Insecticidal Evaluation of Isomeric Methylthio Isopropylphenyl *N*-Methylcarbamates

E. E. Gilbert, J. O. Peterson, and G. L. Walker

4-(Methylthio)-3-isopropylphenyl *N*-methylcarbamate (I) is considerably more toxic than three of its positional isomers in direct spray and plant systemic tests on four insect species, and in similar tests in comparison with four commercial carbamates. The high activity of I may in part result from adjacent placement of the methylthio and isopropyl groups, both of which are bulky and electron-rich.

Numerous ring-substituted phenyl *N*-methylcarbamates have been studied as insecticides (Metcalf and Fukuto, 1965). These include various isopropyl (Metcalf and Fukuto, 1965) and methylthio (Schegk *et al.*, 1967) derivatives, many of which are very active. The isopropyl group has, in fact, been concluded (Metcalf and Fukuto, 1965) to have "optimum size" as a ring substituent for the inhibition of fly cholinesterase. However, only one compound (II) has been reported (Schegk *et al.*, 1967) which contains both of these groups. It, therefore, seemed of interest to prepare and evaluate several of them. Data on four such compounds, including the one already known, are reported here. Compound II has the isopropyl group situated ortho to the carbamate moiety, while all of those prepared by us are meta-oriented. Meta orientation of the alkyl group has given maximum anticholinesterase activity (Metcalf and Fukuto, 1965) in many compounds of this type considered to date. One such material is the 3-isopropyl *N*-methylcarbamate (V), which has been studied extensively (Metcalf and Fukuto, 1965; Metcalf *et al.*, 1960), and is, therefore, included for comparison.

PREPARATION OF TEST COMPOUNDS

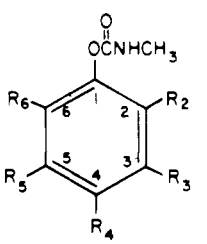
The compounds prepared were I to V, inclusive.

Compound I was prepared as follows (Farah and Gilbert, 1963, 1966):

$$1\text{-(HS)-2-}(C_3H_7)C_6H_4 \xrightarrow[(2)\ Br_2]{(1)\ CH_3I} 1\text{-(Br)-3-}(C_3H_7)\text{-4-}(CH_3S)C_6H_3 \xrightarrow[Cu\text{-}CuO]{NaOH} 1\text{-(HO)-3-}(C_3H_7)\text{-4-}(CH_3S)C_6H_3 \xrightarrow{CH_3NCO} I$$

2-Isopropyl benzenethiol (Pitt-Consol Chemical Co., 152 grams, 1.0 mole) and sodium hydroxide (40 grams, 1.0 mole) were dissolved in 800 ml. of methanol, and methyl iodide (142 grams, 1.0 mole), dissolved in 100 ml. of methanol, was added over 1 hour dropwise with stirring, followed by refluxing for 1 hour. The cooled reaction mixture was poured into 2000 ml. of water, and the oil layer separated. Vacuum distillation gave 158 grams (95% yield) of 2-(methylthio)isopropylbenzene (b.p. 122–4° at 25 mm.).

2-(Methylthio)isopropylbenzene (83 grams, 0.5 mole) was dissolved in 200 ml. of carbon disulfide, and a trace of iron powder was added, followed by dropwise addition of bromine (80 grams, 0.5 mole) with stirring over about 60 minutes at reflux (ca. 46°). The mixture was then re-



	R_2	R_3	R_4	R_5	R_6
I	H	i-Pr	CH_3S	H	H
II	i-Pr	H	CH_3S	H	H
III	H	i-Pr	H	H	CH_3S
IV	CH_3S	i-Pr	H	H	H
V	H	i-Pr	H	H	H
VI (Baygon)	i-PrO	H	H	H	H
VII (Zectran)	H	CH_3	$(CH_3)_2N$	CH_3	H
VIII (Mesurol)	H	CH_3	CH_3S	CH_3	H
IX (Sevin)	(1-Naphthyl)	...	...	...	...

Allied Chemical Corp., Morris Township, N.J. 07960

fluxed 3 hours, when HBr evolution was complete. Distillation gave 115 grams (92% yield) of 4-(methylthio)-3-isopropylbromobenzene (b.p. 166° at 25 mm.). The compound was shown to be pure by gas-liquid chromatography (GLC).

