

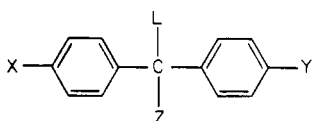
## ARTICLES

Insecticidal Activity of 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) Analogues

Sameer Abu-El-Haj, M. A. H. Fahmy, and T. R. Fukuto\*

A number of new 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) analogues were synthesized and evaluated for toxicity to houseflies and mosquito larvae. The design of these compounds was based on a previously postulated model for the DDT target site. Several of the compounds were effective insecticides and one of them, 1,1-dichloro-2,2-bis(*p*-ethoxyphenyl)propane, was equal to DDT in activity. This compound represents a marked departure from conventional DDT analogues owing to the substitution of a methyl group for the hydrogen on the  $\alpha$ -carbon atom.

In a previous report from this laboratory (Fahmy et al., 1973) a model for the hypothetical 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) receptor site was proposed to account for the variation in insecticidal activity of a series of DDT analogues. Briefly stated, the receptor was visualized as a cavity or pouch of approximately the same dimensions as DDT but of limited flexibility to accommodate unsymmetrical DDT analogues. Maximum perturbation of the nerve membrane was anticipated when maximum interaction between the DDT-type molecule and receptor site occurred, particularly with respect to the four key substituents X, Y, L, and Z of structure A. For



maximum interaction, the overall size of the DDT molecule (summation of the size of X, Y, L, and Z) was crucial and any deviation from the optimum size resulted in reduced interaction and, therefore, reduced insecticidal activity. The model, within reasonable limits, provided the basis for the design of new DDT analogues and this report is concerned with the insecticidal properties of some of these compounds.

## MATERIALS AND METHODS

**General.** All proton magnetic resonance ( $^1\text{H}$  NMR) spectra were obtained with a Varian T-60 spectrometer in deuteriochloroform using  $\text{Me}_4\text{Si}$  as the internal standard. Infrared spectra (IR) of liquid products were obtained neat in silver chloride cells with a Perkin-Elmer 700A spectrometer. A Nujol mull was used for solid products. Mass spectra (MS) were obtained by direct insertion probe in a Finnigan Model 1015 mass spectrometer at an ionizing voltage of 70 eV. All intermediates were routinely subjected to  $^1\text{H}$  NMR and infrared analyses. All melting points were obtained by capillary tube and are uncorrected.

**1,1,1-Trifluoro-2,2-bis(*p*-alkoxyphenyl)ethanes.**  $\alpha,\alpha,\alpha$ -Trifluoro-*p*-alkoxyacetophenones were prepared

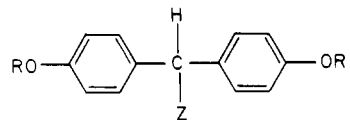
according to Dishart and Levine (1956) by the reaction between trifluoroacetic acid and excess Grignard reagent prepared from the *p*-alkoxybromobenzene. The trifluoro-*p*-alkoxyacetophenones were converted to the corresponding carbinols by reduction with sodium borohydride according to Chaikin and Brown (1949). The structures of these intermediates were confirmed by infrared and  $^1\text{H}$  NMR analysis. The synthesis of the 1,1,1-trifluoro-2,2-bis(*p*-alkoxyphenyl)ethanes from the respective carbinols and alkoxybenzenes was carried out by using anhydrous aluminum chloride as the catalyst (Palmer and McVie, 1968). The following procedure for the synthesis of 1,1,1-trifluoro-2,2-bis(*p*-ethoxyphenyl)ethane is typical. To a stirred, ice-cooled mixture of 10 g of 1,1,1-trifluoro-2-hydroxy-2-(*p*-ethoxyphenyl)ethane and 50 mL of ethoxybenzene was added in increments 3.8 g of aluminum chloride. The mixture was brought to room temperature and then heated at 50 °C for 1 h. Ice and water was added and the organic layer was washed in turn with 10% hydrochloric acid and water. Removal of the excess ethoxybenzene gave the product, an oil which distilled at 168–172 (0.1 mm). Elemental analyses and physical properties of the various 1,1,1-trifluoro-2,2-bis(*p*-alkoxyphenyl)ethanes are given in Table I. The structures also were supported by IR,  $^1\text{H}$  NMR, and MS analyses. Compounds which could not be distilled were purified by silica gel column chromatography using hexane and hexane-ether (10:1) as the eluting solvents.

