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Note

Synthesis of 5-aryl-2-[spiro-(1,3-dithiolane)-2,4′-(3′- chloro-2′-azetidinon)-1′-yl]-1,3,4-oxa (thia)-diazoles and 5-aryl-2-[spiro-(1,3-dithiolane)-2,2′-(4′- thiazolidinon)-3′-yl]-1,3,4-oxa(thia)diazoles as antimicrobial agents

Mukhtar Hussain Khan & Nizamuddin*
Agrochemical Research Laboratory,
Department of Chemistry, University of Gorakhpur,
Gorakhpur 273 009, India

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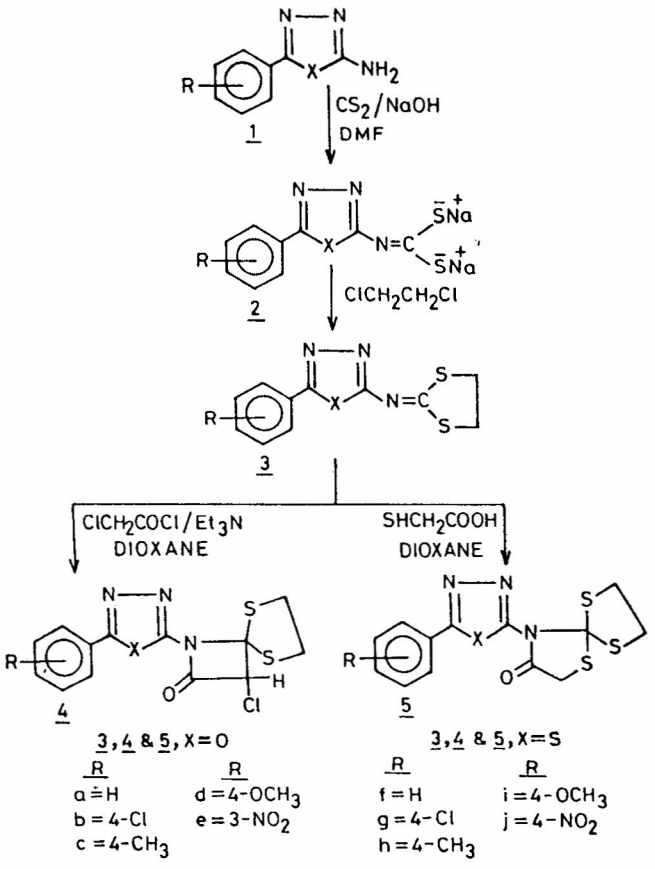
5-Aryl-2-[spiro-(1,3-dithiolane)-2,4′-(3′-chloro- 2′-azetidinon)-1′-yl]-1,3,4-oxa(thia)diazoles **4** and 5- aryl-2-[spiro-(1,3-dithiolane)-2,2′-(4′-thiazolidinon)- 3′-yl]- 1,3,4-oxa (thia)-diazoles **5** have been synthesised from 5-aryl-2-(1,3-dithiolan-2-yl)imino-1,3,4-oxa(thia) diazoles **3** with chloro acetyl chloride and mercapto acetic acid, respectively. These compounds have been screened on *Aspergillus niger, Pyricularia oryzae, Fusarium oxysporum* and *Cephalosporum sacchari*; and *Escherichia coli, Solmonella typhi* and *Bacillus aureus* for their antifungal and antibacterial activities, respectively.

The 1,3-dithiolane derivatives exhibit various biological activities like fungicidal[1,2], bactericidal[1,2] and insecticidal[3,4]. Likewise 2-azetidinone[5-8] and 4- thiazolidinone[9-11] rings show a wide range of biological activities like fungicidal, bactericidal and antimicrobial. In view of this and encouraged by satisfactory performance of some oxadiazolyl-2-azetidinones[5], thiadiazolyl-2-azetidinones[8] and triazolyl-4-thiazolidinones[9] as fungicides, we considered it worthwhile to combine these above moieties in a molecular frame work to see how much their incorporation imparts towards the biological acivities. Keeping these facts in mind we undertook the synthesis of title compounds **4** and **5**.