4-(Methylthio)-3-isopropylbromobenzene (24.5 grams, 0.1 mole), 100 ml. of 10% sodium hydroxide, 1.25 grams of copper powder, and 4.0 grams of cuprous oxide were charged to a 300-ml. stainless steel autoclave and heated at 250° for 10 hours. The cooled mixture was filtered and extracted three times with methylene chloride. The aqueous layer was acidified to pH 1 with HCl, then extracted with ethyl ether. Removal of the ether gave 18 grams of crude 4-(methylthio)-3-isopropylphenol. Distillation at 100 mm. gave 11.5 grams (65% yield) (b.p. 157–9°). The compound was shown to be pure by GLC.

4-(Methylthio)-3-isopropylphenol (5.5 grams, 30 mmoles), methyl isocyanate (2.0 grams, 35 mmoles), and 3 drops of triethylamine were dissolved in 20 ml. of isopropyl ether. The container was sealed and allowed to stand for 50 hours. During this time, compound I (6.3 grams) precipitated from solution. It melted at 80–3°; concentration of the filtrate gave 0.6 gram more (m.p. 82–4°). The total yield was 95% of theory. Recrystallization from benzene–petroleum ether gave a melting point of 82–4°. Analysis. Calculated: 60.2% C, 7.1% H, 13.4% S. Found: 60.4, 7.3, 13.2.

Compound II (prepared by J. J. Murray). Although this compound is known (Schegk *et al.*, 1967), its preparation has not been described. 4-(Methylthio)-2-isopropylphenol was made by a procedure developed at this laboratory (Farah and Gilbert, 1963, 1964), as follows:

$$1\text{-(HO)-2-}(C_3H_7)C_6H_4 \xrightarrow[H_2SO_4]{(CH_3S\text{-})_2} 1\text{(HO)-2-}(C_3H_7)\text{-4-}(CH_3S)C_6H_3$$

A mixture of 2-isopropylphenol (68 grams, 0.5 mole) and concentrated sulfuric acid (25 grams) was heated to 140° with stirring. Methyl disulfide (47 grams, 0.5 mole) was added dropwise over 1 hour. (Whenever the temperature dropped to 130°, addition was discontinued until it rose again to 140°.) The mixture was then refluxed 3 hours (126°). It was cooled and the bottom acid layer was separated and discarded. The top organic layer was water-washed and distilled at 2 mm. The yield was 25 grams (b.p. 137–40°). Since 31 grams of starting phenol was recovered, the yield was 50% of theory. The product was shown to be 82% pure by GLC. The infrared spectrum of the compound purified by preparative GLC showed the expected 1,2,4 orientation (overtone region 1865 and 1740 $cm.^{-1}$; deformation mode 810 $cm.^{-1}$). The crude phenol was converted to compound II by reaction with methyl isocyanate by using the procedure described for compound I. It melted at 96.5–98.5° [Schegk *et al.* (1967) give 98.5°]. Analysis. Calculated: 60.2% C, 7.1% H, 13.4% S. Found: 60.0, 7.1, 13.6.

Compound III (prepared by R. J. DuBois). 3-Isopropylphenol reacted with methyl disulfide by the procedure described for compound II. This gave a mixture of approximately 50% 4-(methylthio)-, 45% 6-(methylthio)-, and 5% 2-(methylthio)-3-isopropylphenol. Redistillation gave a fraction (b.p. 112–17° at 10 mm.), comprising 85% 6-(methylthio)-and 15% 2-(methylthio)-3-isopropylphenol. This fraction reacted with methyl isocyanate as described for compound I. Two recrystallizations gave III, (m.p. 142–4°), shown to be over 99% pure by GLC. Analysis of a purified sample of the phenol gave: Calculated: 65.9% C, 7.8% H, 17.6% S. Found: 65.8, 7.8, 17.9.