**1,1,1,2,2-Pentafluorobis(*p*-alkoxyphenyl)propanes and 1,1-Difluoro-1-chlorobis(*p*-alkoxyphenyl)ethanes.** These compounds, also listed in Table I, were prepared as described above for the trifluoro analogues by using pentafluoropropionic acid or chlorodifluoroacetic acid as the starting materials. Solid products were purified by recrystallization from ethyl alcohol and liquid products by column chromatography, employing the same system as described above.

**Para-Substituted  $\alpha,\alpha$ -Dihaloacetophenones.** The *p*-chloro-, *p*-bromo-, *p*-methoxy-, and *p*-ethoxy- $\alpha,\alpha$ -dichloroacetophenones were prepared according to Durrans (1922) by dichlorination of the appropriate para-substituted acetophenone with sulfuryl chloride. The products were recrystallized from ethanol. The corresponding *p*-chloro- and *p*-bromo- $\alpha$ -bromo- $\alpha$ -chloroacetophenones were prepared by stepwise chlorination and bromination

Division of Toxicology and Physiology, Department of Entomology, University of California, Riverside, California 92521.

Table I. Physical and Insecticidal Properties of DDT Analogues of the General Structure:



| compd | R                                       | R'                                       | Z                             | bp/mm (mp)<br>°C | $n_D^{25}$ | analysis            |                     | housefly<br>LD <sub>50</sub> ,<br>μg/g | <i>Culex fatigans</i><br>LC <sub>50</sub> , ppm |
|-------|-----------------------------------------|------------------------------------------|-------------------------------|------------------|------------|---------------------|---------------------|----------------------------------------|-------------------------------------------------|
|       |                                         |                                          |                               |                  |            | calcd               | found               |                                        |                                                 |
| 1     | CH <sub>3</sub>                         | CH <sub>3</sub>                          | CF <sub>3</sub>               | 134/0.5          | 1.5336     | C, 64.87<br>H, 5.10 | C, 65.04<br>H, 5.22 | >500                                   | 0.64                                            |
| 2     | CH <sub>3</sub>                         | C <sub>2</sub> H <sub>5</sub>            | CF <sub>3</sub>               | 142-5/0.25       | 1.5281     | C, 65.79<br>H, 5.50 | C, 65.51<br>H, 5.58 | >500                                   | 0.72                                            |
| 3     | CH <sub>3</sub>                         | <i>n</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>3</sub>               | 153/0.05         | 1.5270     | C, 66.65<br>H, 5.90 | C, 66.64<br>H, 5.96 | >500                                   | >1.0                                            |
| 4     | CH <sub>3</sub>                         | <i>i</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>3</sub>               | 134/0.05         | 1.5173     | C, 66.65<br>H, 5.90 | C, 66.36<br>H, 5.70 | >500                                   | >1.0                                            |
| 5     | CH <sub>3</sub>                         | <i>n</i> -C <sub>4</sub> H <sub>9</sub>  | CF <sub>3</sub>               | 178/0.15         | 1.5180     | C, 67.44<br>H, 6.25 | C, 67.26<br>H, 6.39 | >500                                   | >1.0                                            |
| 6     | CH <sub>3</sub>                         | <i>n</i> -C <sub>5</sub> H <sub>11</sub> | CF <sub>3</sub>               |                  | 1.5159     | C, 68.15<br>H, 6.25 | C, 68.96<br>H, 6.41 | >500                                   | >1.0                                            |
| 7     | C <sub>2</sub> H <sub>5</sub>           | C <sub>2</sub> H <sub>5</sub>            | CF <sub>3</sub>               | 168-72/0.1       | 1.5201     | C, 66.65<br>H, 5.90 | C, 66.23<br>H, 5.72 | >500                                   | 0.55                                            |
