J. Indian Chem. Soc.,
Vol. LVIII, May 1981, pp. 508-511

Studies on Potential Pesticides. Part XIII : Synthesis and Evaluation of S-(3-Substituted Phenoxymethyl-4-Aryl/Cyclohexyl-4H-1,2,4-Triazol-5-yl)-2-Mercaptomethyl Benzimidazoles for Antibacterial and Insecticidal Activities

ANIL K. SEN GUPTA and HEMANT K. MISRA

Department of Chemistry, Lucknow University, Lucknow-226 007

Manuscript received 12 December 1979, revised 11 November 1980, accepted 10 March 1981

A number of benzimidazole derivatives were synthesized from S-[3-(substituted phenoxymethyl)-4-aryl/cyclohexyl-4H-1,2,4-triazol-5-yl]-mercaptoacetic acids by condensation with *o*-phenylenediamine in presence of 4*N* hydrochloric acid. The N^1-(substituted phenoxyacetyl)-N^4-aryl/cyclohexyl-3-thiosemicarbazides, 3-(substituted phenoxymethyl)-4-aryl/cyclohexyl-5-mercapto 1, 2, 4-triazoles and S-[3-(substituted phenoxymethyl)-4-aryl/cyclohexyl-4H-1,2,4-triazol-5-yl]-mercaptoacetic acids were also synthesized. All the new compounds were screened for antibacterial and insecticidal activities. Most of these were found to possess significant antibacterial and insecticidal activities. Relationship between their biocidal character and chemical structure has been studied.

BENZIMIDAZOLE and some of its derivatives are already known for their antibacterial[1,2], insecticidal[3,4], fungicidal[5], virucidal[6] and anthelmintic[7] activities. Similarly, certain 4H-1,2,4-triazole derivatives have also been reported to possess pesticidal potentialities[8]. Some of these have even been patented as bactericidal[9], insecticidal[10], virucidal[11] and fungicidal[12] agents. Extending our previous work[13-18] on synthesis of new triazoles and their derivatives, we incorporated 4-aryl/cyclohexyl-4H-1,2,4-triazole ring in the benzimidazole derivatives at 2-position and studied their effect on pesticidal potentialities of the triazole derivatives.

Present communication concerns our work of preparing several new substituted 5-mercapto-4H-1,2,4-triazoles(III) by cyclization of thiosemicarbazide derivatives(II) in sodium hydroxide solution. The 5-mercapto 1,2,4-triazoles(III) were treated with monochloroacetic acid to get S-[3-(substituted phenoxy methyl)-4-aryl/cyclohexyl-4H-1,2,4-triazol-5-yl)] mercaptoacetic acid(IV). Finally the mercaptoacetic acids(IV) were condensed with *o*-phenylenediamine to get the title compounds.

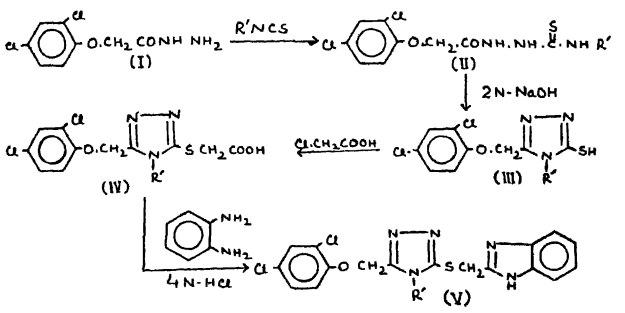
The structures of the various compounds thus synthesized were confirmed by ir and nmr spectroscopy. The ir spectra of triazoles(III) were in agreement with those reported in the literature[19]. The presence of two strong bands around 1300 cm^{-1} showed their existence predominantly in thione-form, but a weak band at 2550 cm^{-1} also indicated their presence in thiol-form as well in a tautomeric mixture. All the spectra of II and III displayed bands in the region 3300 cm^{-1} attributable to the free NH group and broad bands with multiple peaks in the region 3000-2700 cm^{-1} assignable to the intramolecularly hydrogen bonded NH group. A broad band appearing around 1700 cm^{-1} was attributed to the presence of CO group in II. Similarly a band around 1600 cm^{-1} showed the presence of C=N group in III. The ir spectra of triazoles(III) also showed a broad band at 1390 cm^{-1}. The ir spectra of IV and V showed the absence of ν SH vibration at 2550 cm^{-1}, and a band from 1255 to 1265 cm^{-1} was assigned for N−N=C (cyclic) grouping in compound V.

The nmr ($CDCl_3$) spectra of the compounds displayed signals at δ 8.93-8.73 (m, 3H, CON*H*, N*H*, C−N*H*, exchangeable with D_2O) and 3.12 (2H, CH_2). The signal due to CH_2 and NH observed at δ 5.36 as a broad band integrated for three protons. Absorptions due to aromatic protons occurred at δ 6.76 (three protons at aryl ring) and 5.82 (s, 2, SCH_2).