The required 2-amino-5-aryl-1,3,4-oxadiazoles[12] **1** have been prepared by oxidative cyclisation of appropriate aldehyde thiosemicarbazones with bromine in anhyd. sodium acetate and glacial acetic acid. The thiadiazoles **1** have been prepared[13] by dehydrative cyclisation of appropriate 1-aroyl-3- thiosemicarbazide with conc. H_2SO_4 in cold. These 2-amino-1,3,4- oxa(thia)diazoles were treated with NaOH, CS_2 in DMF to get the corresponding disodium dithiocarbamate[14] **2**, which was stirred with 1,2-dichloroethane to obtain 5-aryl-2-(1,3-dithiolan-2- yl)imino-1,3,4-oxa(thia)diazoles **3**. Cyclocondensation of **3** with chloroacetyl chloride in dry dioxane in the presence of triethylamine and mercaptoacetic acid in dioxane, respectively gave the title compounds **4** and **5** (Scheme I).

Antifungal screening. The antifungal activity of the compounds of the type **4** and **5** was determined against *Aspergillus niger, Pyricularia oryzae,*



Scheme I

Table I— Physical data of the compounds **3**, **4** and **5**

Compd	R	X	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calcd)		
						C	H	N
3a	H	O	110	65	$C_{11}H_9N_3OS_2$	50.35	3.33	16.11
						(50.19	3.42	15.97)
3b	4-Cl	O	125	73	$C_{11}H_8N_3OS_2Cl$	44.26	2.78	14.24
						(44.37	2.69	14.12)
3c	4-CH_3	O	105	70	$C_{12}H_{11}N_3OS_2$	51.78	3.87	15.31
						(51.99	3.97	15.16)
3d	4-OCH_3	O	112	71	$C_{12}H_{11}N_3O_2S_2$	49.29	3.85	14.52
						(49.15	3.75	14.33)
3e	3-NO_2	O	135	66	$C_{11}H_8N_4O_3S_2$	42.65	2.81	18.32
						(42.86	2.60	18.18)
3f	H	S	155	64	$C_{11}H_9N_3S_3$	47.52	3.29	15.16
						(47.31	3.23	15.05)
3g	4-Cl	S	164	72	$C_{11}H_8N_3S_3Cl$	42.19	2.64	13.53
						(42.11	2.55	13.40)
3h	4-CH_3	S	187	73	$C_{12}H_{11}N_3S_3$	49.24	49.24	3.64
						(49.15	3.75	14.33)
3i	4-OCH_3	S	190	67	$C_{12}H_{11}N_3OS_3$	46.69	3.43	13.73
						(46.60	3.57	13.59)
3j	4-NO_2	S	172	70	$C_{11}H_8N_4O_2S_3$	40.88	2.40	17.39
						(40.74	2.47	17.28)
4a	H	O	152	63	$C_{13}H_{10}N_3O_2S_2Cl$	45.84	2.84	12.52
						(45.95	2.95	12.37)
4b	4-Cl	O	185	71	$C_{13}H_9N_3O_2S_2Cl_2$	41.50	2.29	11.09
						(41.71	2.41	11.23)
4c	4-CH_3	O	135	68	$C_{14}H_{12}N_3O_2S_2Cl$	47.46	3.54	11.69
						(47.52	3.39	11.88)
4d	4-OCH_3	O	165-6	66	$C_{14}H_{12}N_3O_3S_2Cl$	45.56	3.34	11.51
						(45.47	3.25	11.37)
4e	3-NO_2	O	175	62	$C_{13}H_9N_4O_4S_2Cl$	40.41	2.18	14.70
						(40.57	2.34	14.56)
4f	H	S	208	61	$C_{13}H_{10}N_3OS_3Cl$	44.03	2.90	11.66
						(43.88	2.81	11.81)
4g	4-Cl	S	180	67	$C_{13}H_9N_3OS_3Cl_2$	40.13	2.19	10.94
						(40.00	2.31	10.77)
4h	4-CH_3	S	205	70	$C_{14}H_{12}N_3OS_3Cl$	45.60	3.38	11.50
						(45.47	3.25	11.37)
4i	4-OCH_3	S	212	69	$C_{14}H_{12}N_3O_2S_3Cl$	43.72	3.19	10.78
						(43.58	3.11	10.89)
4j	4-NO_2	S	198	74	$C_{13}H_9N_4O_3S_3Cl$	38.85	2.39	13.79
						(38.95	2.25	13.98)
5a	H	O	192	62	$C_{13}H_{11}N_3O_2S_3$	46.49	3.33	12.59
						(46.29	3.26	12.46)
5b	4-Cl	O	177-8	69	$C_{13}H_{10}N_3O_2S_3Cl$	41.88	2.81	11.46
						(41.99	2.69	11.31)
5c	4-CH_3	O	135	64	$C_{14}H_{13}N_3O_2S_3$	47.68	3.87	11.76
						(47.86	3.70	11.97)