| 8     | C <sub>2</sub> H <sub>5</sub>           | <i>i</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>3</sub>               | 152/0.3          | 1.5162     | C, 67.44<br>H, 6.25 | C, 67.91<br>H, 6.44 | >500                                   |                                                 |
| 9     | <i>i</i> -C <sub>3</sub> H <sub>7</sub> | <i>i</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>3</sub>               |                  | 1.5183     | C, 68.15<br>H, 6.79 | C, 68.52<br>H, 6.64 | >500                                   | >1.0                                            |
| 10    | CH <sub>3</sub>                         | CH <sub>3</sub>                          | C <sub>2</sub> F <sub>5</sub> |                  | 1.5090     | C, 58.96<br>H, 4.36 | C, 59.17<br>H, 4.81 | >500                                   | >1.0                                            |
| 11    | CH <sub>3</sub>                         | C <sub>2</sub> H <sub>5</sub>            | C <sub>2</sub> F <sub>5</sub> |                  | 1.5102     | C, 60.00<br>H, 4.76 | C, 60.42<br>H, 4.89 | >500                                   | >1.0                                            |
| 12    | CH <sub>3</sub>                         | <i>n</i> -C <sub>3</sub> H <sub>7</sub>  | C <sub>2</sub> F <sub>5</sub> |                  |            | C, 60.96<br>H, 5.11 | C, 60.46<br>H, 5.37 | >500                                   | >1.0                                            |
| 13    | CH <sub>3</sub>                         | <i>n</i> -C <sub>4</sub> H <sub>9</sub>  | C <sub>2</sub> F <sub>5</sub> |                  | 1.4990     | C, 61.85<br>H, 5.45 | C, 61.67<br>H, 5.73 | >500                                   |                                                 |
| 14    | CH <sub>3</sub>                         | <i>n</i> -C <sub>5</sub> H <sub>11</sub> | C <sub>2</sub> F <sub>5</sub> |                  | 1.4926     | C, 62.68<br>H, 5.76 | C, 62.34<br>H, 5.83 | >500                                   |                                                 |
| 15    | C <sub>2</sub> H <sub>5</sub>           | C <sub>2</sub> H <sub>5</sub>            | C <sub>2</sub> H <sub>5</sub> |                  | 1.4971     | C, 60.96<br>H, 5.11 | C, 61.14<br>H, 7.11 | >500                                   | >1.0                                            |
| 16    | CH <sub>3</sub>                         | CH <sub>3</sub>                          | CF <sub>2</sub> Cl            | (61-2)           |            | C, 61.45<br>H, 4.83 | C, 61.48<br>H, 4.89 | >55                                    | 0.07                                            |
| 17    | C <sub>2</sub> H <sub>5</sub>           | C <sub>2</sub> H <sub>5</sub>            | CF <sub>2</sub> Cl            | (67-8)           |            | C, 63.43<br>H, 5.61 | C, 63.40<br>H, 5.71 | 48                                     | 0.066                                           |
| 18    | <i>i</i> -C <sub>3</sub> H <sub>7</sub> | <i>i</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>2</sub> Cl            |                  | 1.5264     | C, 65.12<br>H, 6.28 | C, 65.57<br>H, 7.12 | 123                                    | 0.27                                            |
| 19    | <i>n</i> -C <sub>3</sub> H <sub>7</sub> | <i>n</i> -C <sub>3</sub> H <sub>7</sub>  | CF <sub>2</sub> Cl            |                  | 1.5307     | C, 65.12<br>H, 6.28 | C, 65.24<br>H, 6.13 | 96                                     | 0.18                                            |
| 20    | <i>n</i> -C <sub>4</sub> H <sub>9</sub> | <i>n</i> -C <sub>4</sub> H <sub>9</sub>  | CF <sub>2</sub> Cl            |                  | 1.5249     | C, 66.57<br>H, 6.85 | C, 66.41<br>H, 6.65 | 210                                    | >1.0                                            |

of the appropriate acetophenone according to Langley (1944) and Aston et al. (1955). Products were recrystallized from 95% ethanol. *p*-Chloro- $\alpha,\alpha$ -dibromoacetophenone was prepared by bromination of *p*-chloroacetophenone.

