Mol. weight	% inhibition against SRV	
					in vivo	*in vitro*
Br	H	140	$C_{19}H_{15}N_4O_2Br$	411	24	36
Br	Br	157	$C_{19}H_{14}N_4O_2Br_2$	490	19	20

(i) Yields varied from 50–55 %
(ii) The elemental analyses were within satisfactory limits.
(iii) IR (cm^{-1}) 2. 2900 (CH), 1600 (C=N).
(iv) PMR (δ) 2. 1 4–1.6 (triplet, 3H, CH_3 of ethyl), 3.2–3.4 (quartet, 2H, CH_2 of ethyl), 5.4 (singlet, 2H, O–CH_2–), 7.0–7.2 (hump, 7H, Ar-H).

Table 2 *5-(6',8'-Disubstituted-2'-ethylquinazolin-4'-oxymethyl)-2-mercapto-1,3,4-oxadiazoles (III) and their antiviral activity*

R	R^1	M.P. (°C)	Molecular formula	Mol. weight	% inhibition against SRV	
					in vivo	*in vitro*
H	H	180	$C_{13}H_{12}N_4O_2S$	288	24	31
Br	H	200	$C_{13}H_{11}N_4O_2SBr$	367	NS	NS
Br	Br	236	$C_{13}H_{10}N_4O_2SBr_2$	446	9	12

(NS = Not screened)
(i) Yields varied from 60–65%.
(ii) The elemental analyses were within satisfactory limits.
(iii) IR (cm^{-1}) 3. 3300 (NH), 2950 (CH), 1130 (C=S).
(iv) PMR (δ) 3. 1.2–1.4 (triplet, 3H, CH_3 of ethyl), 2.9–3.3 (quartet, 2H, CH_2 of ethyl), 5.3 (singlet, 2H, $-O-CH_2-$), 7.2 (singlet, 2H, Ar–H), 8 (singlet, 1H, NH).

Table 3 *5-(6',8'-Disubstituted-2'-(ethylquinazolin-4'-oxymethyl)-2-methyl-(2''-benzimidazolyl)/N-phenyl-N'-acetylureido-1,3,4-oxadiazoles (IV) and their antiviral activity*

R	R^1	R^2	M.P. °C	Molecular formula	Mol. weight	% inhibition against SRV	
						in vivo	*in vitro*
H	H	N'-acetyl-N-phenyl-ureido	193	$C_{22}H_{20}N_6O_4S$	464	40	43
Br	Br	N'-acetyl-N-phenyl-ureido	225	$C_{22}H_{18}N_6O_4SBr_2$	622	18	21
Br	Br	2-benzimidazolyl-methyl	265	$C_{21}H_{16}N_6O_2SBr_2$	576	48	53

(i) Yields varied from 45–50%
(ii) The elemental analyses were within satisfactory limits.
(iii) IR (cm^{-1}) 1. 3300 (NH), 2950 (CH), 1640 (C=O), 1590 (C=N).
3. 3300 (NH), 2900 (CH), 1580 (C=N). PMR (δ) 1. 1.2–1.5 (triplet, 3H, CH_3 of ethyl), 3.0 (quartet, 2H, CH_2 ethyl), 5.5 (singlet, 2H, $-OCH_2-$), 6.5 (singlet, 2H; CH_2-C-), 8.0 (hump, 7H, Ar-H), 10.88 (singlet, 1H, –O–NH), 12.63 (singlet, 1H, –O–NH–O). 3. 1.5 (triplet, 3H, CH_3 of ethyl), 3.2 (quartet, 2H, CH_2 of ethyl), 5.7 (singlet, 4H, $-OCH_2$, $S-CH_2$), 7.8 (hump, 7H, Ar-H), 10.13 (h, N =C–NH of benzimidazole nucleus).

dried and recrystallised from methanol IV thus synthesised are given in table 3, yield = 55%.

5-(6'-8'-Disubstitued-2'-ethyl-quinazolin-4-oxymethyl)-3-[3/4-(2''-benzimidazolyl)-anilino]-methyl-1,3,4-oxadiazolyl-2-thione (V). (V, R=R'=H).

In a typical reaction, mixture of III (1.4 g, 0.005 mol) dissolved in methanol (50 ml) and formaldehyde (0.3 ml, 0.005 mol) was heated for 5 min and then scratched for 10 min. Thereafter meta-(2-benzimidazolyl)-aniline (1.0 g, 0.005 mol) was added. The resulting reaction mixture was refluxed on water bath for 6 hr. After cooling, the solid which separated out was filtered, dried and recrystallised from methanol, yield = 1.5 g (70%) m.p. 195°C. Other compounds (V) were synthesised by the same method and are given in table 4.

