SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME NEW GUANIDINES

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The synthesis of some N-substituted-N′-aryl-N″-ethyl/benzyl guanidines (II) and (III) and their precurser thiocarbamides (I) has been carried out. All these compounds have been screened *in vitro* for their antifungal activity against *Helminthosporium oryzae, Drechslera papendor fii* and *Alternaria alternata*. In general, N-substituted-N′-aryl-N″-benzyl guanidines except N-(*p*-pyrolidinopropoxyphenyl)-N′-*p*-tolyl-N″-benzyl guanidine possess high antifungal activity against all the test fungi at concentration 2% and comparatively less at 0.2%. None of these compounds exhibit fungicidal activity at lower concentrations (0.02 and 0.002%).

Compounds N-octylethylene thiourea and—2-heptadecyl-2-imidazoline possessing an optimum lipoid solubility, promoted by alkyl or aryl substituents together with a reactive centre provided by polar groups, have been shown to exhibit fungicidal activity[1]. Many thiocarbamides have been found to possess marked antifungal activity[2]. Furthermore various guanidines have been reported to exhibit antifungal, antibacterial[3,4], and antitubercular activity[5,6]. In view of these observations, it was considered of interest to synthesise some N-substituted-N′-aryl-N″-ethyl/benzyl guanidines possessing lipoid soluble alkyl substituents together with polar groups. These compounds were synthesised by the reaction of ethyl or benzylamine with 1-aryl-3-*p-tert.* aminopropoxyphenyl thiocarbamides (I) in the presence of yellow lead oxide.

These guanidines and their precurser thiocarbamides were screened for their *in vitro* antifungal activity against *Helminthosporium oryzae, Drechslera papendorfii* and *Alternaria alternata* at concentrations 2, 0.2, 0.02 and 0.002% (*W/V*). The efficiency of these compounds to exhibit antifungal activity was ascertained by comparing them with the reference fungicide, thiram 75W.

EXPERIMENTAL

Preparation of p-tert. aminopropoxy anilines

The following *p-tert.* aminopropoxy anilines used in the present study were synthesised according to the methods reported in the literature[7,8].

p-Morpholinopropoxyaniline ; m.p., 176°C, yield, 69%.

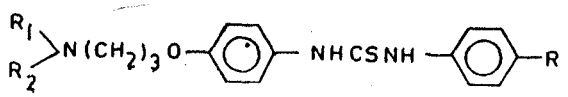
p-Pyrrolidinopropoxyaniline; m.p. 98°C, yield, 60%.

p-Piperidinopropoxyaniline; m.p., 112°C, yield, 62%.

Satisfactory analysis for *C*, *H* and *N* was found.

Synthesis of 1-*aryl*-3-*p-tert. aminopropoxyphenyl thiocarbamides*

A mixture of appropriate *p-tert.* aminopropoxyaniline (0.01 mole) and the appropriate isothiocyanate (0.01 mole) in ethanol (25 ml) was refluxed for 1 hr. The reaction mixture was concentrated to about 5 ml and cooled. The solid mass that separated out was filtered, washed with little ether, dried and recrystallised from ethanol. The thiocarbamides (I) reported in Table 1 were characterised by their sharp melting points, analysis and by the presence of characteristic absorption bands at 3250cm^{-1} (*N-H* stretching), 1600 and 1550 cm^{-1} (*C=C*, aromatic), 1470 and 1355 cm^{-1} (C=*S*), 1230 and 1045 cm^{-1} (C-*O*, ether) and 825cm^{-1} (disubstituted benzene) in the i.r. spectrum of 1-*p*-bromophenyl- (*p*-morpholinopropoxyphenyl)-thiocarbamide (I*b*).



