J. Indian Chem Soc.,
Vol. LI, March 1974 pp. 402-404

# Search for New Insecticides IV
# Synthesis of some Phenoxyacetyl Thiosemicarbazide Derivatives

S. S. TIWARI, A. K. SEN GUPTA and JASWANT KUMAR

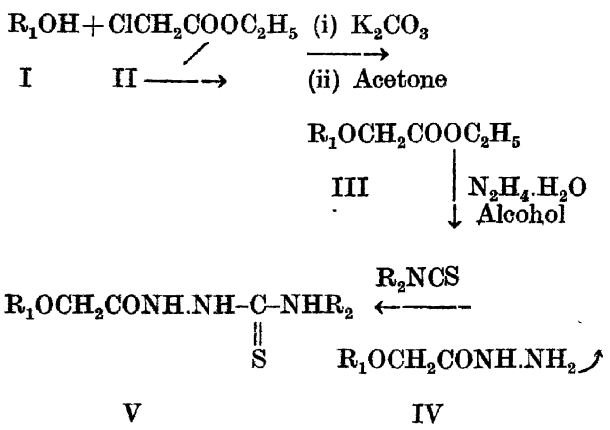
Department of Chemistry, University of Lucknow, Lucknow

*Manuscript received* 26 *April* 1972; *revised* 12 *September* 1973; *accepted* 9 *November* 1973

**Twenty one phenoxy-acetyl thiosemicarbazides have been synthesized as possible insecticidal agents by the condensation of substituted phenoxy acetic acid hydrazide with aryl isothiocyanate and some of them have been screened for their anti-cholinesterase activity.**

GAHEN *et al.*[2] has shown various semicarbazides to be more poisonous to catterpillars and other insects than derris dust. Fungicidal and herbicidal properties of phenoxy acetic acids and their derivatives have also been reported[3]. Organo-sulphur compounds have been used widely as possible insecticides, fungicides and acaricides[4-8]. Keeping these views in mind, several thiosemicarbazides have been synthesized with a view to study their insecticidal and other biological properties. The various substituents present in the nucleus are expected to enhance the lipoid solubility of the compound so as to enable these drugs to reach the site of action.

In all twenty one phenoxy acetyl thiosemicarbazides (V) have been prepared according to scheme given below :




## Experimental

(Melting points are uncorrected).

*Preparation of substituted phenoxy acetyl hydrazides (IV)* :

A mixture of 0.2 mole of substituted phenol (I) 0.2 mole of chloroethylacetate (II) and 0.2 mole of anhydrous potassium carbonate in 100 ml of acetone was refluxed on water-bath under anhydrous condition for 18 hr, filtered and the excess of solvent was removed under reduced pressure. The residue, thus obtained, was dissolved in ethanol (50 ml.). Hydrazine hydrate 80% (0.2 mole) was added to it and refluxed for 6 hr. The exces sof ethanol was distilled off under reduced pressure. The crude product which separated out on cooling, was filtered and recrystallized from ethanol,[4-9] yield 50–70% (Table 1).

TABLE 1

$ROCH_2—C(=O)—NH—NH_2$

| Sl. No. | R | Mol. formula | M.P. °C | % of Nitrogen Calcd. | % of Nitrogen Found |
|---|---|---|---|---|---|
| 1. | 2,4-dibromophenyl | $C_8H_8O_2N_2Br_2$ | 144 | 8.64 | 8.15 |
| 2. | 4-tert.butyl phenyl | $C_{12}H_{18}O_2N_2$ | 88 | 12.60 | 12.55 |
| 3. | 2,4,6-tribromophenyl | $C_8H_7O_2N_2Br_3$ | 142 | 8.16 | 7.90 |
| 4. | 2-Nitro-4-chloro phenyl | $C_8H_8N_3O_4Cl$ | 182 | 17.10 | 16.54 |
| 5. | 3-Methyl phenyl | $C_9H_{12}O_2N_2$ | 80 | 17.12 | 16.84 |

*Substituted phenoxy acetyl thiosemicarbazides (V)* :

A mixture of 0.01 mole of phenoxy acetic hydrazide (IV) and 0.01 mole of substituted arylisothiocyanate in 30 ml of ethanol was refluxed on water bath for 5 hr. The mixture was allowed to stand over night. A solid mass which separated out, was filtered and recrystallized from ethanol, yield 50–70% (Table 2).

