Synthesis and Pesticidal Activities of Some New Substituted 1,2,4-Triazoles and Their Derivatives

Anil K. Sen GUPTA and Hemant K. MISRA

Organic Chemistry Laboratories, University of Lucknow, Lucknow 226007, India

Received August 29, 1979

In a continued search for new potential pesticidal agents, two new substituted 1,2,4-triazole derivatives were synthesized. These were condensed with various substituted 1,3,4-thiadiazole and *N*-chloroacetyl-*N'*-aryl urea derivatives. The compounds thus obtained were screened for their insecticidal and bactericidal activities. Most of these have been found to possess significant pesticidal activities. The relation between their pesticidal properties and chemical structure has been studied.

As a number of organic compounds having 1,2,4-triazole ring system are known for their pesticidal activities[1～3] and some of these have even been patented as bactericidal,[4] insecticidal,[5] virucidal[6] and fungicidal[7] agents, we thought of incorporating an additional heterocyclic moiety, 1,3,4-thiadiazole and *N*-chloroacetyl-*N'*-aryl urea, in the triazole nucleus and studying their effect on pesticidal potentialities of the triazole derivatives.

The new substituted 1,2,4-triazoles (**II**) were prepared by cyclization of thiosemicarbazide derivatives (**I**) in sodium hydroxide solution according to the following scheme;

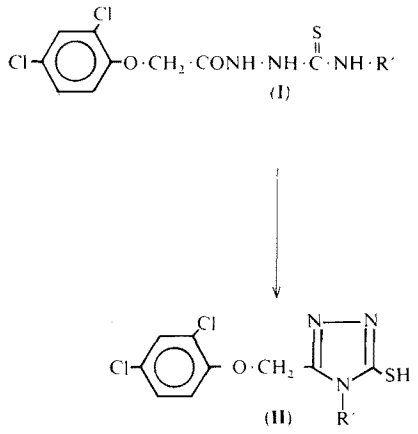

FIG. 1

Thus, the new compounds prepared by us are 3-(2, 4-dichlorophenoxymethyl)-4-aryl-5-mercapto-1,2,4-triazole derivatives. The structures of these compounds have been established from their elemental analysis and IR spectroscopy. IR spectra of these triazole derivatives were in agreement with those already reported in literature.[8] Presence of two strong bands around 1300 cm^{-1} showed their existence predominantly in thione-form, but a weak band at 2550 cm^{-1} also indicated their presence in thiol-form as well in a tautomeric mixture. Further, a band around 1600 cm^{-1} showed the presence of C=N grouping.

By condensation of these two triazole derivatives (**II**) with different 2-chloroacetylamino-5-alkyl-1,3,4-thiadiazoles (**III**), a number of new 3-(2,4-dichlorophenoxymethyl)-4-aryl-5-[*N*-(2'-alkyl-1',3',4'-thiadiazol-5'-yl)carbamoylmethylthio]-1,2,4-triazole derivatives (**IV**) were obtained. Similarly, by their condensation with suitable *N*-chloroacetyl-*N'*-aryl ureas (**V**), 3-(2,4-dichlorophenoxymethyl)-4-aryl-5-[*N*-(*N*-arylcarbamoyl)carbamoylmethylthio]-1, 2, 4-triazole derivatives (**VI**) were synthesised.

The structures of the final compounds have been established from their correct analytical data. The IR spectra of (**IV**) and (**VI**) showed the absence of ν SH vibration at 2550 cm^{-1}. The IR spectra of **IV** showed absorption bands at 1600 cm^{-1} (C=N), 1690 cm^{-1} (CO), 1660 cm^{-1} (CONH) and a band from 1255 to 1265 cm^{-1} for N−N=C (cyclic) grouping. The IR spectra of compounds (**VI**) showed absorption