**2-Hydroxy-2-(para-substituted phenyl)-1,1-dihalopropanes.** These intermediates were prepared by the reaction between equivalent amounts of methyl lithium and the appropriate para-substituted  $\alpha,\alpha$ -dihaloacetophenone in ether at 0 °C. The products were liquids and were purified by silica gel column chromatography using benzene as the eluting solvent. Structures were confirmed by IR and <sup>1</sup>H NMR analyses.

**2,2-Bis(para-substituted phenyl)-1,1-dihalopropanes.** These compounds were prepared by the condensation of an alkoxybenzene and 2-hydroxy-2-(para-substituted phenyl)-1,1-dihalopropane in the presence of sulfuric acid. The following procedure is typical. A mixture of 1.8 g of 2-hydroxy-2-(*p*-ethoxyphenyl)-1,1-dichloropropane, 25 mL of ethoxybenzene, and 0.5 mL of concentrated sulfuric acid was stirred at room temperature for 6 h. The mixture was taken up in ether, washed with aqueous sodium bicarbonate and water, and dried over magnesium sulfate. Removal of the solvent and excess ethoxybenzene gave an oil which was purified by

silica gel column chromatography using hexane and hexane-ether (9:1) as the eluting solvents. Structures, elemental analyses, and physical properties of these compounds are presented in Table II. Additional evidence for structure confirmation was provided by IR, <sup>1</sup>H NMR, and MS analyses.

1,1,1-Trifluoro-2,2-bis(*p*-methoxyphenyl)propane was prepared from anisole and trifluoroacetone according to Farah et al. (1965).

**Bioassay.** Insecticidal activities were determined against the susceptible S<sub>NAIDM</sub> strain of houseflies, *Musca domestica*, held at 72 °F, and fourth-instar mosquito larvae, *Culex fatigans*, according to usual procedures (Metcalf and March, 1949; Mulla et al., 1966).

## RESULTS AND DISCUSSION

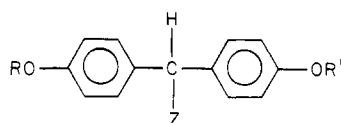
Data for the toxicity of the various DDT analogues which were synthesized and examined for insecticidal activity are presented in Tables I and II. Analogues in which the bis-substituted phenyl moiety is attached to a terminal carbon atom are presented in Table I and those substituted in the 2 position are in Table II.

**2,2-Bis(alkoxyphenyl)ethanes and 3,3-Bis(alkoxyphenyl)propanes.** These compounds contain a hydrogen

Table II. Physical and Insecticidal Properties of DDT Analogues of the General Structure:

