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Synthesis and Antifungal Activity of Some Bis-(2-arylimino-3-yl-thiazolidinones) and Bis-(1-aryl-3-yl-2-thiohydantoins) derived from Hydroquinone

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Some *bis*-(2-arylimino-3-yl-thiazolidin-4-ones) and *bis*-(1-aryl-3-yl-2-thiohydantoins) were synthesised from *bis*-(4-aryl-3-thiocarbamides) and screened for their antifungal activity against *Aspergillus flavus, Helminthosporium tetramera* and *Pennicillium decombens*.

INTRODUCTION

Some *bis*-thiazolidinones exhibit antitubercular[1], hypnotic[2] and antifungal activity. The presence of N—C—S linkage has been postulated to account for the antifungal activity of 4-thiazolidinones[3–7]. Thiohydantoins are also associated with a broad biocidal spectrum[8, 9]. It was, therefore, considered of interest to convert hydroquinone to *bis*-(4-aryl-3-thiocarbamides) (III), which on cyclisation with monochloroacetic acid/sodium acetate and monochloroacetic acid/pyridine were converted to *bis*-(2-arylimino-3-yl-thiazolidin-4-ones) (IV) and bis(1-aryl-3-yl-2-thiohydantoins) (V) respectively. The steps involved in the synthesis are shown in scheme 1.

All these compounds III, IV, V 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 and 90 MHz spectrometer using TMS as internal standard. Hydroquinone diacetic acid (I) and hydroquinone diacetyl chloride (II) were prepared by the reported procedure[10].

Hydroquinone diacetyl *bis*-(4-aryl-3-thiocarbamides) (III)

A mixture of ammonium thiocyanate (0.11 mol) and acetone (50 mL) was placed in a flask and solution of hydroquinone diacetyl chloride (0.05 mol) in acetone (50 mL) was added through a dropping funnel with stirring. Aryl amine (0.1 mol) in acetone (50 mL) was then added to the reaction mixture in small portions. When the addition was over, the reaction mixture was refluxed for 2 h, cooled and poured into ice cold water. The resulting precipitate was filtered and washed with water and crystallised from DMF + DMSO (1 : 1). Various hydroquinone diacetyl *bis*-(4-aryl-3-thiocarbamides) thus prepared are recorded in Table 1.

TABLE-1
ANALYTICAL AND SPECTRAL DATA OF HYROQUINONE DIACETYL *BIS*-(4-ARYL-3-THIOCARBAMIDES) (III)

Compd. No.	R	m.p. (°C)	Yield %	Molecular formula	Analysis (%) Found(Calcd.)	
					N	S
III_a	C_6H_5	160	84.74	$C_{24}H_{22}N_4O_4S_2$	11.34 (11.39)	12.95 (12.90)
III_b	p-ClC_6H_4	180	77.00	$C_{24}H_{20}N_4O_4S_2Cl_2$	9.94 (9.99)	11.36 (11.31)
III_c	p-BrC_6H_4	225	69.00	$C_{24}H_{20}N_4O_4S_2Br_2$	8.58 (8.53)	9.81 (9.76)
III_d	p-$OCH_3C_6H_4$	205	78.00	$C_{26}H_{26}N_4O_6S_2$	10.10 (10.06)	11.55 (11.50)
III_e	p-$CH_3C_6H_4$	160	73.88	$C_{26}H_{26}N_4O_4S_2$	10.72 (10.76)	12.26 (12.21)
III_f	p-$NO_2C_6H_4$	210	60.38	$C_{24}H_{20}N_6O_8S_2$	14.38 (14.34)	10.95 (10.91)
III_g	o-$CH_3C_6H_4$	130	62.00	$C_{26}H_{26}N_4O_4S_2$	10 72 (10.69)	12.26 (12.31)
III_h	o-ClC_6H_4	230	63.51	$C_{24}H_{20}N_4O_4S_2Cl_2$	9.94 (9.98)	11.36 (11.31)
III_i	o-$OCH_3C_6H_4$	170	69.14	$C_{26}H_{26}N_4O_6S_2$	10.10 (10.15)	11.55 (11.51)
III_j	o-$NO_2C_6H_4$	210	77.78	$C_{24}H_{20}N_6O_8S_2$	14.38 (14.33)	10.95 (10.90)
III_k	m-$CH_3C_6H_4$	125	97.36	$C_{26}H_{26}N_4O_4S_2$	10.72 (10.67)	12.26 (12.21)
III_l	m-ClC_6H_4	150	84.96	$C_{24}H_{20}N_4O_4S_2Cl_2$	9.94 (9.89)	11.36 (11.32)
III_m	m-$OCH_3C_6H_4$	230	60.20	$C_{26}H_{26}N_4O_6S_2$	10.10 (10.06)	11.55 (10.66)
III_n	m-$NO_2C_6H_4$	>250	54.35	$C_{24}H_{20}N_6O_8S_2$	14.38 (14.33)	10.95 (10.90)
III_e	ν_{max} (cm^{-1})	(KBr) :	3320 (N--H, Stretch), 1670 (—CONH—), 1610 (C=C, aromatic), 1225 (—NHCSNH—), 820 (1,4-disubstituted benzene)			
		ppm (δ) :	6.86–74 (m, 12H, ArH) 2.25 (S, 4H, 2–OCH_2) 1.25 (S, 6H, $2CH_3$)			