Experimental

Melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were recorded in a Perkin-Elmer 137 spectrophotometer in KBr. Nmr spectrum was recorded on a Varian A-60D spectrophotometer in $CDCl_3$ using TMS as an internal standard. All compounds were checked for their purity on tlc plates and characterized by elemental analysis.

N^1-(2,4-Dichlorophenoxyacetyl)-N^4-aryl/cyclohexyl-3-thiosemicarbazides(II) : Mixtures of 2,4-dichlorophenoxyacetic acid hydrazide (0.01 mol) with



different aryl/cyclohexyl isothiocyanates (0.01 mol) in dry benzene (30 ml) were refluxed on steam bath for 4 to 7 hrs. Each reaction mixture was then cooled in an ice bath and the solid compound thus obtained was filtered and crystallised from ethanol. The various compounds thus prepared are listed in Table 1.

3-(2,4-Dichlorophenoxymethyl)-4-aryl/cyclohexyl-5-mercapto-4H-1,2,4-triazoles(III) : Thiosemicarbazide II (0.005 mol) was dissolved in 10 ml of 2*N* sodium hydroxide solution. The clear solution was heated on a water bath for 4 hrs, filtered after cooling and neutralized with dil. hydrochloric acid. The precipitated compound, thus formed, was filtered and crystallised from ethanol. All new triazole derivatives are listed in Table 2.

S-[3-(2,4-Dichlorophenoxymethyl)-4-aryl/cyclohexyl-4H-1,2,4-triazole-5-yl)]-mercaptoacetic acids(IV) : Following Muhlhausen's[20] method, the various 5-mercapto-4-aryl/cyclohexyl-4H-1,2,4-triazoles III (0.15 mol) were added to monochloroacetic acid (0.207 mol) in 104 ml sodium carbonate (0.414 mol) solution. The mixtures were refluxed for 4 to 5 hrs. The reaction mixtures were cooled and acidified with dil. hydrochloric acid to precipitate the acids (IV). The precipitated acids were then crystallised from hot water and were obtained in 50-70% yield. All these compounds are listed in Table 3.

S-[3-(2,4-Dichlorophenoxymethyl)-4-aryl/cyclohexyl-4H-1,2,4-triazol-5-yl]-2-mercaptomethyl benzimidazoles(V) : Following Phillips'[21] method, the various newly prepared substituted mercaptoacetic acids (0.03 mol) were refluxed for 8 hrs with *o*-phenylenediamine (0.02 mol) in 20 ml of 4*N* hydrochloric acid. The reaction mixtures were cooled and filtered. The filtrates were neutralized with ammonia to precipitate benzimidazoles. The compounds were crystallised from alcohol and gave 60-75% yield. All these compounds are listed in Table 4.

TABLE 1—N¹-(2,4-DICHLOROPHENOXYACETYL)-N⁴-ARYL/CYCLOHEXYL-3-THIOSEMICARBAZIDE(II)

Sl. No.	R′	m.p °C	Yield %	Molecular formula	Antibacterial Activity* *S. aureus*	*B. pumilus*	*B. subtilis*	Insecticidal Activity Mean K.D. Time (hrs) % concentration 0.5	0.1
1.	4-Chlorophenyl	86	56	$C_{15}H_{12}Cl_3N_3O_2S$	++	+++	+	10.0	12.0
2.	2-Ethylphenyl	111	60	$C_{17}H_{17}Cl_2N_3O_2S$	+	++	+	13.0	15.0
3.	4-Ethoxyphenyl	178	56	$C_{17}H_{17}Cl_2N_3O_3S$	+	+	−	14.0	15.0
4.	1-Naphthyl	147	63	$C_{19}H_{15}Cl_2N_3O_2S$	+	+	+	15.0	17.0
5.	Cyclohexyl	200	65	$C_{15}H_{19}Cl_2N_3O_2S$	++	+++	+++	14.0	16.0
6.	Benzyl	175	72	$C_{16}H_{15}Cl_2N_3O_2S$	++	++	+++	13.0	14.0
	Parathion	—	—					4.5	5.5

+ Elemental analysis (C, H, N) were within ±0.5% of the theoretical value.
* −=No inhibition ; +=Zone size 6-8 mm ; ++=Zone size 9-14 mm ; +++=Zone size 15-20 mm ; ++++=Zone size greater than 20 mm.