BIO-ASSAY

Antifungal acthvity—Four compounds (III 1, IV 3, V 1 and 2) were tested for their antifungal action against *Fusarium* sp. and *Aspergillus niger* by following the agar plate diffusion method[7] at two concentrations 1:100 and 1:1000. Percent inhibition was calculated by the formulae $[(C-T)/C] \times 100$ where C is the fungus colony diameter in the plane control having only solvent instead of compounds while T is the colony

Table 4 *5-(6',8'-Disubstituted-2'-ethylquinazolin-4'-oxymethyl)-3-[m or p-(2''-benzimidazolyl)-anilino]-methyl-1,3,4'-oxadiazolyl)-2-thiones (V) and their antiviral activity*

R	R^1	R^3	M P. °C	Molecular formula	Mol. weight	% inhibition against SRV	
						in vivo	*in vitro*
H	H	*m*-(2''-benzimidazolyl)-	195	$C_{27}H_{23}N_7O_2S$	509	4	6
H	H	*p*-(2''-benzimidazolyl)-	207	$C_{27}H_{23}N_7O_2S$	509	8	10
Br	H	*m*-(2''-benzimidazolyl)-	210	$C_{27}H_{22}N_7O_2SBr$	588	8	12
Br	H	*p*-(2''-benzimidazolyl)-	188	$C_{27}H_{22}N_7O_2SBr$	588	24	30
Br	Br	*m*-(2''-benzimidazolyl)-	190	$C_{27}H_{21}N_7O_2SBr_2$	667	26	50
Br	Br	*p*-(2''-benzimidazolyl)-	205	$C_{27}H_{21}M_7O_2SBr_2$	667	29	38

(i) Yields varied from 60–70 %
(ii) The elemental analyses were within satisfactory limits.
(iii) IR (cm^{-1}) 1. 3300 (NH), 2900 (CH), 1600 (C=N), 1120 (C=S).
2. 3400 (NH), 2900 (CH, 1610 (C=N), 1140 (C=S).
(iv) PMR (δ) 1. 1.8 (triplet, 3H, CH_3 of ethyl), 3.0 (quartet, 2H, CH_2 of ethyl), 5.3 (singlet, 2H, $-OCH_2$), 6.2 (singlet, 2H, $N-CH_2-N$), 7.5 (hump, 10H, Ar-H), 8 6 (singlet, 1H, –NH–Ar), 10.13 (singlet, 1H, NH of benzimidazole moiety).

diameter in the treated petridish. III 1, IV 3, V 1 and V 2 caused 96.2 %, 40 %, 85 %, 62.9 % at conc. 1:100, 70.3 %, 26 %, 62.9 %, 59.2 % at conc. 1:1000 respectively against *Fusarium* sp. and 88.2 %, 18 %, 88 %, 82.3 % at 1 : 100 almost nil at 1 : 1000 conc. against *A. niger*.

From SAR point of view it could be concluded that the 5-substituted-2-mercapto-oxadiazole inhibited the fungus significantly (88–96 %) and its derivative substituted at position-3 (V 1 and V 2) also caused a good inhibition although somewhat less than that of its parent compound (III 1). It indicates that free thione group at position-2 of oxadiazole moiety plays a significant role in its antifungal character since when it was substituted as position-2 (IV 2) a sharp decrease in the activity is observed. At the same time in case of V 1 and V 2 presence of benzimidazolyl moiety at *meta*-position of phenyl ring makes the compound more antifungal than that when it is present at *para* position (V 2). It was also observed that 1:100 conc. of the compound is a minimum inhibitory concentration in the case of *Aspergillus niger*.

Antiviral activity against plant virus SRV—All the synthesised compounds (except III 2) were tested for their ability to reduce viral infectivity against *sunnhemp rosette virus* at a concentration of 1 mg/ml both *in vivo* as well as *in vitro* using *Cyamopsis tetragonoloba* as a host plant by the reported method[9,10]. Results are calculated by the formula $[(C-T)/C] \times 100$ (where C = lesions on controlled leaf, T = lesions on treated leaf) and are listed in tables 1 to 4. It is seen that the presence of phenyl group at position-2 makes the compound more antiviral and the compound having mercapto groups at this position and the presence of *N*-phenyl-*N'*-acetylureido and 2-methylbenzimidazolyl moieties also enhance their antiviral activity. It is also observed that compounds having benzimidazolyl-anilino-methyl group at position-3 do not show any marked activity. However the presence of benzimidazolyl moiety at position-4 of aniline ring does seem to increase the antiviral activity as compared to the one having this moiety at position-3.