Hydroquinone diacetyl *bis*-(2-arylimino-3-yl-thiazolidin-4-ones) (IV)

A mixture of hydroquinone diacetyl *bis*-(4-aryl-3-thiocarbamides) (0.01 mol), monochloroacetic acid (0.02 mol) and anhydrous sodium acetate (0.02 mol) was refluxed in dimethyl formamide (50 mL) for 8–10 h. The reaction mixture was cooled, poured into ice-cold water and kept overnight. The precipitate thus obtained was filtered, dried and crystallised from ethanol. The compounds

(Table 2) were characterised by their melting points and analytical data along with spectral analysis.

TABLE-2

ANALYTICAL AND SPECTRAL DATA OF HYDROQUINONE DIACETYL *BIS* (2-ARYLIMINO-3-YL-THIAZOLIDIN-4-ONES) (IV)

Compound No.	R	m.p. (°C)	Yield %	Molecular Formula	Analysis (%) Found/(Calculated) N	S
IV$_a$	C_6H_5	225	50.30	$C_{28}H_{22}N_4O_6S_2$	9.75 (9.71)	11.14 (11.09)
IV$_b$	*p*-ClC_6H_4	190	51.32	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.60)	9.95 (9.90)
IV$_c$	*p*-BrC_6H_4	220	60.27	$C_{28}H_{20}N_4O_6S_2Br_2$	7.67 (7.62)	8.76 (8.71)
IV$_d$	*p*-$OCH_3C_6H_4$	220	92.74	$C_{30}H_{26}N_4O_8S_2$	8.83 (8.78)	10.09 (10.04)
IV$_e$	*p*-$CH_3C_6H_4$	100	66.09	$C_{30}H_{26}N_4O_6S_2$	13.29 (13.24)	10.12 (10.07)
IV$_f$	*p*-$NO_2C_6H_4$	220	58.73	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.60)	9.63 (9.58)
IV$_g$	*o*-$CH_3C_6H_4$	150	65.66	$C_{30}H_{26}N_4O_6S_2$	13.29 (13.24)	10.12 (10.07)
IV$_h$	*o*-ClC_6H_4	200	77.76	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.65)	9.95 (9.90)
IV$_i$	*o*-$CH_3C_6H_4$	180	90.00	$C_{30}H_{26}N_4O_8S_2$	8.83 (8.88)	10.09 (10.14)
IV$_j$	*o*-$NO_2C_6H_4$	220	50.62	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.69)	9.63 (9.68)
IV$_k$	*m*-$CH_3C_6H_4$	150	68.03	$C_{30}H_{26}N_4O_6S_2$	13.29 (13.24)	10.12 (10.07)
IV$_l$	*m*-ClC_6H_4	150	65.42	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.62)	9.95 (9.91)
IV$_m$	*m*-$OCH_3C_6H_4$	220	95.28	$C_{30}H_{26}N_4O_8S_2$	8.83 (8.78)	10.09 (10.04)
IV$_n$	*m*-$NO_2C_6H_4$	>250	62.53	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.60)	9.63 (9.60)
IV$_a$	ν_{max} (cm^{-1})	(KBr) :	3010, 2900 (C—H), 1690 (C=O, exocylic), 1650 (C=O, endocyclic), 1630 (C=N), 1600 (C=C aromatic), 1230 (C—S—C, thiazolidinone), 810 (1,4-disubstituted benzene)			
		ppm(δ) :	6.9–7.4 (m, 14ArH) 4.55 (S, 4H, $2CH_2$) 2.25 (S, 4H, $2OCH_2$)			

Hydroquinone diacetyl *bis*-(1-aryl-3-yl-2-thiohydantoins) (V)