Contd..

Table I— Physical data of the compounds **3**, **4** and **5** — *Contd*

Compd	R	X	m.p. (C°)	Yield (%)	Mol. formula	Found (%) (Calcd)		
						C	H	N
5d	4-OCH_3	O	169-70	70	$C_{14}H_{13}N_3O_3S_3$	45.57	3.59	11.54
						(45.78	3.54	11.44)
5e	3-NO_2	O	180	68	$C_{13}H_{10}N_4O_4S_3$	40.67	2.69	14.53
						(40.84	2.62	14.66)
5f	H	S	235	66	$C_{13}H_{11}N_3OS_4$	44.34	3.28	11.77
						(44.19	3.12	11.90)
5g	4-Cl	S	240	67	$C_{13}H_{10}N_3OS_4Cl$	40.41	2.66	10.72
						(40.26	2.58	10.84)
5h	4-CH_3	S	198-200	71	$C_{14}H_{13}N_3OS_4$	46.17	3.43	11.69
						(46.03	3.56	11.51)
5i	4-OCH_3	S	245	64	$C_{14}H_{13}N_3O_2S_4$	43.66	3.28	10.79
						(43.86	3.39	10.97)
5j	4-NO_2	S	224	69	$C_{13}H_{10}N_4O_3S_4$	39.13	2.65	14.13
						(39.20	2.51	14.07)

Fusarium oxysporum and *Cephalosporum sacchari* at 100 and 10 ppm concentration by agar growth technique[15]. The results were compared with standard fungicide carbendazim tested under similar conditions.

The antifungal data of the tested compounds reveals that the compounds **4g, 4i, 5g** and **5i** show activity 75-85% at 100 ppm concentration against *P. oryzae* and *F. oxysporum* but it decreases sharply at 10 ppm concentration (Table II). The compounds **4** and **5** having oxadiazole moiety are less toxic than the corresponding compounds **4** and **5** having thiadiazole moiety. It has been observed further that the introduction of nitro group in compounds **4** and **5** reduces the activity as compared with chloro and methoxy substituted compounds **4** and **5**.

Antibacterial screening. The antibacterial activity of the title compounds were tested against *Escherichia coli, Solmonella typhi* and *Bacillus aureus* by filter paper disc method[16] with necessary modifications. All the test chemicals dissolved in DMSO and filter paper disc of 0.6 mm diameter containing 100 μg per disc were prepared, dried and placed on the surface of bacteria seeded agar plates. These were incubated at 37°C for 24 hr.

The antibacterial activity was determined by the following formula

$$\text{Activity} = \frac{Y - 0.6}{X - 0.6} \times 100$$

where X (mm) is the diameter of the inhibition zone by tetracyclin and $Y_{(mm)}$ is the diameter of the inhibition zone by the sample. The diameter of the paper disc was 0.6 mm.

Compounds **4b, 4c, 4g** and **4h** showed strong antibacterial activity whereas **5b, 5c, 5g** and **5h** showed moderate antibacterial activity against *E. coli* and *S. typhi* (Table II).

The antibacterial activity data of the tested compounds reveals that the spiro association of 2-azetidinone with 1,3-dithiolane moiety showed better activity than the spiro association of 4- thiazolidinone with 1,3-dithiolane moiety.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer - 881 spectrophotometer, ^{1}HNMR spectra on a Perkin Elmer R-32 spectrometer at 90 MHz in $CDCl_3$ and DMSO-d_6 using TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on a Jeol D-300 spectrometer.