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Synthesis of N-substituted-N'-aryl-N''-ethylbenzyl guanidines

A mixture of appropriate 1-aryl-3-(*p*-tert. aminopropoxyphenyl)—thiocarbamide (0.01 mole), yellow lead oxide (0.015 mole) and absolute ethanol (50 ml) was refluxed in a sealed tube for 6 hr. The reaction mixture was filtered and removal of the solvent under reduced pressure yielded the crude product, which was washed several times with water, dried and recrystallised from ethanol-petroleum ether. These compounds are recorded in Table 2(II). The structure of these compounds was supported by the i.r. spectrum of N-(*p*-pyrrolidino-propoxyphenyl)-N'-*p*-methoxyphenyl-N'' -benzyl guanidine (III) showing absorption bands at 3210 and 3040 cm^{-1} (*N-H* stretching), 2920 cm^{-1} (CH_2), 1615 cm^{-1} (*C=C*, aromatic), 1490 cm^{-1} (*C=N*), 1285, 1228 and 1020 cm^{-1} (*C=O*, ether) and 820 and 725 cm^{-1} (*p*-disubstituted benzene).

TABLE 1

ANALYTICAL DATA AND ANTIFUNGAL ACTIVITY OF 1-ARYL-3-*p*-*TERT.* AMINOPROPOXYPHENYL THIOCARBAMIDES

S. No.	NR_1R_2	R	M.P.* (°C)	Yield (%)	Molecular Formula	Anaysis (%)			
						Found		Reqd.	
						C	*H*	*C*	*H*
Ia	morpholino	*H*	180	54	$C_{20}H_{25}N_3O_2S$	64.39	6.38	64.69	6.73
Ib	morpholino	*Br*	160	68	$C_{20}H_{24}BrN_3O_2S$	53.04	5.12	53.33	5.33
Ic	morpholino	CH_3	186	52	$C_{21}H_{27}N_3O_2S$	65.11	6.76	65.45	7.01
Id	morpholino	OCH_3	179	66	$C_{21}H_{27}H_3O_2S$	62.48	6.36	62.84	6.73
Ie	piperidino	*H*	165	56	$C_{21}H_{27}N_3OS$	68.00	7.02	68.29	7.31
If	piperidino	*Br*	163	64	$C_{21}H_{26}BrN_3OS$	55.82	5.68	56.25	5.80
Ig	piperidino	CH_3	151	53	$C_{22}H_{29}N_3OS$	68.50	7.25	68.92	7.57
Ih	piperidino	OCH_3	163	69	$C_{22}H_{29}N_3O_2S$	67.87	6.89	66.16	7.26
Ii	pyrrolidino	*H*	162	52	$C_{20}H_{25}N_3OS$	67.32	6.83	67.80	7.04
Ij	pyrrolidino	*Br*	168	64	$C_{20}H_{24}BrN_3OS$	55.00	5.31	55.29	5.52
Ik	pyrrolidino	CH_3	180	51	$C_{21}H_{27}N_3OS$	67.79	7.02	68.29	7.31
Il	pyrrolidino	OCH_3	186	61	$C_{21}H_{27}N_3O_2S$	65.12	6.72	65.45	7.01
	$Thiram 75W								

S. No.	NR_1R_2	Diameter** of zones of inhibition in mm for pathogenic fungi at concentration (percent, W/V)†											
		Alternaria alternata				*Drechlera papendorfii*				*Helminthosporium oryzae*			
		2	0.2	0.02	0.002	2	0.2	0.02	0.002	2	0.2	0.02	0.002
Ia	morpholino	—	—	—	—	—	—	—	—	—	—	—	—
Ib	morpholino	18	—	—	—	19.5	—	—	—	20	—	—	—
Ic	morpholino	17	—	—	—	18	—	—	—	18	—	—	—
Id	morpholino	—	—	—	—	—	—	—	—	—	—	—	—
Ie	piperidino	—	—	—	—	—	—	—	—	—	—	—	—
If	piperidino	21	16	—	—	24	18	—	—	31	21.5	—	—
Ig	piperidino	21	15	—	—	23	17	—	—	30	21	—	—
Ih	piperidino	—	—	—	—	—	—	—	—	—	—	—	—
Ii	pyrrolidino	—	—	—	—	—	—	—	—	—	—	—	—
Ij	pyrrolidino	27	17.5	—	—	26	17	—	—	36	20	—	—
Ik	pyrrolidino	23	15	—	—	20	14	—	—	25	18	—	—
Il	pyrrolidino	—	—	—	—	—	—	—	—	—	—	—	—
$	Thiram 75W	40	28	—	—	40	32	25	—	36	28	14	—

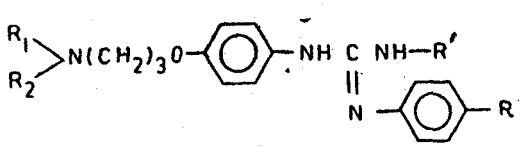
*Melting points were taken in open capillary tubes and are uncorrected.