| compd | R                              | R'                             | Z                  | $n_D^{25}$ | analysis            |                     | housefly<br>LD <sub>50</sub> , µg/g | <i>Culex fatigans</i><br>LC <sub>50</sub> , ppm |
|-------|--------------------------------|--------------------------------|--------------------|------------|---------------------|---------------------|-------------------------------------|-------------------------------------------------|
|       |                                |                                |                    |            | calcd               | found               |                                     |                                                 |
| 21    | Cl                             | OCH <sub>3</sub>               | CHCl <sub>2</sub>  | 1.5988     | C, 58.27<br>H, 4.55 | C, 58.05<br>H, 4.60 | 72                                  | 0.115                                           |
| 22    | Cl                             | OCH <sub>3</sub>               | CHClBr             | 1.6416     | C, 51.33<br>H, 4.04 | C, 51.52<br>H, 3.87 | 68                                  | 0.145                                           |
| 23    | Br                             | OCH <sub>3</sub>               | CHCl <sub>2</sub>  | 1.6055     | C, 51.33<br>H, 4.04 | C, 50.96<br>H, 3.86 | 87                                  | 0.23                                            |
| 24    | Br                             | OCH <sub>3</sub>               | CHBrCl             | 1.6014     | C, 45.91<br>H, 3.61 | C, 46.21<br>H, 4.70 | 98                                  | 0.18                                            |
| 25    | OC <sub>2</sub> H <sub>5</sub> | OC <sub>2</sub> H <sub>5</sub> | CHCl <sub>2</sub>  | 1.5772     | C, 64.59<br>H, 6.27 | C, 64.68<br>H, 7.21 | 10                                  | 0.06                                            |
| 26    | OCH <sub>3</sub>               | OCH <sub>3</sub>               | CF <sub>3</sub>    | 1.5342     | C, 65.79<br>H, 5.52 | C, 66.18<br>H, 5.27 | > 500                               | > 1.0                                           |
| 27    | OPr- <i>n</i>                  | OPr- <i>n</i>                  | CF <sub>3</sub>    | 1.5167     | C, 68.84<br>H, 6.87 | C, 68.98<br>H, 6.79 | > 500                               | > 1.0                                           |
| 29    | OCH <sub>3</sub>               | OPr- <i>n</i>                  | CF <sub>2</sub> Cl | 1.5326     | C, 64.32<br>H, 5.96 | C, 64.22<br>H, 5.59 | > 500                               | > 1.0                                           |

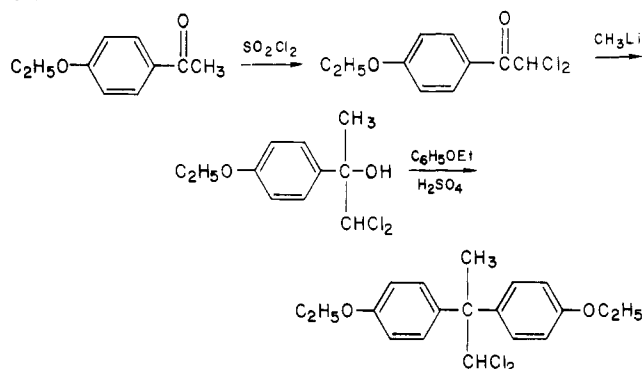
atom on the  $\alpha$ -carbon atom and may be considered to be direct analogues of DDT. The model (Fahmy et al., 1973)



used for the design of these compounds suggested that decrease in the size of Z could be compensated for by an increase in the size of the ring substituent (RO and R'O). Therefore, a series of analogues in which Z was kept at trifluoromethyl and one of the alkoxy ring substituents was increased in size were initially prepared. Owing to their biodegradable susceptibility (Kapoor et al., 1972), ring substituents were restricted to alkoxy moieties. To our disappointment, all of these compounds (1-9) were virtually devoid of insecticidal activity even though R' was increased in size to *n*-pentyl (R = methyl). Owing to the possibility that the trifluoromethyl moiety in the Z position was too small to interact properly with the DDT receptor site, an analogous series of compounds in which Z was maintained as pentafluoroethyl were prepared (10-15) but these also were insecticidally inactive. It is apparent from the toxicological data that analogues in which the substituent Z is totally substituted with fluorine atoms are inactive as insecticides. However, substitution of only one of the fluorine atoms by chlorine resulted in a notable increase in insecticidal activity (16-20) and highest activity was observed with 1-chloro-1,1-difluorobis(*p*-ethoxyphenyl)ethane (17).

**2,2-Bis(para-substituted phenyl)-1,1-dihalopropanes.** Because of the overall poor insecticidal activity observed with the perfluoro analogues and the apparent absence of compensating effects by the larger alkoxy ring substituents on the toxicity of these compounds, attention was turned to the 2,2-bis(para-substituted phenyl)-1,1-dihalopropanes (cf. Table II). These DDT analogues differ from those of Table I in that the hydrogen on the  $\alpha$ -carbon atom is substituted by a methyl group. The rationale behind the examination of compounds of this type lies in the larger size of methyl compared to hydrogen and it was expected that reduction in the size of the Z moiety would be compensated for by the methyl group. The compounds

Scheme I



presented in Table II were more difficult to synthesize than those in Table I and, therefore, a smaller number were prepared.

