# Studies on Biologically Active Heterocycles. Part I. Synthesis and Antifungal Activity of Some New Aroyl Hydrazones and 2,5-Disubstituted-1,3,4-oxadiazoles

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A series of new 1-(2,4-dichlorobenzoyl) hydrazones and 2-aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles have been synthesized from 2,4-dichlorobenzoylhydrazine and different aldehydes. Subsequent ring closure of the substituted aroyl hydrazones yielded the 1,3,4-oxadiazoles. All the compounds were characterized by their sharp melting point, microanalysis, ir, 'H nmr and mass spectra and screened for their fungitoxic properties against *Alternaria tenuis* and *Curvularia verruciformis*. A few of the compounds showed good activity.

J. Heterocyclic Chem., 23, 793 (1986).

During the course of our extensive program directed towards the synthesis of novel heterocycles of potential biological application, a variety of new 1,2,4-triazoles, 1,3,4-oxadiazoles, mercaptotriazoles and fused heterocyclic systems were synthesized and screened for biological activities [1-5].

Earlier reports reveal that several hydrazones of substituted aroylhydrazine exhibit bacteriostatic [6], antiparasite [6], psychotropic [7] and antifungal [6,8,9] activities. It has been shown [8] that the biological activity associated with these hydrazones was attributed to the presence of -CONHN = C- moiety. The 1,3,4-oxadiazoles have been reported to be biologically versatile compounds having bactericidal, fungicidal, herbicidal, analgesic, antiproteolytic, hypoglycemic, antiinflammatory, tranquilizing and CNS depressant [10-16] properties. The above observations created the interest for the synthesis of the previously unreported series of aroyl hydrazones 2a-k and 2,5-disubstituted-1,3,4-oxadiazoles **3a-h** containing a 2,4-dichlorophenyl moiety and to study their fungicidal properties. The synthesis of the title compounds 2a-k and 3a-h was accomplished in accordance with the sequence of reactions depicted in the Scheme 1.



Following the method of Yale et al [17], 1-(2,4-dichlorobenzyol)hydrazine (1) was obtained by refluxing ethyl 2,4-dichlorobenzoate and hydrazine hydrate (99%) in absolute ethanol. Condensation of this hydrazine 1 with appropriate alkyl/aryl/aralkylaldehydes yielded the corresponding hydrazones 2a-k. The hydrazones 2a-k on oxidative cyclization in presence of either Ferric chloride [18] or Lead dioxide [19] gave 1,3,4-oxadiazoles 3a-h. These methods gave low yield and the products were not easily isolable and in certain cases no reaction took place. Following another method [20], 2,5-disubstituted-1,3,4oxadiazoles 3a-h were synthesized by a route in which hydrazine 1 was condensed with appropriate aliphatic or aromatic acids in presence of phosphorus oxychloride (Scheme 1).

The products were identified by elemental analysis, (Table 1 and 2), ir, 'H nmr and mass spectra. In the ir spectra the hydrazones **2a-k** showed the bands ( $\nu$  cm<sup>-1</sup>), 3190-3160 (NH), 1675-1650 (-CONH-), 1615-1580 (C = N). The spectra of 1,3,4-oxadiazoles **3a-h** on the other hand lacked the C = O absorption bands. The 'H nmr spectra of the hydrazones **2a-k** showed peaks at  $\delta$  10.2-10.6 ppm (-CONH-) and 8.2-8.4 ppm (-CH = N-). The 'H nmr spectra of 1,3,4-oxadiazoles **3a-h** showed the characteristic peaks. The fragmentation of these compounds under electron impact was generally found to follow the general pattern anticipated for oxadiazoles [21].

# Determination of Fungitoxic Activity.

The new synthetic compounds were screened for fungitoxic properties. The method of the American Phytopathological Society [22] modified by Horsfall and Rich [23] was used for screening on two test organisms *Curvularia verruciformis*-Agarwal and Sahni and *Alternaria tenuis*-Nees. The screening result is shown in Table 3. No activity was exhibited by 1,3,4-oxadiazoles **3a-h**. Only three acyl hydrazones having phenolic hydroxyl group (**2f**, **2h** and **2j**) showed activity against both the organisims.