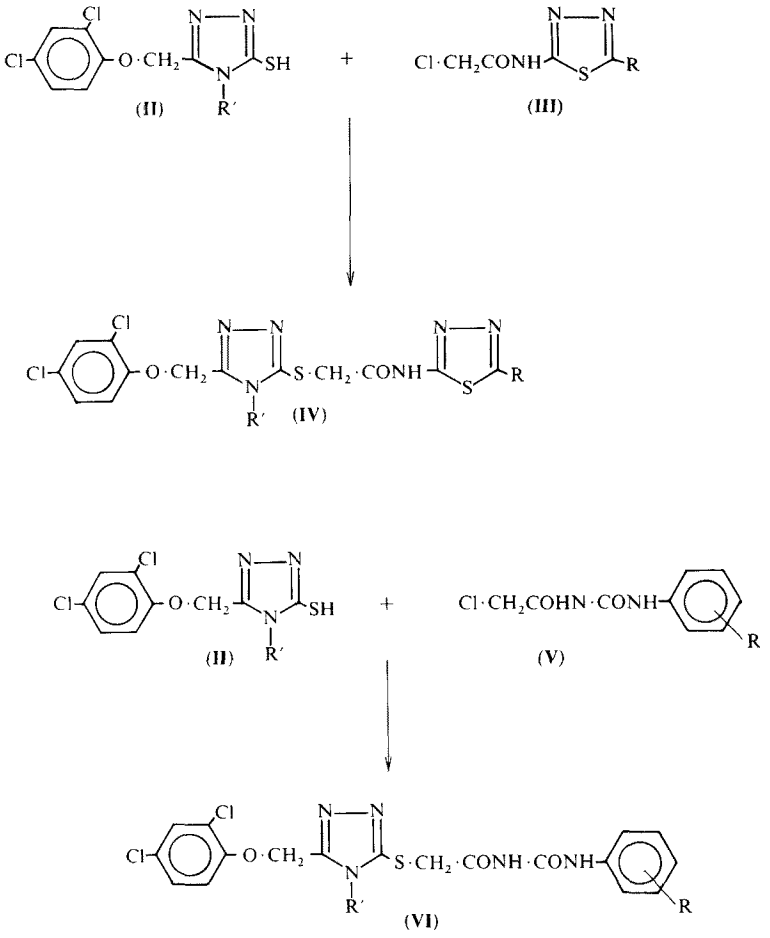

FIG. 2

peaks at 3280 cm^{-1} (NH vibration), 1720 and 1690 cm^{-1} (CO) and 1550 cm^{-1} (CNH).

2-Chloroacetylamino-5-alkyl-1,3,4-thiadiazoles were prepared by the method of Mavro *et al.*[9] Substituted aryl ureas were prepared from KCNO and different amines[10] and corresponding *N*-chloroacetyl-*N'*-aryl ureas by the method of Jacobs.[11]

EXPERIMENTAL

Melting points were taken in open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer in KBr pellets.

3-(2,4-Dichlorophenoxymethyl)-4-aryl-5-mercapto-1,2,4-triazole (**II**). 2,4-Dichlorophenoxyacetyl-N^4-aryl-3-thiosemicarbazide (**I**), (0.005 mol) was dissolved in 10 ml of 2 N sodium hydroxide solution. The clear solution thus obtained was heated under reflux for 4 hr. It was, then, filtered after cooling and neutralized with dilute hydrochloric acid. The precipitated compound was filtered and washed with water and then crystallized from ethanol. Triazole derivatives thus prepared are listed in Table I.

3-(2,4-Dichlorophenoxymethyl)-4-aryl-5-[*N-(2'-alkyl-1',3',4'-thiadiazol-5'-yl)-carbamoylmethylthio*]-*1,2,4-triazole* (**IV**). A suspension of 3.66 g (0.01 mol) 3-(2,4-dichlorophenoxymethyl)-4-benzyl-5-mercapto-1,2,4-triazole and sodium hydroxide (0.01 mol) in ethanol (30 ml) was kept for heating under reflux, 2.06 g (0.01 mol) 2-chloroacetylamino-5-ethyl-1,3,4-thiadiazole (**III**) was added to it after a few minutes, and heating was then continued for about 4 hr. After this, the reaction mixture was allowed to cool and the solid mass obtained on adding water to it was filtered and crystallized from ethanol.

All compounds synthesized in this series were prepared in similar manner and are listed in Table II.