TABLE 2—3-(2,4-DICHLOROPHENOXYMETHYL)4-ARYL/CYCLOHEXYL-5-MERCAPTO-4H-1,2,4-THIAZOLE(III)

Sl. No.	R′	m.p. °C	Yield %	Molecular formula	Antibacterial Activity* *S. aureus*	*B. pumilus*	*B. subtilis*	Insecticidal Activity Mean K.D. Time (hrs) % concentration 0.5	0.1
1.	4-Chlorophenyl	160	62	$C_{15}H_{10}Cl_3N_3OS$	++	++	+	7.5	8.5
2.	2-Ethylphenyl	163	56	$C_{17}H_{15}Cl_2N_3OS$	++	+	+	10.5	11.5
3.	4-Ethoxyphenyl	188	65	$C_{17}H_{15}Cl_2N_3O_2S$	++	+	+	13.0	14.0
4.	1-Naphthyl	189	58	$C_{19}H_{13}Cl_2N_3OS$	+	+	−	15.0	17.0
5.	Cyclohexyl	236	60	$C_{15}H_{17}Cl_2N_3OS$	++	++	+	14.0	16.0
6.	Benzyl	187	67	$C_{16}H_{13}Cl_2N_3OS$	++	++	+	8.5	9.5
	Parathion	—	—					4.5	5.5

+ Elemental analysis (C, H, N) were within ±0.5% of the theoretical value.
* −=No inhibition ; +=Zone size 6-8 mm ; ++=Zone size 9-14 mm ; +++=Zone size 15-20 mm ; ++++=Zone size greater than 20 mm.

TABLE 3—S-[(2,4-DICHLOROPHENOXYMETHYL)-4-ARYL/CYCLOHEXYL-4H-1,2,4-TRIAZOLE-5-YL]-MERCAPTOACETIC ACID(IV)

Sl. No.	R'	m.p. °C	Yield %	Molecular formula	Antibacterial Activity* *S. aureus*	*B. pumilus*	*B. subtilis*	Insecticidal Activity Mean K.D. Time (hrs.) % concentration 0.5	0.1
1.	4-Chlorophenyl	112	62	$C_{17}H_{12}Cl_2N_6O_2S$	++	+++	+	8.5	10.0
2.	2-Ethylphenyl	173	56	$C_{19}H_{17}Cl_2N_6O_2S$	++	+	−	10.5	12.0
3.	4-Ethoxyphenyl	165	57	$C_{19}H_{17}Cl_2N_6O_4S$	+	+	+	12.0	14.0
4.	1-Naphthyl	118	61	$C_{21}H_{15}Cl_2N_6O_2S$	+	−	−	12.0	15.0
5.	Cyclohexyl	183	65	$C_{17}H_{19}Cl_2N_6O_2S$	++	++	+	12.0	14.0
6.	Benzyl	218	63	$C_{18}H_{15}Cl_2N_6O_2S$	++	+++	++	10.0	11.5
	Parathion	—	—					4.5	5.5

+ Elemental analysis (C, H, N) were within ± 0.5% of the theoretical value.

* − =No inhibition ; + =Zone size 6-8 mm ; ++ =Zone size 9-14 mm ; +++ =Zone size 15-20 mm ; ++++ =Zone size greater than 20 mm.

TABLE 4—S-[3-(2,4-DICHLOROPHENOXYMETHYL)-4-ARYL/CYCLOHEXYL-4H-1,2,4-TRIAZOLE-5-YL)]-2-MERCAPTOMETHYL BENZIMIDAZOLE(V)

Sl. No.	R'	m.p. °C	Yield %	Molecular formula	Antibacterial Activity* *S. aureus*	*B. pumilus*	*B. subtilis*	Insecticidal Activity Mean K.D. Time (hrs) % concentration 0.5	0.1
1.	4-Chlorophenyl	137	62	$C_{23}H_{16}Cl_2N_6OS$	++	+	++	8.5	9.5
2.	2-Ethylphenyl	189	57	$C_{25}H_{21}Cl_2N_5OS$	++	+	++	10.5	13.0
3.	4-Ethoxyphenyl	103	60	$C_{25}H_{21}Cl_2N_5O_2S$	+	+	+	11.5	14.0
4.	1-Naphthyl	162	61	$C_{27}H_{19}Cl_2N_5OS$	+	+	+	12.0	14.0
5.	Cyclohexyl	173	64	$C_{23}H_{23}Cl_2N_5OS$	+	++	++	11.0	13.0
6.	Benzyl	122	60	$C_{24}H_{19}Cl_2N_5OS$	+	++	+++	12.0	14.0
	Parathion	—	—					4.5	5.5

+ Elemental analysis (C, H, N) were within ±0.5% of the theoretical value.

* − =No inhibition ; + =Zone size 6-8 mm ; ++ =Zone size 9-14 mm ; +++ =Zone size 15-20 mm ; ++++ =Zone size greater than 20 mm.

