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Studies on Potential Pesticides—Part XIV : Synthesis and Biological Activities of some new Thiosemicarbazide and Triazole Derivatives

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Abstract. Some new N^1-[5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-N^4-aryl-thiosemicarbazides have been synthesised by the condensation of appropriate hydrazines with arylisothiocyanates. Cyclisation of these thiosemicarbazides in alkaline medium gives 3-[5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-4-aryl-5-mercapto-1,2,4-triazoles. All these compounds have been evaluated for their antibacterial properties and some of these have been screened for their anti fungal activity and AChE inhibition.

1. Introduction

In recent years, thiosemicarbazides have been reported to possess potential antibacterial[1], antifungal[2,3] and antiacetylcholinesterase[4] activities.

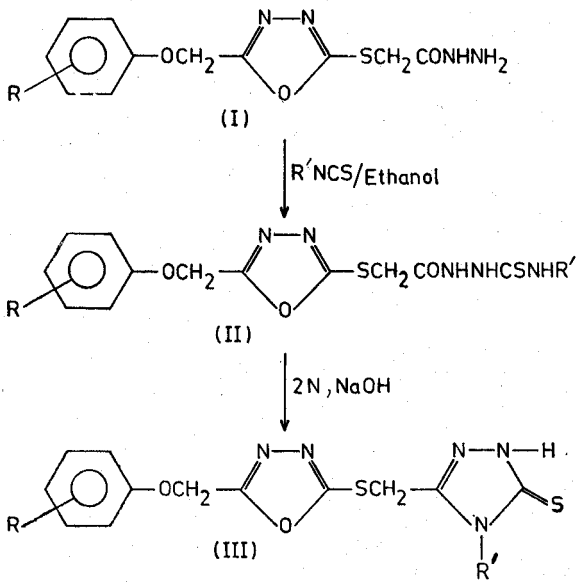
Triazoles have also gained recognition as good bactericides[5], anticonvulsants[6], fungicides[7] and herbicides[8]. Recently triazole analogues have been reported[9,10] to possess antifungal properties against *Puccinia recondita, Aspergillus niger* and *Apergillus flavus.*

A number of thiosemicarbazides and triazoles[10,11] showed antibacterial activity against *Escherichia coli, Staphylococcus aureus, Salmonella typhi* and *Bacillus magaterium* to a great extent.

The present paper describes the synthesis of thiosemicarbazides (II), by the condensation of 5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetic acid hydrazine(I) with various substituted phenyl isothiocyanates. These thiosemicarbazides are cyclised with *NaOH*(2*N*) to give triazoles of the type (III). All these compounds have been screened for their antibacterial activity and a few of them for antifungal and antiacetylcholinesterase inhibition.

2. Experimental Procedure

5-(Substituted phenoxymethyl)-2-mercapto-1,3,4-oxadiazoles[12] and 5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetic acid hydrazines[13] required for this work were synthesised by the known procedure.



N^1-[5-(Substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-N^4-arylthiosemicarbazides II

Equimolar solutions (0.01 mole) of appropriate 5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetic acid hydrazine and arylisothiocyanate in ethanol were refluxed on steam bath for 3 hours. The solid mass separated on cooling was crystallised with ethanol. The different semicarbazides are recorded in Table 1.

3-[5-(*Substituted phenoxymethyl*)-1,3,4-*oxadiazolyl-2-thioacetyl*]-4-*aryl*-5-*mercapto*-1,2,4-*triazoles III*

0.005 mole of the appropriate thiosemicarbazide, (II), was dissolved in, *NaOH* (2*N*; 20 ml); the clear solution was heated over a steam bath for 4-6 hours, filtered and neutralised with dilute acetic acid. The solid mass thus obtained was crystallised with ethanol. The various products are listed in Table 2.

3. Pharmacological Studies

All the synthesised compounds were evaluated for their antibacterial inhibition against *Staphylococcus aureus*, *Bacillus pumilus* and *Bacillus subtilis* by adopting agar plate diffusion technique[14]. The zones of inhibition measured in milimeter, are indicated against each in Tables 1 and 2.

The results of this screening have shown that all the thiosemicarbazides and triazoles inhibited the growth of test organisms to a great extent. The bacterium *B. pumilus* was more effectively inhibited as compared to the other two organisms.

A few thiosemicarbazides and the four triazoles were screened for *fungicidal* action against *Fusarium roseun*, *Aspergillus niger* and *Helminthosporium* species using agar

Table 1. N^1-[5-(Substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-N^4-aryl thiosemicarbazide (II).