Compound IV. 2-(Methylthio)-3-isopropylphenol was isolated by preparative GLC from the fraction containing 15% of this isomer cited under compound III. A 5-foot × 1/4-inch Varian Aerograph column, packed with 15% FFAP on Chromosorb W, was used at a helium flow of 55 ml. per minute. Analysis. Calculated: 65.9% C, 7.8% H, 17.6% S. Found: 66.0, 7.9, 17.8. It was converted to compound IV by reaction with methyl isocyanate as detailed under compound I. IV melted at 135-8°.

Nuclear magnetic resonance and infrared spectra were consistent with the assigned orientations of the phenolic intermediates for compounds I to IV.

Compound V was prepared from 3-isopropylphenol and methyl isocyanate by the procedure described for compound I. This known compound is one of the more active phenyl carbamate insecticides (Metcalf and Fukuto, 1965; Metcalf *et al.*, 1960).

TEST METHODS

Cranberry bean plants in 2 1/2-inch pots, with all foliage removed except one primary leaf, were sprayed for 2 seconds on the upper surface and 5 seconds on the under surface. Spray was delivered from a De Vilbis atomizer nozzle at 20 p.s.i. The approximate volume of spray on the upper surface was 0.19 ml., and on the under surface was 0.48 ml. The deposits were allowed to dry on the plants, and five larvae were then confined on each plant with 6-inch screen wire spheres. Mortality records were made 3 days after treatment. The spray was an aqueous suspension made by dilution of an acetone solution of the compound to the strength indicated. This test was used on Mexican bean beetle larvae (3rd instar) [*Epilachna varivestis* (Mulsant)] and southern armyworm larvae (4th and 5th instars) [*Prodenia eridania* (Cramer)]. This procedure was also used on mites [*Tetranychus urticae* (Koch)], but the plants were not defoliated and were infested with mites one day before spraying.

Aphids [*Acyrthosiphon pisum* (Harris)] were tested as follows: English broad bean plants were sprayed for 2 seconds on the upper surface and 5 seconds on the under surface. Adult female aphids (10 per test) were brushed from infested broad bean plants into 5-inch screen wire hemispheres and sprayed for 5 seconds. The aphids were caged over the previously sprayed plants and mortality records were made 3 days later.

Tests on German cockroaches [*Blattelle germanica* (Linnaeus)] were conducted by coating the bottom half of half-pint bottles with 6 mg. of toxicant prior to introducing the insects. The bottles were coated by dissolving the toxicant in acetone, followed by evaporation of the solvent with a stream of air.

The systemic tests were run by pipetting an acetone solution of toxicant on plant stems about 1 inch above the soil level. Capillary pipets graduated in 0.001 ml. were used. The insects were placed on the plants 1 day after treatment

and mortality records were made 4 days later. Cranberry bean plants were used for the tests on Mexican bean beetle and southern armyworm larvae and on mites. Young English broad bean plants were used in the tests on pea aphids.

TEST RESULTS

The results reported in Table I show that I (Gilbert and Otto, 1967) is far more active than the other experimental carbamates (II to V) on three out of four of the test species used in the spray test. (None of these compounds was highly toxic to southern armyworm larvae.) I also appears more active than commercial carbamates VI to IX on all test species except southern armyworm larvae; the greatest margin of difference is noted on mites.

Systemic tests (Table II) again show the superiority of I to the other experimental carbamates since it gave excellent results with two out of four test species, while only one of the other compounds (V) showed any systemic activity, and this was limited to one insect. Phenyl carbamate insecticides characteristically have limited systemic activity (Kenaga, 1966).

Comparison of I with commercial carbamates shows that it and VIII have similar systemic activity, while the other compounds have little or none. Compound VII is outstandingly active on southern armyworm larvae in the spray test, but completely inactive in the systemic test. There are several possible reasons for this difference.

Compound I was also compared with the four commercial carbamates for the control of cockroaches. None of the compounds gave over 10% knockdown after 1 hour. Kill after 24 hours was 100% for VI, VII, and VIII, 60% for I, and 50% for IX. I is evidently not especially active on this insect.

Compound I also gave good control of plum curculio adults, potato aphids, foxglove aphids, greenhouse whitefly, and yellow fever mosquito larvae. Comparisons of I with the other carbamates were not run on these insects.