Biological activity : Using agar plate diffusion technique[22], all the newly synthesized compounds were tested *in vitro* for antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* and *Bacillus pumilus.* Insecticidal activity against adult male and female cockroaches were determined by micrometer syringe method[23]. The results of screening all the compounds synthesized have been shown in Tables 1 to 4.

The results obtained indicated that all compounds exhibit antibacterial activity against one or the other type of bacteria. It seems that the benzimidazole derivatives are comparatively more active against the test bacteria. 4-Chlorophenyl, cyclohexyl and benzyl substituted compounds were found to be comparatively more active. Contrary to this, bulky substitution i.e., 1-naphthyl decreases the activity amongst the test compounds.

The insecticidal results indicate that all compounds synthesized in this series possess good insecticidal activity. The K. D. time (hrs) was compared with the standard insecticide Parathion. The highest insecticidal activity was shown by 3-(2,4-dichlorophenoxymethyl)-4-(4-chlorophenyl)-5-mercapto-1,2,4-triazole (Compound no. 1 ; Table 2). Furthermore, it appears that benzimidazole and mercapto-acetic acid derivatives possess better insecticidal activity than thiosemicarbazide and triazole derivatives.

Acknowledgement

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, Director, Central Drug Research Institute, Lucknow for allowing microanalysis of the compounds. One of us (H. K. M.) is grateful to the CSIR for award of a Senior Research Fellowship.

References

1. O. KIYOSHI, *Japan kokai*, 77 70,024 ; *Chem. Abs.*, 1978, **88**, 33180d.
2. S. BAHADUR, A. K. GOEL and R. S. VERMA, *J. Indian Chem. Soc.*, 1976, **53**, 1163.
3. O. P. D. GEORGE and M. JOHN, *Japan kokai* 76 141,870 ; *Chem, Abs.*, 1977, **87**, 53304e.
4. D. WERNER, B. WOLFGANG, H. INGEBORG, S. HANS and B. WILHELM, *Ger. Offen.*, 2,612,313 ; *Chem. Abs.*, 1978, **88**, 37969r.

5. W. HANS, D. GUENTER and H. PAUL *Ger. (East)*, 127,636 ; *Chem. Abs.*, 1978, **88**, 136680w.

6. P. C. JOHNSON, C. J. WESLEY and W. J. HOWARD, *Ger. Offen.*, 2,638,551 ; *Chem. Abs.*, 1977, **87**, 53298f.

7. Y. TASHIKA and K. TAKANASHI, *Japan Patent*, 20, 220(66) ; *Chem. Abs.*, 1967, 66, 65472m.

8. H. SINGH and L. D. S. YADAV, *Agric. Biol. Chem.*, 1976, **40**, 759.

9. G. ASATO, G. BARKELHAMMER and W. H. GASTROCK, *U. S. Pat.*, 3,940,411 (1976) ; *Chem. Abs.*, 1976, **85**, 5644c.

10. G. LAURENZ and M. WILLY, *Ger. Offen.*, 2,739,084 (1977), *Chem. Abs.*, 1978, **88**, 190844r.

11. J. J. WITKOWSKI and R. K. ROBINS, *Ger. Offen.*, 2,511,829 (1975) ; *Chem. Abs.*, 1976, **84**, 4966b.

12. M. C. SHEPHARD and P. A. WORTHINGTON, *Ger. Offen.*, 2,726,043 (1977) ; *Chem. Abs.*, 1978, **88**, 105354p.

13. A. K. SEN GUPTA and H. K. MISRA, *Indian J. Chem.*, 1979, **17B**, 185.

14. A. K. SEN GUPTA and H. K. MISRA, *Indian J. Chem.*, 1979, **18B**, 381.

15. A. K. SEN GUPTA and H. K. MISRA, *Agric. Biol. Chem*, 1980, **44**, 1009.

16. A. K. SEN GUPTA and H. K. MISRA. *Defence Science Journal*, 1980, **30**, 59.

17. A. K. SEN GUPTA and H. K. MISRA, *J. Antibac. Antifung. Agents.*, 1980, **8**, 107.

18. A. K. SEN GUPTA and H. K. MISRA, *J. Pharm. Sci., U. S. A.* (In press).

19. M. OZIEWORISKA, *Spectrochim. Acta.*, 1967, **23**, 1195.

20. F. KROLLPFEIFFER, A. ROSENBERG and C. MUHLHAUSEN, *Ann.*, 1935, **515**, 113.

21. M. A. PHILLIPS, *J. Chem. Soc.*, 1978, 2393.

22. R. S. VARMA and W. L. NOBLES, *J. Pharm. Sci.*, 1968, **57**, 1801.

23. R. NASH, *Ann. Appl. Biol.*, 1954, **41**, 652.