*Enzyme prepration*

Adult rats weighing approximately 150 g were decapitated and the brains were removed quickly, weighed and homogenized in ice cold 0.25 *M* sucrose in motor driven Teflon Pyrex homogenizer. The final concentration of the crude homogenate was 10%. (w/v).

TABLE 2

$$R_1OCH_2\overset{O}{\overset{\|}{C}}NH—NH\overset{S}{\overset{\|}{C}}—NH—R_2$$

| Sl. No. | $R_1$ | $R_2$ | Mol. formula | M.P. °C | % of Nitrogen Calcd. | % of Nitrogen Found |
|---|---|---|---|---|---|---|
| 1. | 4-Tert. butyl phenyl | 4-Methoxy phenyl | $C_{20}H_{25}O_3N_3S$ | 198 | 10.85 | 10.96 |
| 2. | 4-Tert. butyl phenyl | 2-Methyl phenyl | $C_{20}H_{25}O_2N_3S$ | 125 | 11.31 | 11.03 |
| 3. | 4-Tert. butyl phenyl | Phenyl | $C_{19}H_{23}N_3O_2S$ | 165 | 11.73 | 11.47 |
| 4. | 4-Tert. butyl phenyl | 4-Chloro phenyl | $C_{19}H_{22}O_2N_3SCl$ | 175–78 | 10.72 | 10.62 |
| 5. | 2,4-Dibromo phenyl | 4-Methoxy phenyl | $C_{16}H_{15}O_3N_3Br_2S$ | 110 | 8.50 | 8.81 |
| 6. | 2,4-Dibromo phenyl | 2-Methoxy phenyl | $C_{16}H_{15}O_2N_3Br_2S$ | 165 | 8.80 | 9.16 |
| 7. | 2,4-Dibromo phenyl | Phenyl | $C_{15}H_{13}O_2N_3Br_2S$ | 158 | 9.10 | 8.90 |
| 8. | 2,4-Dibromo phenyl | 4-Chloro phenyl | $C_{15}H_{12}O_2N_3Br_2SCl$ | 185–87 | 8.40 | 8.61 |
| 9. | 2,4-Dibromo phenyl | 4-Indo phenyl | $C_{15}H_{12}O_2N_3Br_2SI$ | 165 | 7.10 | 7.53 |
| 10. | 2,4-Dibromo phenyl | Cyclohexyl | $C_{15}H_{15}O_2SBr_2$ | 201–202 | 9.03 | 9.29 |
| 11. | 2-Bromo-4-tert. butylphenyl | 4-Methoxy phenyl | $C_{20}H_{24}O_3N_3BrS$ | 130 | 9.00 | 8.60 |
| 12. | 2-Bromo-4-tert. butylphenyl | 2-Methyl phenyl | $C_{20}H_{24}O_2N_3BrS$ | 162 | 9.30 | 9.51 |
| 13. | 2-Bromo-4-tert. butylphenyl | 4-Iodo phenyl | $C_{19}H_{21}O_2N_3BrIS$ | 125 | 7.47 | 7.35 |
| 14. | 2-Bromo-4-tert. butylphenyl | 4-Chloro phenyl | $C_{19}H_{21}O_2N_3BrSCl$ | 160–62 | 8.80 | 8.87 |
| 15. | 2-Chloro-4-biphenyl | Phenyl | $C_{21}H_{18}O_2N_3SCl$ | 100 | 10.10 | 10.31 |
| 16. | 2-Chloro-4-biphenyl | 4-Methoxy phenyl | $C_{22}H_{20}O_3N_3SCl$ | 68 | 9.40 | 8.89 |
| 17. | 2-Chloro-4-biphenyl | 4-Iodo phenyl | $C_{21}H_{17}O_2N_3SCl$ | 181 | 7.80 | 7.35 |
| 18. | 2-Nitro-4-chloro phenyl | 4-Methoxy phenyl | $C_{16}H_{15}O_5N_4SCl$ | 290(d) | 13.60 | 13.26 |
| 19. | 2-Nitro-4-chloro phenyl | Phenyl | $C_{15}H_{13}O_4N_4SCl$ | 280(d) | 14.70 | 13.75 |
| 20. | 2-Nitro-4-chloro phenyl | Cyclohexyl | $C_{15}H_{19}O_4N_4SCl$ | 90 | 14.40 | 14.01 |
| 21. | 2,4,6-Tribromo phenyl | 4-Iodo phenyl | $C_{15}H_{11}O_2N_3Br_3SI$ | 168–70 | 6.22 | 6.41 |

All melting points are uncorrected. Yield ranges from 50–70%.