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ON THE STEREOSELECTIVITY OF STOBBE CONDENSATION WITH ORTHO SUBSTITUTED AROMATIC ALDEHYDES: THE (E, Z) CONFIGURATION OF MONOBENZYLIDENESUCCINATES AND DIBENZYLIDENESUCCINIC ANHYDRIDES

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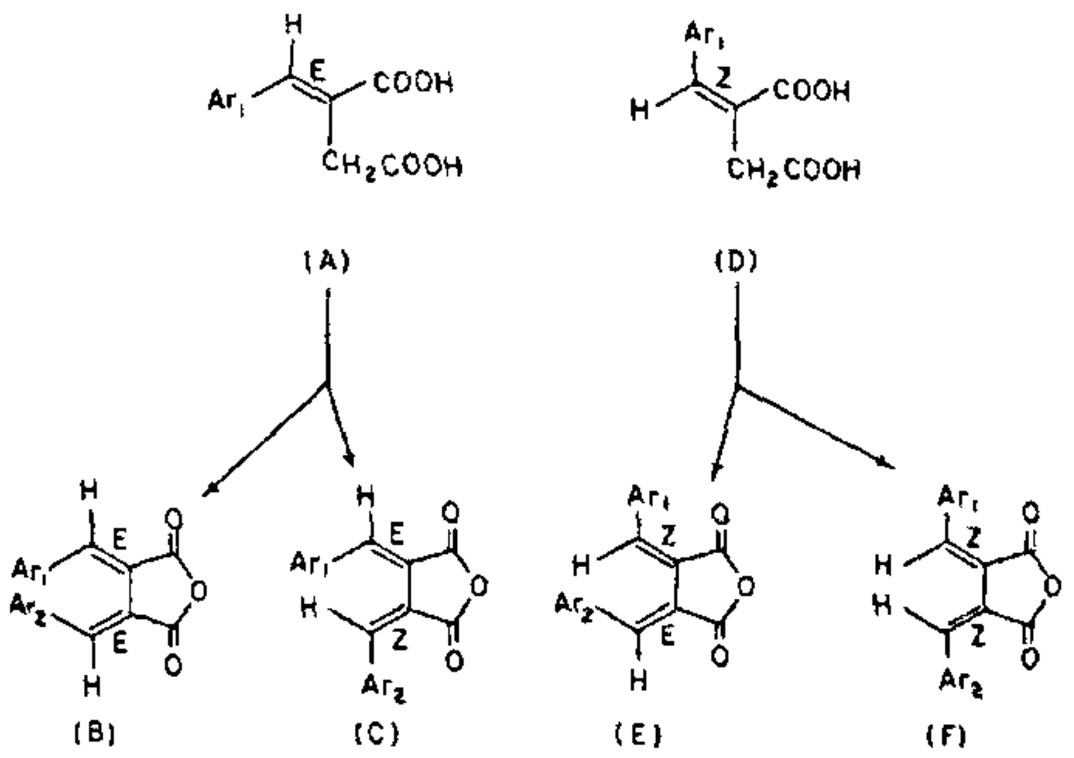
ABSTRACT

The geometrical configuration (E or Z) of several monobenzylidenesuccinates and dibenzylidenesuccinic anhydrides has been established unequivocally by a study of their respective PMR spectra. The Stobbe condensation between mono-ortho substituted or ortho unsubstituted aromatic aldehydes has been found to be stereoselective in giving only the (E)-monobenzylidenesuccinates. The second Stobbe reaction involving the (E)-monobenzylidenesuccinates and ortho monosubstituted or ortho unsubstituted aromatic aldehydes has been found to be stereoselective giving only the (E,E)-derivatives.

STOBBE condensation of aromatic aldehydes with dimethyl succinate in the presence of a base like tertiary butoxide or methoxide gives monobenzylidenesuccinic half-esters[1] or acids[2]. The monobenzylidenesuccinates when subjected to further Stobbe condensation give dibenzylidene half-esters or diacids respectively. The diacids on heating with acetyl chloride give the corresponding anhydrides (V). Theoretically speaking, two geometrical isomers (E or Z) (A or D, chart I) are possible with monobenzylidenesuccinates and from them four isomers (E,E, E,Z, Z,E and Z,Z) (B, C, E, and F) are possible with dibenzylidene derivatives. When the aryl groups are identical ($Ar_1 = Ar_2$), the number of isomers reduces to three (C ≡ E).

Chart I



During the course of our investigation, for over some years, on synthetic experiments in lignans[3-9] a number of these mono and di-Stobbe products have been prepared as intermediates. The geometrical configuration of these isomers at the respective double bonds has not been unequivocally established, although assumptions have been made by analogies, occasionally wrongly, in these as well other laboratories[10-14a,b] on similar derivatives. A detailed study on these derivatives has now been made and the geometrical configuration at the respective double bonds has been established with the help of PMR spectral data and with an understanding on the mechanism of the Stobbe condensation.