TABLE I. THE YIELD, PHYSICAL CONSTANTS AND MICROANALYTICAL DATA OF NEW TRIAZOLE DERIVATIVES (II)

Compound No.	R′	mp (°C)	Yield (%)	Molecular formula	% of N	
					Calcd.	Found
1	Benzyl	187	67	$C_{16}H_{13}Cl_2N_3OS$	11.47	11.34
2	2-Ethylphenyl	163	56	$C_{17}H_{15}Cl_2N_3OS$	11.05	10.99

TABLE II. THE YIELD AND THE PHYSICAL CONSTANTS OF NEW TRIAZOLE COMPOUNDS (IV)

Compound No.	R′	R	mp (°C)	Yield (%)	Molecular formula	% of N	
						Calcd.	Found
3	Benzyl	CH_3	155	63	$C_{21}H_{18}Cl_2N_6O_2S_2$	16.12	16.37
4	Benzyl	C_2H_5	135	67	$C_{22}H_{20}Cl_2N_6O_2S_2$	15.70	15.97
5	Benzyl	C_3H_7	137	60	$C_{23}H_{22}Cl_2N_6O_2S_2$	15.30	15.47
6	2-Ethylphenyl	CH_3	191	57	$C_{22}H_{20}Cl_2N_6O_2S_2$	15.70	15.67
7	2-Ethylphenyl	C_2H_5	193	60	$C_{23}H_{22}Cl_2N_6O_2S_2$	15.30	15.40
8	2-Ethylphenyl	C_3H_7	181	49	$C_{24}H_{24}Cl_2N_6O_2S_2$	14.92	14.87

TABLE III. THE PHYSICAL CONSTANTS AND THE MICROANALYTICAL DATA OF NEW TRIAZOLYL UREA DERIVATIVES (VI)

Compound No.	R′	R	mp (°C)	Yield (%)	Molecular formula	% of N	
						Calcd.	Found
9	Benzyl	H	139	60	$C_{25}H_{21}Cl_2N_5O_3S$	12.91	12.75
10	Benzyl	2-CH_3	147	55	$C_{26}H_{23}Cl_2N_5O_3S$	12.59	12.44
11	Benzyl	3-CH_3	135	57	$C_{26}H_{23}Cl_2N_5O_3S$	12.59	12.63
12	Benzyl	4-CH_3	141	60	$C_{26}H_{23}Cl_2N_5O_3S$	12.59	12.60
13	Benzyl	2-OCH_3	133	63	$C_{26}H_{23}Cl_2N_5O_4S$	12.23	12.15
14	Benzyl	2-Cl	138	65	$C_{25}H_{20}Cl_3N_5O_3S$	12.13	12.10
15	Benzyl	4-Cl	134	68	$C_{25}H_{20}Cl_3N_5O_3S$	12.13	12.17
16	Benzyl	2-Et	145	65	$C_{27}H_{25}Cl_2N_5O_3S$	12.28	12.40
17	2-Ethylphenyl	H	187	57	$C_{26}H_{23}Cl_2N_5O_3S$	12.59	12.63
18	2-Ethylphenyl	2-CH_3	186	58	$C_{27}H_{25}Cl_2N_5O_3S$	12.28	12.43
19	2-Ethylphenyl	3-CH_3	191	63	$C_{27}H_{25}Cl_2N_5O_3S$	12.28	12.17
20	2-Ethylphenyl	4-CH_3	193	65	$C_{27}H_{25}Cl_2N_5O_3S$	12.28	12.50
21	2-Ethylphenyl	2-OCH_3	187	67	$C_{27}H_{25}Cl_2N_5O_4S$	11.94	12.00
22	2-Ethylphenyl	2-Cl	185	65	$C_{26}H_{22}Cl_3N_5O_3S$	11.84	11.71
23	2-Ethylphenyl	4-Cl	170	70	$C_{26}H_{22}Cl_3N_5O_3S$	11.84	11.93
24	2-Ethylphenyl	2-Et	191	63	$C_{28}H_{27}Cl_2N_5O_3S$	12.00	12.07