The route used for the synthesis of 2,2-bis(*p*-ethoxyphenyl)-1,1-dichloropropane (25) is given as an example in Scheme I. In general, moderate yields (50-60%) were obtained with each reaction. The synthesis of the carbinol from the dichloro-*p*-ethoxyacetophenone was first accomplished by reaction of the latter with methyl magnesium iodide but the yield using this reagent was poor. Use of methyllithium resulted in a yield of the carbinol of about 60%.

Toxicological data in Table II show that 25 is highly toxic to the test insects examined. Under the same bioassay conditions, the toxicity of DDT is 14 µg/g (LD<sub>50</sub>) to houseflies and 0.07 ppm (LC<sub>50</sub>) to mosquito larvae and 25, therefore, is more effective to these insects than DDT. Moreover, 25 had no effect on white mice given oral dosages as high as 800 mg/kg. In a separate test against the Super Pollard resistant strain (R<sub>SP</sub>) of houseflies, the LD<sub>50</sub> of 25 was determined to be 50 µg/g, a value which is at least 100-fold smaller than the >5000 µg/g reported for the LD<sub>50</sub> of DDT to this strain (Metcalf and Fukuto, 1968). The high tolerance of the R<sub>SP</sub> strain to DDT is attributed to rapid detoxication of DDT to DDE by the action of DDT dehydrochlorinase. Compound 25, which cannot be dehydrochlorinated in the usual manner owing to the presence of the  $\alpha$ -methyl group, therefore, would be expected to be toxic to this strain. The LD<sub>50</sub> of 50 µg/g

for **25** suggests that the  $R_{SP}$  flies are capable of detoxification by other mechanisms. In this regard the  $LD_{50}$  of **25** synergized with 5:1 piperonyl butoxide for the  $S_{NAIDM}$  strain was  $7.5 \mu\text{g/g}$ . The results indicate that **25** is detoxified to a small extent by the mixed function oxidase enzymes.

Except for the trifluoromethyl derivative (**26**), the other analogues also showed insecticidal activity but none were as potent as **25**. The absence of insecticidal activity of **26** and **27** again points out the deactivating influence of the trifluoromethyl moiety in the Z position. Because of the variety of substitutions which were made relative to the original DDT molecule it was not possible to analyze the data by multiple regression analysis (Fahmy et al., 1973). However, comparison may be made with some of the compounds in Table II with those of the DDT type in which Z is trichloromethyl and L is hydrogen. The direct analogue of compound **25** is 1,1,1-trichloro-2,2-bis(*p*-ethoxyphenyl)ethane. The housefly  $LD_{50}$  and *Culex* larvae  $LC_{50}$  of this compound are  $7.0 \mu\text{g/g}$  and 0.04 ppm, respectively. While **25** is slightly less toxic to these insects than the corresponding DDT analogue, the toxicities are close enough to support the rationale used for the synthesis of these compounds. A similar comparison may be made with compound **21** and 1,1,1-trichloro-2-*p*-chlorophenyl-2-*p*-anisylethane (housefly  $LD_{50}$   $41.5 \mu\text{g/g}$  and *Culex* larvae  $LC_{50}$  0.058 ppm).

Although the insecticidal activities of the compounds in Table II appear to be slightly less than their related DDT analogues, the results, nevertheless, indicate that derivatives which contain an  $\alpha$ -methyl group also may possess high insecticidal activity. To our knowledge, this is the first case where significant insecticidal activity has

been demonstrated with compounds of this type. It should be pointed out that the present study was exploratory in nature and only a few compounds were synthesized and evaluated. The approach, however, appears to be worthwhile and a large number of related derivatives remain to be examined. Further work is in progress.