DISCUSSION

Although no general conclusions relating chemical structure to insect toxicity appear warranted from this brief study, it seems of interest to consider the structural features of I in the light of the structure-activity relationships discussed by Metcalf and Fukuto (1965). Those authors emphasize the difficulty of generalizing about the insecticidal activity of multisubstituted phenyl carbamates because of species specificity and the complexity of steric, mesomeric, and inductive interaction.

The methylthio and isopropyl substituents have the electron-donating character often associated with high activity in carbamates, such as compounds V to VIII. More specifically, I has an *m*-isopropyl group, which has been concluded to possess both optimum size and optimum position for high insect toxicity.

On the other hand, several carbamates with regions of high electron density ortho to one another are easily detoxified. Although compound I appears to satisfy this structural requirement, its high degree of activity suggests that it is not easily detoxified. The fact that I has only two ring substituents (in addition to the carbamate moiety)

Table I. Spray Test Comparison of Experimental and Commercial Carbamates

(Per cent kill)

% Toxicant in Spray × 10^3	Mexican Bean Beetle Larvae					Pea Aphids					Southern Armyworm Larvae					Mites				
	Experimental Carbamates																			
	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V
240											100		0							
120								70			20	0						83		
60								50		10	0				100			56		
30			100					20	0	0				0	80			32		
15			80												40	100	55			0
7.5			60			100									0	98	16		15	
3.8			40	80		100										79	6		0	
1.9				0		80	40													
0.94		40			40		10													
0.47	100	0			0		0													
0.23	20																			
0.12	0																			

	Commercial Carbamates																			
	I	VI	VII	VIII	IX	I	VI	VII	VIII	IX	I	VI	VII	VIII	IX	I	VI	VII	VIII	IX
240											100			100					100	
120											20	100		...					...	
60										70	0	40		...			71		...	8
30							100			40		20		0			47	100	...	
15							...		20	...		0			100	100	...	...	50	
7.5						100	0	100	0	10			100		80	98	10	25		
3.8						100		10		0			100		0	79	4	11		
1.9		100	100	100	100	80		0												
0.94		100	100	10	80															
0.47	100	20	40	0	60															
0.23	20	0	20		0															
0.12	0		0																	

Table II. Systemic Effectiveness of Experimental and Commercial Carbamates[a]

Isomer Tested	Mg. Toxicant per Plant	Mexican Bean Beetle Larvae	Pea Aphids	Southern Armyworm Larvae	Mites
		Experimental Carbamates			
I	0.48	100	100	0	9
	0.24	100	100	0	9
	0.12	80	0	0	6
II	0.48	0	0	0	4
	0.24	...	...	0	7
III	0.48	0	0	0	0
	0.24	0	0	0	0
IV	0.48	0	0	0	0
	0.24	...	...	...	...
V	0.48	100	0	0	0
	0.24	60	0	0	0
		Commercial Carbamates			
VI	0.24	20	0	0	9
	0.12	0	0	0	5
VII	0.24	0	0	0	7
	0.12	0	0	0	7
VIII	0.24	100	90	0	5
	0.12	80	53	0	0
IX	0.24	0	0	0	0
	0.12	0	0	0	0

[a] Per cent mortality after 4 days.

might suggest less facile detoxification compared with VII and VIII (each with three substituents), since each additional substituent provides a possible avenue for attack by a detoxification enzyme.

The structural feature of I which markedly differentiates it from other known active carbamates is the unusually high degree of steric hindrance between the two relatively bulky ortho-situated methylthio and isopropyl groups. The substantial degree of such hindrance is indicated by the reluctance of the methylthio group to enter the ring ortho to the isopropyl group during the preparation of III, which was noted above. From the viewpoint of an approaching detoxifying enzyme, in effect these two groups may, as a result, function as only one. As concluded by Metcalf and Fukuto in considering other carbamates, steric effects may play a dominant role. This suggests that further study of steric relationships in carbamate insecticides might yield fruitful results.

Compound IV resembles I in having adjacent methylthio and isopropyl substituents, but in IV the methylthio group is situated between the isopropyl and carbamate moieties and is, therefore, too shielded to react with enzyme systems. This may in part explain the comparatively low activity of IV compared to I.

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