Compound No.	*R*	*R'*	M. P. (°C)	Yield (%)	Mol. formula	Percentage Nitrogen		Antibacterial activity		
						Found	required	*S. aureus*	*B. pumilus*	*B. subtilis*
1.	4-CH_3	2-chlorophenyl	116	67	$C_{19}H_{18}ClN_5O_3S_2$	15.00	15.08			
2.	4-CH_3	3-chlorophenyl	173	62	$C_{19}H_{18}ClN_5O_3S_2$	15.10	15.08	++	++	−
3.	4-CH_3	4-chlorophenyl	188	58	$C_{19}H_{18}ClN_5O_3S_2$	15.15	15.08	++	−	+++
4.	4-CH_3	benzyl	180	58	$C_{20}H_{21}N_5O_3S_2$	15.70	15.80	−	−	++
5.	4-CH_3	2-methoxyphenyl	166	60	$C_{20}H_{21}N_5O_4S_2$	15.15	15.25	++	++	−
6.	4-*Cl*	2-chlorophenyl	167	55	$C_{18}H_{15}Cl_2N_5O_3S_2$	14.45	14.46	−	++	++
7.	4-*Cl*	4-methylphenyl	164	60	$C_{19}H_{18}ClN_5O_3S_2$	15.35	15.41	++	+++	+
8.	2,4-*di-cl*	2-chlorophenyl	166	62	$C_{18}H_{14}Cl_3N_5O_3S_2$	13.45	13.48	++	−	−
9.	2,4-*di-cl*	3-chlorophenyl	179	58	$C_{18}H_{14}Cl_3N_5O_3S_2$	13.55	13.48	++	++	−
10.	2,4-*di-cl*	4-chlorophenyl	193	65	$C_{18}H_{14}Cl_3N_5O_3S_2$	13.42	13.48	−	+++	+++
11.	2,4-*di-cl*	benzyl	200	60	$C_{19}H_{17}Cl_2N_5O_3S_2$	14.00	14.05	+++	−	++
12.	2,4-*di-cl*	2-methoxyphenyl	170	55	$C_{19}H_{17}Cl_2N_5O_4S_2$	15.52	13.61	−	++	++

For antibacterial activity : − = no inhibition; + = zone size 6-8 mm; ++ = zone size 8-1.4 mm; +++ = zones size greater than 1.4 mm.

Table 2. 3-[5-(Substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-4-aryl-5-mercapto-1,2,4-triazoles (III).

Compound No.	*R*	*R'*	M.P. (°C)	Yield (%)	Mol. formula	Percentage nitrogen		Antibacterial activity		
						Found	required	*S. aureus*	*B. pumilus*	*B. subtilis*
13.	4-chloro	4-Benzyl	212	67	$C_{19}H_{16}ClN_2O_2S_2$	15.65	15.69	−	+++	++
14.	4-methyl	benzyl	185	62	$C_{20}H_{19}N_5O_2S_2$	16.35	16.47	++	++	+++
15.	4-methyl	3-chlorophenyl	214	65	$C_{19}H_{16}ClN_5O_2S_2$	15.61	15.69	++	−	−
16.	4-methyl	2-methoxy phenyl	184	60	$C_{20}H_{19}N_5O_3S_2$	15.83	15.87	++	+	+++

For antibacterial activity : − = no inhibition; + = zone size 6-8 mm; ++ = zone size 8-1.4 mm; +++ = zone greater than 1.4 mm

plate technique[15]. The percentage inhibition is given in Tables 3 and 4 for thiosemicarbazides and triazoles respectively.

These compounds inhibited the fungal growth upto 60 per cent. Fungus species *F. roseum* and *Helminthosporium* species are comparatively more affected. However, *m*-chloro substitution in compounds No. 2, 9 and 15 at R′ minimised the inhibition to a great extent.

The method of Hestrin[16] was employed to determine *antiacetylcholinesterase* activity. Compounds No. 3, 4, 10, 12, 13, 14 and 16 were dissolved in propylene glycol (100%) used at a concentration of 3.8×10^{-4}M for AChE screening. A control containing equal volume of propylene glycol was run in parallel. The percentage inhibition and I_{50} value for the said compounds have been recorded in Table 5.