Compound				Molecular	Analysis (%) Found (Calcd.)		
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No.	к	Yield	Мр (°С)	formula	C	Н	N
2a	-CH,	79	146	C <sub>9</sub> H <sub>8</sub> Cl <sub>2</sub> ON <sub>2</sub>	46.68	3.42	12.25
					(46.75	3.46	12.12)
2Ь	-iso-C <sub>3</sub> H <sub>7</sub>	93	162	$C_{11}H_{12}Cl_2ON_2$	50.90	4.59	10.75
					(50.96	4.63	10.81)
<b>2</b> c	$-CH = CHCH_3$	87	197	$C_{11}H_{10}Cl_2ON_2$	51.40	3.83	10.80
					(51.36	3.89	10.89)
2d	2-Furyl	90	202	$C_{12}H_8Cl_2O_2N_2$	50.92	2.91	9.85
					(50.88	2.82	9.89)
2e	-C <sub>6</sub> H <sub>5</sub>	88	170	C14H10Cl2ON2	57.39	3.50	9.69
					(57.33	3.41	9.55)
2f	2-OHC <sub>6</sub> H <sub>4</sub>	82	145	$C_{14}H_{10}Cl_2O_2N_2$	54.40	3.30	9.19
					(54.36	3.23	9.06)
$2\mathbf{g}$	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	94	170	$C_{15}H_{12}Cl_2O_2N_2$	55.69	3.72	8.59
-					(55.72	3.71	8.66)
2h	2,4-di-(OH)C <sub>6</sub> H <sub>3</sub>	93	235	$C_{14}H_{10}Cl_2O_3N_2$	51.72	3.10	8.52
					(51.69	3.07	8.61)
<b>2i</b>	$-CH = CH - C_6H_5$	92	209	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> ON <sub>2</sub>	60.20	3.78	8.75
				÷	(60.19	3.76	8.77)
2j	3,4-(OCH3)(OH)C6H3	80	193	C15H12Cl2O3N2	\$3.10	3.58	8.30
-					(53.09	3.53	8.25)
2k	4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	92	214	C16H15Cl2ON3	57.20	4.49	12.48
					(57.14	4.46	12.50)

## Table 1

# Physical Data of 2,4-Dichlorobenzoyl Hydrazones 2a-k

Table 2

# Physical Data of 2-Aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-Oxadiazoles 3a-h

Compound					Analysis (%) Found (Calcd.)		
				Molecular			
No.	R	Yield	Mp (°C)	formula	С	Н	Ν
3a	-C <sub>6</sub> H <sub>5</sub>	86	113	C14H8Cl2ON2	57.62	2.81	9.65
					(57.73	2.74	9.62)
3b	4-OCH₃C₀H₄	85	145	$C_{15}H_{10}Cl_2O_2N_2$	56.12	3.20	8.71
					(56.07	3.11	8.72)
3c	4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	82	208	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> ON <sub>3</sub>	57.42	3.79	12.59
					(57.48	3.89	12.57)
3d	$-CH = CH - C_6H_5$	82	148	C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> ON <sub>2</sub>	60.55	3.18	8.80
					(60.56	3.15	8.83)
3e	3,4-di-ClC <sub>6</sub> H <sub>3</sub>	89	187	C14H6Cl2ON2	46.52	1.72	7.70
					(46.66	1.66	7.77)
3f	-(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	84	183	$C_{16}H_{12}Cl_2ON_2$	60.20	3.75	8.72
					(60.18	3.76	8.77)
3g	2-Cl-C <sub>6</sub> H₄	91	153	C <sub>14</sub> H <sub>7</sub> Cl <sub>2</sub> ON <sub>2</sub>	51.59	2.20	8.69
0					(51.61	2.15	8.60)
3h	2-OH-C <sub>6</sub> H₄	82	141	C14H8Cl2O2N2	54.78	2.65	9.02
					(54.72	2.60	9.12)

## EXPERIMENTAL

Melting points were determined with a Büchi oil heated apparatus in open capillaries and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer 237B spectrophotometer using potassium bromide discs, unless otherwise stated ( $\nu$  max in cm<sup>-1</sup>). Nuclear magnetic

resonance ('H nmr) spectra were recorded in solutions stated with TMS as the internal reference in 60 MHz on a Varian T-60 spectrometer (Chemical shift in  $\delta$  ppm) and mass spectra were recorded on an AEIMS-30 instrument at 70 ev. 2,4-Dichlorobenzhydrazide (1) was prepared from ethyl 2,4-dichlorobenzoate following the method of Yale et al [17] yield 63%, mp 163°.

Table 3

Percentage Inhibition of Conidial Germination in the Test Solutions

Compound	Test Organisms				
No.	Curvularia verruciformis	Alternaria tenuis			
2a	_	_			
$\mathbf{2b}$		_			
2c	_	-			
2d	_	-			
<b>2e</b>					
2f	+	+ +			
2g	—	_			
2h	+ + +	+ + +			
<b>2i</b>	_	_			
2i	++	+ +			
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- = No inhibition, + = 0.25%, + + = 26.50%, + + + = 51.75%and + + + + = 76.100% inhibition.

## 1-(2,4-Dichlorobenzoyl) Hydrazones 2a-k.

#### General Procedure.

To a hot ethanolic solution of 2,4-dichlorobenzhydrazide (1) (0.01 mole), a solution of corresponding aldehyde (0.01 mole) in 10 ml ethanol was added and the reaction mixture was refluxed for 2-3 hours. On cooling the separated solid was filtered and recrystallized from ethanol to yield the hydrazones **2a-k**; ir, 3190-3160 (NH), 1673-1650 (-CONH-), 1615-1580 (C = N); 'H nmr (deuteriochloroform/DMSO-d<sub>e</sub>): 10.2-10.6 (-CONH-), 8.2-8.4 (-CH = N-). The physical properties and yields for the compounds are given in Table 1.

2-Aryl/aralkyl-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles **3a-h**. Method A [18].