3-(2,4-Dichlorophenoxymethyl)-4-aryl-5-[N-(N-arylcarbamoyl)carbamoylmethylthio]-1,2,4-triazole (**VI**). To a solution of 3.66 g (0.01 mol) of 3-(2,4-dichlorophenoxymethyl)-4-benzyl-5-mercapto-1,2,4-triazole in ethanol (30 ml), 0.4 g (0.01 mol) of sodium hydroxide was added and the mixture was kept for heating under reflux. After a few minutes, 2.42 g (0.01 mol) *N*-chloroacetyl-*N'*-(2-methoxyphenyl) urea (**V**) was added to it, and the heating was then continued for about 5 hr. Finally, the reaction mixture was allowed to cool and the solid obtained on adding water to it was filtered and crystallized from ethanol.

All urea derivatives were prepared in similar manner and are listed in Table III.

Evalution of the newly synthesized compounds for toxicity

TABLE IV. INSECTICIDAL AND BACTERICIDAL DATA OF THE TEST COMPOUNDS

Compound No.	Insecticidal activity* mean K.D. time (hr) Percentage concentration		Antibacterial activity against**		
			S. aureus	*B. subtilis*	*B. pumilus*
	0.5%	0.1%			
1	8.5	9.5	++	++	+
2	10.5	11.5	++	+	+
3	8.0	9.5	+	++	+
4	8.5	10.5	++	−	++
5	9.0	10.0	+	+	+
6	7.0	9.5	+	+	++
7	8.5	11.5	+	+	++
8	10.0	11.5	−	++	+
9	9.0	10.5	+++	++	++
10	8.5	9.5	+	−	+
11	7.0	9.0	++	++	++
12	7.5	9.5	+++	+++	++
13	8.0	9.0	+	+	−
14	8.0	9.5	+	+	++
15	7.5	8.5	+++	+++	++
16	6.5	8.0	+	−	−
17	7.0	8.5	+	−	−
18	7.5	8.5	+	+	+
19	7.0	8.5	+	−	+
20	8.0	10.5	+++	++	+++
21	8.0	10.0	+	+	−
22	8.5	10.0	−	−	+
23	7.5	8.5	++	−	+
24	8.0	9.0	+	−	−
Parathion	4.5	5.5	−	−	−
Acetone	40	40	−	−	−
Chloramphenicol	—	—	+++	+++	+++
Tetracyclin	—	—	++++	++	+++

− = No inhibition; + = Zone size 6~8 mm.
++ = Zone size 9~14 mm; +++ = Zone size 15~20 mm.
++++ = Zone size greater than 20 mm.
* No. of replications for each test sample, 10; ml inject/animal (replication), 0.02 ml.
** Filter paper (Whatman No. 41) discs (5 mm diameter) saturated with the solution of the test compound (10 mg/ml in ethanol) were placed on the nutrient agar plates after drying up the solvent. Each disc contained 150 μg of the substance. The plates were incubated at optimum growth temperature of 37°C and the zones of inhibition around the discs were measured after 24 hr.

All newly synthesized compounds (**II**, **IV** and **VI**) were screened for their insecticidal activities against adult male and female cockroaches, following the method of Joshi[12] and Nash.[13] Antibacterial spectra of these compounds were evaluated by agar plate diffusion technique[14] against *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus pumilus*. The results of these insecticidal and antibacterial tests are given in Table IV.

RESULTS AND DISCUSSION

All the newly synthesized compounds (**II**, **IV** and **VI**) displayed pesticidal activities. When, any one of these was injected into the test cockroaches, the latter fell on their backs after about 2 hr. This was followed by kicking of legs, convulsions of abdomen and flickering of antennae for about 6 hr. The knockdown or moribund state was reached between 7.0~8.5 to 10.0~11.5 hr after injecting a compound. Percentage mortality during this period varied from 50 to 80 (Table IV).