**Three replicates averaged.

†The solutions of these concentrations were prepared by dissolving these compounds in ethanol.

$Used as a reference fungicide.

—Shows no zone of inhibition.



(II) R'- —CH_2 CH_3 R'- —$CH_2C_6H_4$

TABLE 2

ANALYTICAL DATA AND ANTIFUNGAL ACTIVITY OF N-SUBSTITUED-N′-ARYL-N″-ETHYL/BENZYL GUANIDINES

S. No	NR_1R_2	R	M P * π (°C)	Yield (%)	Molecular Formula	Analysis (%) Found C	Found H	Reqd C	Reqd H
IIa	morpholino	*H*	83	41	$C_{22}H_{30}N_4O_2$	69.03	7.58	69.11	7.85
IIb	morpholino	*Br*	104-5	46	$C_{22}H_{29}BrN_4O_2$	57.18	6.18	57.26	6.29
IIc	morpholino	OCH_3	96	39	$C_{23}H_{32}N_4O_2$	66.99	7.76	66.68	7.58
IId	piperidino	*Br*	85	43	$C_{23}H_{31}BrN_4O$	59.89	6.59	60.13	6.75
IIe	piperidino	OCH_3	99	36	$C_{24}H_{34}N_4O_2$	70.08	8.12	70.24	8.29
IIf	pyrrolidino	*H*	783	38	$C_{22}H_{30}N_4O$	72 10	8.08	72.13	8.19
IIg	pyrrolidino	*Br*	71	33	$C_{22}H_{27}BrN_4O$	59.08	6.42	59.32	6.51
IIIa	morpholino	H	88	43	$C_{27}H_{32}N_4O_2$	72.73	7.02	72.97	7.20
IIIb	morpholino	*Br*	75	39	$C_{27}H_{34}BrN_4O_2$	61.63	5.68	61.95	5.92
IIIc	morpholino	CH_3	54	35	$C_{28}H_{34}N_4O_2$	73.09	7.13	73.36	7.42
IIId	morpholino	OCH_3	68-9	39	$C_{28}H_{34}N_4O_3$	70.49	7.00	70.83	7.17
IIIe	piperidino	*H*	61	46	$C_{28}H_{34}N_4O$	75.89	7.54	76.01	7.69
IIIf	piperidino	*Br*	59	34	$C_{28}H_{33}BrN_4O$	64.14	6.04	64.49	6.33
IIIg	piperidino	CH_3	69	47	$C_{29}H_{36}N_4O$	76.02	7.49	76.31	7.89
IIIh	piperidino	OCH_3	78	46	$C_{29}H_{36}N_4O_2$	73.56	7.30	73.72	7.62
IIIi	pyrrolidino	*H*	95-7	49	$C_{27}H_{32}N_4O$	75.42	7.18	75.70	7.47
IIIj	pyrrolidino	*Br*	80	45	$C_{27}H_{31}BrN_4O$	63.69	6.12	63.90	6.11
IIIk	pyrrolidino	CH_3	78	37	$C_{28}H_{34}N_4O$	75.87	7.43	76.01	7.69
IIIl	pyrrolidino	OCH_3	72	48	$C_{28}H_{34}N_4O_2$	73.18	7.30	73.36	7.42
$	Thiram 75W								