*Determination of acetylcholinesterase activity* :

Acetyl cholinesterase activity was determined colorimetrically with acetyl choline as the substrate (10). The reaction mixture consists of 43 m *M* Tris buffer (*p*H 7.4) and 350 m *M* sodium chloride (these represent the final concentrations). Water, acetyl thiocholine, and 0.3 ml of brain homogenate were added to adjust the final volume to a total of 2 ml. The enzyme preparation, with and without different substituted phenoxy acetyl thiosemicarbazides, were preincubated with the reaction mixture at a constant temperature (37°) for 10 min. in the absence of acetyl thiocholine. Acetyl thiocholine was then added and the reaction was allowed to continue for an additional 10 min at 37°, with occasional shaking. Then, after the addition of the substrate, 0.5 ml of 25% (w/v) trichloro acetic acid was added and the resultant solution was centrifuged for 5 min at 500 × g. An aliquot of the clear supernatant liquid was withdrawn and the enzymatically formed thiocholine was determined colorimetrically[11]. The determinations were carried out in triplicate, the blank values being substracted. The change in extinction, as a measure of the thiocholine content, was used as an index of the enzyme activity.

## Discussion

The four compounds found to inhibit acetyl cholinesterase activity of rat brain are given in Table 3.

TABLE 3

$$R_1O.CH_2C.NH.NHC.NH—R_2$$

| Sl. No. | $R_1$ | $R_2$ | Inhibition |
|---|---|---|---|
| 1. | 4-Tert.butyl phenyl | 4-Chloro phenyl | 5.70 |
| 2. | 2,4-Dibromophenyl | Phenyl | 8.50 |
| 3. | 2-Nitro-4-chlorophenyl | Phenyl | 70.30 |
| 4. | 2-Bromo-4-tert.butyl phenyl | 4-Methoxy phenyl | 54.32 |
| 5. | 2-Bromo-4-tert.butyl | 4-Iodo phenyl | 57.40 |

The compound no. III possessing 2-nitro-4-chlorophenyl at $R_1$ position and phenyl group at $R_2$ position was found to be the most potent inhibitor of acetyl cholinesterase. Although these results have not been able to correlate the structural activity relationship yet have indicated that substitution of a nitro group along with a chloro in the same phenyl nucleus

difinetely *enhanced* the antiacetyl cholinesterase activity, as the simpler thio-semicarbazides (1 & 2) shown the least activity.

The compounds were used at a final concentration of $2 \times 10^{-3}$ *M*.

**Acknowledgement**

The authors wish to express their sincere thanks to Professor Ram Gopal, Head of the Chemistry Department, Lucknow University, Lucknow for providing the laboratory facilities and to Dr. Surendra S. Parmar, Professor of Medicinal Chemistry and Chemical Pharmacology, Department of Pharmacology and Therapeutics, K.G.'s Medical College, Lucknow for his kind assistance in the screening of the compounds.

**References**

1. S. S. Tewari, A. K. Sen Gupta and Jaswant Kumar, *Indian J. Pharmacy*, 1970, **32**, 92.
2. J. B. Gahan, M. C. Swangle and K. M. Phillips, U.S. *Dept. Agr. Bull.* F-541, 1941.
3. R. C. Srivastava, Search for New Pesticides. Ph.D. Thesis, Lucknow University, 1968.
4. B. T. P. Barker, C. T. Gimingham and S. P. Wiltshire, *Rep. Agr. Hort. Res. Sta. Bristol.*, 1919. p. 57,
5. B. T. P. Barker and T. Wallace, *Rep. Agric. Hort. Res. Sta. Bristol.*, 1921, p. 122.
6. R. W. Nash, *J. four. and hort. Sci.*, 1929, 7.
7. W. A. Roach and M. O. Glynne, *Ann. Biol.*, 1928, **15**, 168.
8. H. C. Young, *Ann. Missouri, Botan. Garden*, 1922, **2**, 403.
9. Harihar Singh, *Synthesis of some possible antitubercular compounds*. Ph.D. Thesis, Lucknow University, 1968.
10. S. S. Parmar, N. C. Sutter and M. Nickerson, *Canad. J. Physiol. Biochem.*, 1961, **37**, 1335.
11. S. S. Parmar, L. D. Joshi, K. Kishore and R. Kumar, *Biochem. Pharmacol.*, 1966, **15**, 729.