Hydrazone 2 (0.01 mole) were dissolved in 25 ml glacial acetic acid and a solution of ferric chloride (15 g) in water was added to it with shaking. The mixture was then stirred for 1 hour and diluted with water (200 ml) and kept at room temperature for 2 days. The separated solid **3** was filtered, washed with water, dried and crystallized to give the pure product.

## Method B [19].

To a solution of hydrazone 2(0.01 mole) in 40 ml glacial acetic acid 2.39 g (0.01 mole) lead dioxide was added. Then the mixture was stirred at 25° for 1 hour and diluted with 200 g ice and 100 ml water. The precipitate was then filtered, washed with water and dried and recrystallized from ethanol.

### Method C [21].

A mixture of 2,4-dichlorobenzhydrazide (1) (0.01 mole) appropriate monocarboxylic acids (0.01 mole) and phosphorus oxychloride (5 ml) was refluxed for 3-5 hours. The cold reaction mixture was poured into ice water and made basic by adding sodium bicarbonate solution. The resulting solid was filtered, dried and recrystallized from chloroform to give the desired oxadiazoles **3a-h**. The physical properties and yields for the compounds are given in Table 2; ir: 1645-1600 (C=N), 1250-1245 (C-O-C); 'H nmr (deuteriochloroform/DMSO-d\_6): 7.0-7.4 (m, Aromatic-H).

#### Acknowledgement.

The authors are grateful to Dr. J. N. Baruah, Director, Regional Research Laboratory, Jorhat, Assam for permitting one of the authors (MMD) to carry out the research work in the laboratory. Authors are also thankful to Dr. S. C. Nath of this laboratory for fungicidal screening of the compounds and the Analytical Division for recording mass, ir, 'H nmr spectra of the compounds.

#### **REFERENCES AND NOTES**

[1] B. N. Goswami, J. C. S. Kataky and J. N. Baruah, J. Heterocyclic Chem., 21, 1225 (1984).

[2] B. N. Goswami, J. C. S. Kataky and J. N. Baruah, Indian J. Chem., 23B, 796 (1984).

[3] B. N. Goswami, J. C. S. Kataky, J. N. Baruah and S. C. Nath, J. Heterocyclic Chem., 21, 205 (1984).

[4] B. N. Goswami, J. C. S. Kataky, J. N. Baruah, S. C. Nath and D. N. Bordoloi, J. Indian Chem. Soc., LXI, 530 (1984).

[5] B. N. Goswami, Ph. D. Thesis of Dibrugarh University, Assam, India, 1984.

[6] S. Bahadur, A. K. Goel and R. S. Verma, J. Indian Chem. Soc., 52, 843 (1975).

[7] K. Sasajima, K. Ono, H. Nakao, I. Marayama, S. Katayama, S. Inaba and H. Yamamoto, German Offen., 2536164 (1976); *Chem. Abstr.*, **84**, 164631 (1976).

[8] L. Giammanco, Ann. Chim. (Rome), 51, 175 (1961).

[9] R. B. Pathak and S. C. Bahel, J. Antibact. Antifung. Agents, 9, 9 (1981).

[10a] S. Giri, H. Singh and L. D. Yadav, Agric. Biol. Chem, 40, 17
(1976); Chem. Abstr., 84, 121736 (1976); [b] V. J. Ram and H. N. Panday,
J. Indian Chem. Soc., 51, 634 (1974).

[11] I. Angelini, L. Angelini and F. Sparaco, British Patent, 1,161,801 (1969); Chem. Abstr., 71, 112936g (1969).

[12] H. Najer, R. Gindicelli, C. Morel and J. Menin, Bull. Soc. Chim, France, 153 (1966).

[13] S. K. Chaudhary, M. Chaudhary, A. Chaudhary and S. S. Parmar, J. Pharm. Sci., 67, 1507 (1978).

[14] V. Kishore, S. Kumar, S. S. Parmar and V. I. Stenberg, Res. Commun. Chem. Pathol. Pharmacol., 11, 581 (1975).

[15] J. J. Piala and H. L. Yale, U. S. Patent, 3,142,022 (1964); Chem. Abstr., 62, 8317b (1964).

[16] H. L. Yale and K. Losee, J. Med. Chem., 9, 478 (1966).

[17] H. L. Yale, K. Losee, J. Martin, H. Hervy, F. M. Pervy and J. Bernstain, J. Am. Chem. Soc., 75, 1933 (1953).

[18] S. P. Hiremath, N. N. Gouder and M. G. Purohit, Indian J. Chem., 21B, 321 (1982).

[19] Rene Milcent and Geo Barbier, J. Heterocyclic Chem., 20, 77 (1983).

[20] T. Ramalingam, A. A. Deshmukh, P. B. Sattur, J. Indian Chem. Soc., LVIII, 269 (1981).

[21a] Q. N. Porter and J. Boldes in "Mass Spectrometry of Heterocyclic Compounds", Wiley Interscience, New York, NY, 1971, p 528-529; [b] J. L. Cotter, J. Chem. Soc., 5491 (1964).

[22] American Phytopathological Society, *Phytopathology*, **33**, 627 (1943).

[23] J. G. Horsfall and S. Rich, Indian Phytopathology, 6 (II), 1 (1953).