5-(4-Chlorophenyl)-2-(1,3-dithiolan-2-yl)-imino- 1,3,4-oxadiazole 3b. A mixture of 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole (0.1 mole), CS_2 (10 mL) and NaOH (0.5 mole in 20 mL water) in DMF was stirred for 4 hr and then added 1,2-dichloroethane (0.1 mole)dropwise and NaOH (0.5 mole in 20 mL water) and the mixture was stirred again for 4

Table II—Antimicrobial activity of compounds 4_{a-j} and 5_{a-j}

Compd	Fungicidal activity at 100 ppm				Antibacterial activity at 100 μg/disc		
	A. niger	P. oryzae	*F. oxysporum*	*C. sachari*	*E. coli*	*S. typhi*	*B. aureus*
4a	45	52	44	44	25	43	20
4b	61	74	73	65	65	74	31
4c	55	55	54	47	60	69	25
4d	61	73	73	66	42	51	18
4e	36	37	37	42	11	18	—
4f	49	54	52	48	18	25	13
4g	70	83	80	68	71	59	21
4h	66	56	58	50	69	70	19
4i	67	80	76	54	28	49	32
4j	43	40	42	44	13	19	—
5a	52	66	59	54	20	24	18
5b	57	73	72	70	44	59	7
5c	52	67	64	55	38	52	15
5d	57	70	69	66	22	24	23
5e	43	48	48	45	7	11	—
5f	68	70	66	61	18	24	10
5g	78	85	83	69	54	42	28
5h	70	70	66	62	49	40	31
5i	70	84	81	69	43	37	37
5j	48	53	52	47	11	7	—
Carbendazim	86	89	89	87			
Tetracycline					100	100	100

hr. It was poured into ice cold water. The resulting solid mass was filtered, washed with ether and water successively, dried and recrystallized from aq. ethanol. m.p. 125°, yield 73%; MS: m/z 297 (M^+); IR (KBr): 1640 (C=N, exo), 1615 (C=N, endo); ^{1}HNMR (DMSO-d_6): 3.0 (s, 4H, 2×CH_2), 7.1-7.8 (m, 4H, ArH).

Other compounds of the type **3** were prepared similarly and are recorded in Table I.

5-(4-Chlorophenyl)- 2 -[spiro-(1,3-dithiolane)-2, 4′-(3′-chloro-2′-azetidinon)-1-yl]-1,3,4-oxadiazole 4b. A solution of 5-(4-chlorophenyl)-2-(1,3-dithiolan-2-yl)imino-1,3,4-oxadiazole (0.01 mole) and triethylamine (0.012 mole) in dry dioxane was stirred in ice bath and to this added chloroacetyl chloride (0.011 mole) dropwise. The solution was stirred for 6 hr, excess of dioxane removed and the residue was poured into water. The resulting solid mass was filtered, washed and recrystallised from aq. ethanol, m.p. 185°, yield 71%; MS: m/z 373 (M^+); IR (KBr): 1700(C=O), 1610(C=N); ^{1}HNMR (DMSO-d_6): 3.1 (s, 4H, 2×CH_2) 4.3 (s, 1H, CH), 7.0-7.6 (m, 4H, ArH).

Other compounds of the type **4** were prepared similarly and are recorded in Table I.

5-(4-Chlorophenyl) -2- [spiro - (1,3-dithiolane)-2,2′- (4′- thiazolidinon)-3′-yl]-1,3,4-oxadiazole 5b. A mixture of 5-(4-chlorophenyl)-2-(1,3-dithiolan-2-yl)imino-1,3,4-oxadiazole (0.01 mole) and mercaptoacetic acid (0.011 mole) in dioxane was refluxed for 6 hr, exces of dioxane removed and the residue was poured into water. The resulting solid mass was filtered, washed with sodium bicarbonate solution and water successively, dried and recrystallised from aq. ethanol. m.p. 177-78°, yield 69%; MS: m/z 371 (M^+); IR (KBr): 1680 (C=O), 1620 (C=N); ^{1}H NMR (DMSO-d_6): 3.1 (s, 4H, 2×CH_2), 3.4 (s, 2H, CH_2), 7.0-7.6 (m, 4H, ArH).

Other compounds of the type **5** were prepared similarly and are recorded in Table I.

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