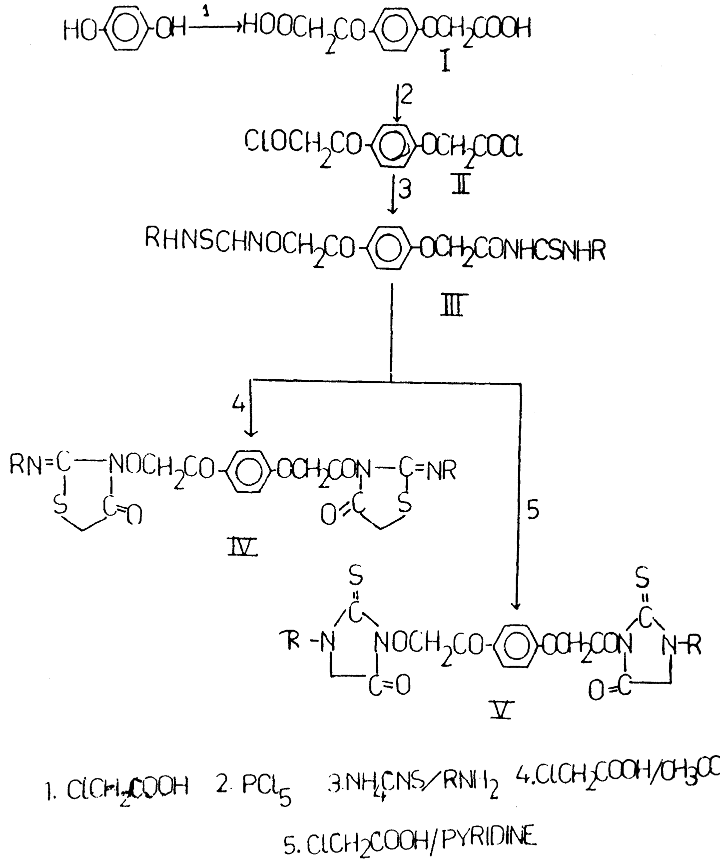
Hydroquinone diacetyl *bis*-(4-aryl-3-thiocarbamides) (0.0025 mol) was dissolved in minimum amount of pyridine. To this mixture alcohol and dioxane

(1 : 1) was added. This mixture was refluxed for 12 h. On cooling, it was poured into ice cold water. Solid mass that separated out was filtered, dried and crystallised from DMSO. Analytical and Spectral data of these compounds are recorded in Table 3.

TABLE-3

ANALYTICAL AND SPECTRAL DATA OF HYDROQUINONE DIACETYL *BIS*-(1-ARYL-3-YL-2-THIOHYDANTOINS) (V)

Compound No.	R	m.p. (°C)	Yield %	Molecular Formula	Analysis (%) Found/(Calculated)	
					N	S
V_a	C_6H_5	200	67.36	$C_{28}H_{22}N_4O_6S_2$	9.65 (9.59)	11.03 (11.08)
V_b	*p*-ClC_6H_4	180	69.93	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.64)	9.95 (10.00)
V_c	*p*-BrC_6H_4	140	42.55	$C_{28}H_{20}N_4O_6S_2Br_2$	7.65 (7.61)	8.74 (8.69)
V_d	*p*-$OCH_3C_6H_4$	230	64.94	$C_{30}H_{26}N_4O_8S_2$	9.12 (9.07)	10.52 (10.47)
V_e	*p*-$CH_3C_6H_4$	200	78.13	$C_{30}H_{26}N_4O_6S_2$	13.29 (13.24)	10.12 (10.17)
V_f	*p*-$No_2C_6H_4$	210	54.22	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.61)	9.60 (9.10)
V_g	*o*-$CH_3C_6H_4$	170	75.95	$C_{30}H_{26}N_6O_4S_2$	13.29 (13.24)	10.12 (10.07)
V_h	*o*-ClC_6H_4	190	54.72	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.64)	9.60 (9.90)
V_i	*o*-$CH_3C_6H_4$	180	64.94	$C_{30}H_{26}N_4O_6S_2$	9.12 (9.17)	10.52 (10.47)
V_j	*o*-$NO_2C_6H_4$	>250	54.22	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.69)	9.63 (9.68)
V_k	*m*-$CH_3C_6H_4$	165	82.28	$C_{30}H_{26}N_4O_6S_2$	13.29 (13.24)	10.12 (10.17)
V_l	*m*-ClC_6H_4	185	75.47	$C_{28}H_{20}N_4O_6S_2Cl_2$	8.70 (8.65)	9.96 (9.90)
V_m	*m*-$OCH_3C_6H_4$	200	65.23	$C_{30}H_{26}N_4O_8S_2$	9.12 (9.07)	10.52 (10.57)
V_n	*m*-$NO_2C_6H_4$	220	44.32	$C_{28}H_{20}N_6O_{10}S_2$	12.65 (12.70)	9.63 (9.68)
V_c	ν_{max} (cm^{-1})	(KBr)	: 1685 (C=O, exocyclic), 1670 (C=O, endocyclic), 1590 (C=C, aromatic), 1340 (C=S), 810 (1,4-disubstituted benzene)			
V_a		ppm (δ)	: 6.9–7.4 (m, 14ArH), 4.55 (S, 4H, $2CH_2$), 2.25 (S, 4H, $2OCH_2$)			



Screening for Antifungal activity

Compounds III, IV and V were screened for their antifungal activity against *A. Flavus, H. tetramera* and *P. decombens* as the test fungi by paper-disc plate method at concentration levels of 2.0 and 0.2% (w/v) in dimethyl sulfoxide. Standard PDA medium was used. Filter paper discs of diameter 12 mm 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 were compared with reference to fungicides, Dithane-Z-78 and Thiram-75W. The compounds IV and V were found to be less fungicidal than their precursor III. On comparison with reference to fungicides, they were found to be less effective.

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