S. No.	NR R	Diameter** of zones of inhibition in mm for pathogenic fungi at concentrations† (percent, W/V) *Alternaria alternata* 2	0.2	0.02	0.002	*Drechslera papendorfii* 2	0.2	0.02	0.002	*Helminthosporium oryzae* 2	0.2	0.02	0.002
IIa	morpholino	17	—	—	—	21	—	—	—	16	—	—	—
IIb	morpholino	—	—	—	—	—	—	—	—	—	—	—	—
IIc	morpholino	—	—	—	—	29	—	—	—	—	—	—	—
IId	piperidino	—	—	—	—	—	—	—	—	—	—	—	—
IIe	piperidino	31	23	—	—	40	27	—	—	30	29	—	—
IIf	pyrrolidino	—	—	—	—	—	—	—	—	—	—	—	—
IIg	pyrrolidino	19	—	—	—	33	20	—	—	31	—	—	—
IIIa	morpholino	28	16	—	—	37	26	—	—	34	25.5	—	—
IIIb	morpholino	16	—	—	—	17	—	—	—	15	—	—	—
IIIc	morpholino	32	17	—	—	35	26	—	—	23	15	—	—
IIId	morpholino	31	18	—	—	37	25	—	—	36	25	—	—
IIIe	piperidino	31	22	—	—	28	16	—	—	27	16	—	—
IIIf	piperidino	24	—	—	—	22.5	—	—	—	24	—	—	—
IIIg	piperidino	17.5	—	—	—	19	—	—	—	21	—	—	—
IIIh	piperidino	37	23	—	—	43	27.5	—	—	39	28.5	—	—
IIIi	pyrrolidino	22	16	—	—	24	20	—	—	25	19	—	—
IIIj	pyrrolidino	21	15	—	—	32	24	—	—	32	27	—	—
IIIk	pyrrolidino	—	—	—	—	—	—	—	—	—	—	—	—
IIIl	pyrrolidino	25	—	—	—	29	—	—	—	19	—	—	—
$	Thiram 75W	40	28	—	—	40	32	25	—	36	28	14	—

*Melting points were taken in open capillary tubes and are uncorrected

**Three replicates averaged.

†The solutions of these concentrations were prepared by dissolving these compounds in ethanol.

$ Used as reference fungicide.

—Shows no zone of inhibition.

SCREENING FOR ANTIFUNGAL ACTIVITY

All these N-substituted-N′-aryl-N″-ethyl/benzyl guanidine (II) and (III) and their precurser thiocarbamides (I) were screened for their antifungal activity against *Helminthosporium oryzae, Drechslera papendorfii* and *Alternaria alternata* as the test fungi by Paper-disc plate method of Thornberry[9] at concentrations 2, 0.2, 0.02 and 0.002% (W/V). Standard PDA medium was used. Filter paper discs of diamete

12 mm were used and the diameter of zones of inhibition formed around each disc after incubating for a period of 48 hr at 25-28°C were recorded. For estimating relative toxicity to know the efficacy of the sample under evaluation a reference fungicide of known toxicity, thiram 75W was included in the test.

Results summarised in Table 1 indicate that the compounds of series (I) having *p*-bromophenyl or *p*-tolyl group at 1-position and *p*-morpholinopropoxyphenyl group at 3-position showed fungicidal activity against all the test fungi at 2%, while those having these groups at 1-position and piperidino or pyrrolidino propoxyphenyl group at 3-position showed fungicidal activity against all the test fungi at 2 and 0.2 %. Compound (Ij) was found to be most active fungicide against all the test fungi at concentrations 2 and 0.2 %, where maximum activity was observed against *Helminthosporium oryzae* at 2%. Most of the compounds of series (II) and (III) in Table 2 showed high activity against all the test fungi at concentrations 2 and 0.2%. None of these compounds showed antifungal activity at lower concentrations (0.02 and 0.002%). In general compounds of series (III), except compound (III k) were found to be more effective fungicides than the compounds of series (II), where compound (III h) exhibited maximum fungitoxicity and was found to be more toxic than thiram 75W against *Drechslera papendorfii* at concentration 2% and against *Helminthosporium oryzae* at concentration 2 and 0.2%. The results of the present study have, however, failed to provide a definite structure-activity relationship of these compounds.

The present study envisages that some N-substituted-N′-aryl-N″-benzyl guanidines, particularly N-(*p*-piperidinopropoxyphenyl)-N′-p-methoxyphenyl N″-benzyl guanidine (III h), a most effective among these, may possibly be developed into an effective fungicide to protect the crops from the fungal diseases associated with the fungi *Alternata*, *Drechslera papendorfii* and *Helminthosporium oryzae*.

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