It was observed that 5-[*N*-(*N*-arylcarbamoyl)carbamoylmethylthio]-1, 2, 4-triazole derivatives (compounds no. 9~24; Table IV), exhibited more pronounced insecticidal activity than the 5-[*N*-(2′-alkyl-1′,3′,4′-thiadiazol-5′-yl)carbamoylmethylthio]-1, 2, 4-triazole derivatives (compounds no. 3~8). Further, the introduction of methyl, methoxy or a chloro group in the aryl ring of the compound no. 9, brings about an increase in the insecticidal activity (compounds no. 10~15). This increase is maximum when the ethyl group is substituted at 2-position of the aryl ring (compound no. 16). On the contrary, introduction of methyl, methoxy, chloro or a ethyl group in the aryl ring of compound no. 17, slightly brings down the insecticidal activity (compounds no. 18~24) except when methyl group is substituted at 3-position of the aryl ring which shows no change in the insecticidal activity.

It was further observed that the benzyl substitution at the 4th position in the triazole ring renders the resultant compounds (no. 9~16) comparatively more insecticidal. This was also confirmed when these were sprayed on the bodies of test cockroaches.

The results obtained from the bactericidal screening indicated that all compounds exhibited antibacterial activity against one or the other type of bacteria. 5-[*N*-(*N*-Arylcarbamoyl)carbamoylmethylthio]-1,2,4-triazole derivatives (compounds no. 9~24; Table IV) displayed more prominent bactericidal activities. It was further noticed that the substitution at the 4th position in the triazole ring, by a benzyl group instead of 2-ethylphenyl group increases the bactericidal activities. Against *Staphylococcus aureus*, all compounds exhibited increased antibacterial activity except the two at no. 8 and 22 in Table IV. Against *Bacillus subtilis* and *Bacillus pumilus*, however, comparatively fewer compounds exhibited bactericidal activity. Amongst 5-[*N*-(*N*-arylcarbamoyl)carbamoylmethylthio]-1,2,4-triazole derivatives, five compounds (no. 9, 11, 12, 15 and 20) displayed as much bactericidal activity as the standards used in the screening shown in Table IV.

Acknowledgments. The authors express their thanks to Prof. S. S. Tewari, Head of the Department of Chemistry, for providing all possible facilities. Deep sense of gratitude is due to Dr. Nitya Nand, Central Drug Research Institute, Lucknow, for allowing microanalysis of the compounds. One of us (H.K.M.) is grateful to the Council of Scientific and Industrial Research, New Delhi, for award of a Senior Research Fellowship.

REFERENCES

1) H. Singh and L. D. S. Yadav, *Agric. Biol. Chem.*, **40**, 759 (1976).
2) V. B. Jigajinni, S. C. Bennur, R. S. Bennur and V. V. Badiger, *J. Karnatak Univ. Sci., India*, **21**, 176 (1976).
3) A. A. MacDonald, German Pat. 2,415,203 (1974); *Chem. Abstr.*, **82**, 43124 (1975).
4) G. Asato, G. Barkelhammer and W. H. Gastrock, U.S. Pat. 3,940,411 (1976); *Chem. Abstr.*, **85**, 5644c (1976).
5) G. Laurenz and M. Willy, Ger. Offen. 2,739,084 (1977); *Chem. Abstr.*, **88**, 190844r (1978).
6) J. J. Witkowski and R. K. Robins, Ger. Offen. 2,511,829 (1975); *Chem. Abstr.*, **84**, 4966b (1976).
7) M. C. Shephard and P. A. Worthington, Ger. Offen. 2,726,043 (1977); *Chem. Abstr.*, **88**, 105354p (1978).
8) M. Oziewori'ska, *Spectrochim. Acta*, **23**, 1195 (1967).
9) F. Gagiu and Al. Mavro, *Bull. Soc. Chim. Fr.*, **3**, 1010 (1967).
10) R. S. Schreiber, "*Organic Synthesis*," Vol. 31, John Wiley, New York, 1951, p. 8.
11) W. A. Jacobs, M. Heidelberger and I. P. Rolf, *J. Am. Chem. Soc.*, **41**, 458 (1919).
12) K. C. Joshi and M. K. Tholia, *Agric. Biol. Chem.*, **38**, 1165 (1974).
13) R. Nash, *Ann. Appl. Biol.*, **41**, 652 (1954).
14) R. S. Varma and S. A. Imam, *Indian J. Microbiol.*, **13**, 45 (1973).