#### LITERATURE CITED

- Aston, J. G., Newkirk, J. D., Jenkins, M. O., Dorsky, J., "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 538.  
Chaikin, S. W., Brown, W. G., *J. Am. Chem. Soc.* **71**, 122 (1949).  
Dishart, K. T., Levine, R., *J. Am. Chem. Soc.* **78**, 2268 (1956).  
Durrans, T. H., *J. Chem. Soc.* **121**, 46 (1922).  
Fahmy, M. A. H., Fukuto, T. R., Metcalf, R. L., Holmstead, R. L., *J. Agric. Food Chem.* **21**, 585 (1973).  
Farah, B. S., Gilbert, E. E., Litt, M., Otto, J. A., Sibila, J. P., *J. Org. Chem.* **30**, 1003 (1965).  
Kapoor, I. D., Metcalf, R. L., Hirwe, A. S., Lu, P. Y., Coats, J. R., Nystrom, R. F., *J. Agric. Food Chem.* **20**, 1 (1972).  
Langley, W. D., "Organic Syntheses", Collect. Vol. I, Wiley, New York, 1944, p 127.  
Metcalf, R. L., March, R. B., *J. Econ. Entomol.* **42**, 721 (1949).  
Metcalf, R. L., Fukuto, T. R., *Bull. WHO* **38**, 633 (1968).  
Mulla, M. S., Metcalf, R. L., Geib, A. F., *Mosquito News* **26**, 236 (1966).  
Palmer, M. H., McVie, G. J., *J. Chem. Soc. B*, 742 (1968).

Received for review October 23, 1978. Accepted November 26, 1978. This investigation was supported from Federal Funds from the Environmental Protection Agency under Grant R804345. The contents do not necessarily reflect the views and policies of the Environmental Protection Agency, nor does mention of trade-names or commercial products constitute endorsement or recommendation for use.

## Toxicity of N-Sulfenylated Derivatives of Insecticidal Methylcarbamate Esters to the Honeybee

Narayana Moorthy Mallipudi and T. Roy Fukuto\*

A series of *N*-arylsulfenyl, *N*-alkylsulfenyl, and *N*-aminosulfenyl derivatives of several commercial insecticidal methylcarbamate esters was examined for toxicity to honeybees and houseflies. All but one of the 34 compounds showed high toxicity to the honeybee. 2-Isopropoxyphenyl *N*-methyl-*N*-(2-methyl-4-*tert*-butylphenylsulfenyl)carbamate with a honeybee  $LD_{50} > 800 \mu\text{g/g}$  was more than 33 times less toxic to honeybees than to houseflies ( $LD_{50}$   $24.5 \mu\text{g/g}$ ). In comparison, the parent carbamate, propoxur, was more toxic to the honeybee ( $LD_{50}$   $4.5 \mu\text{g/g}$ ) than to the housefly ( $LD_{50}$   $24.0 \mu\text{g/g}$ ). The toxicity of 2-isopropoxyphenyl *N*-methyl-*N*-(2-methyl-4-*tert*-butylphenylsulfenyl)carbamate to the honeybee was synergized more than 18-fold by piperonyl butoxide. Compared to propoxur, the *N*-aminosulfenyl derivatives of propoxur were generally of equal toxicity to houseflies, substantially more toxic to mosquito larvae, and much less toxic to mice.

A previous report from this laboratory (Black et al., 1973a) described the favorable toxicological properties of a variety of *N*-arylsulfenyl and *N*-alkylsulfenyl derivatives of some common methylcarbamate insecticides. The insecticidal activity of either parent or derivatized carbamates was approximately the same, but mammalian

toxicity was drastically reduced in the case of the derivatives. Based on a comparative metabolism study in the housefly and white mouse, the desired order of selectivity of the sulfenyl derivative *N*-(2-toluenesulfenyl)carbofuran was attributed to different pathways of metabolism between the insect and mammal (Black et al., 1973b). In houseflies, lethal quantities of carbofuran were formed in vivo after topical application of *N*-(2-toluenesulfenyl)carbofuran, while the mouse preferentially degraded the derivative at the carbamate ester linkage, possibly by carboxylesterase action, to the nontoxic phenol.

\* Division of Toxicology and Physiology, Department of Entomology, University of California, Riverside, California 92521.