Only marginal inhibition of the enzyme acetylcholinesterase has been shown by these compounds except for the benzyl substituted thiosemicarbazide (Compd. No. 2) which has been associated with 80 percent enzyme inhibition; 2,4-di-chloro substitution at *R* in compound No. 10 has markedly enhanced the enzyme inhibition.

Table 3. Fungicidal activity of N^1-[5-(substituted phenoxymethyl)-1,3,4-oxadiazole-2-thioacetyl]-N^4-aryl thiosemicarbazides.

Compound No.	Concentration	Colony diameter (cm)			Percentage inhibition		
		F. roseum	*A. niger*	*Helm. sp.*	*F. roseun*	*A. niger*	*Helm. sp.*
2.	1 : 1,000	3.8	4.1	3.2	36.6	18.0	36.0
	1 : 10,000	4.0	4.5	3.5	33.3	10.0	30.0
	1 : 1,00,000	4.1	4.7	3.7	31.6	6.0	26.0
3.	1 : 1,000	3.0	3.6	2.5	50.0	28.0	50.0
	1 : 10,000	3.3	3.9	2.7	45.0	22.0	46.0
	1 : 1,00,000	3.8	4.0	2.8	36.6	20.0	44.0
6.	1 : 1,000	3.9	4.0	3.2	35.0	20.0	36.0
	1 : 10,000	4.7	4.2	3.6	21.6	16.0	28.0
	1 : 1,00,000	4.8	4.3	3.7	20.0	14.0	26.0
7.	1 : 1,000	1.5	3.2	2.1	75.0	36.0	58.0
	1 : 10,000	2.2	3.8	2.4	63.3	24.0	52.0
	1 : 1,00,000	2.7	3.8	2.4	55.0	24.0	52.0
9.	1 : 1,000	3.9	4.2	2.5	35.0	16.0	50.0
	1 : 10,000	4.3	4.8	2.8	28.3	4.0	44.0
	1 : 1,00,000	4.7	5.0	3.0	21.6	0.0	40.0
10.	1 : 1,000	2.8	4.6	3.1	53.3	8.0	38.0
	1 : 10,000	3.3	5.0	3.3	45.0	0.0	34.0
	1 : 1,00,000	3.7	5.0	4.0	38.3	0.0	20.0
	Control	6.0	5.0	5.0			

Table 4. Fungicidal activity of 3-[5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-4-aryl-5-mercapto-1,2,4-triazoles.

Compound No.	Concentration	Colony diameter (cm)			Percentage inhibition		
		F. roseum	*A. niger*	*Helm. sp.*	*F. roseum*	*A. niger*	*Helm. sp.*
13.	1 : 1,000	2.7	3.4	3.8	55.0	32.0	24.0
	1 : 10,000	3.1	3.8	4.2	48.3	24.0	16.0
	1 : 1,00,000	3.3	3.8	4.3	45.0	24.0	14.0
14.	1 : 1,000	2.8	3.5	3.9	53.3	30.0	22.0
	1 : 10,000	3.0	3.8	4.2	50.0	24.0	16.0
	1 ; 1,00,000	3.5	4.2	5.0	41.6	16.0	0.0
15.	1 : 1,000	2.0	3.1	2.4	66.6	38.0	52.0
	1 : 10,000	2.5	3.6	3.0	58.3	28.0	40.0
	1 : 1,00,000	2.7	3.8	3.5	55.0	24.0	30.0
16.	1 : 1,000	3.9	2.5	3.8	35.0	50.0	24.0
	1 : 10,000	4.4	2.9	4.6	26.6	42.0	8.0
	1 : 1,00,000	5.0	3.2	5.0	16.6	36.0	0.0
	Control	6.0	5.0	5.0			

Table 5. Antiacetylcholinesterase activity of new thiosemicarbazide and triazole derivatives.

Compound No.	Concentration	Percentage inhibition	I_{50}^{a} (1×10^{-4}M)
3.	3.8×10^{-4}	22.54	8.4
4.	3.8×10^{-4}	80.13	2.3
10.	3.8×10^{-4}	65.24	2.9
12.	3.8×10^{-4}	36.44	5.2
13.	3.8×10^{-4}	41.41	4.5
14.	3.8×10^{-4}	32.47	5.8
16.	3.8×10^{-4}	34.45	5.5

a. The I_{50} value indicates the concentration required to produce 50 percent inhibition of enzyme. The I_{50} value for Neostigmine a potent AChE-inhibitor used as standard in the similar conditions, is 1.96×10^{-7}M.

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