Synergism and Species Specificity of Carbamate Insecticides

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Like other classes of insecticides, the carbamates show varying degrees of specificity. This specificity apparently arises from factors other than an insensitivity of the biochemical target, acetylcholinesterase. By the use of 1,2-methylenedioxyphenyl derivatives, many carbamates can be synergized sufficiently against the housefly to match their potential activity as indicated by their potency as fly head ChE inhibitors. Discrepancies can often be accounted for in terms of the poor efficiency or even failure of the synergist used, or by the limited penetration rate of the carbamate. Direct involvement of other elements of the cholinergic system cannot be discounted in some cases. Synergism of the carbamates is not unique to the housefly but occurs with other species also; however, synergists as well as toxicants display species specificity.

Comparisons of the activity spectra of experimental and commercial carbamate ester insecticides (*6*, *23*) demonstrate wide variations in insecticidal action. Although definite activity patterns exist, specificity is not ordinal for the carbamates as a class. Focusing attention on the biological performance of individual carbamates, specificity again often fails to follow the higher taxonomic categories. Carbaryl (Sevin insecticide; 1-naphthyl methylcarbamate), for example, though inactive against the two-spotted spider mite [*Tetranychus telarius* (L.)], controls parasitic mites and ticks (*4*, *11*), eriophyid mites (*9*, *12*), and predacious mites (*21*). Dropping to the family level, carbaryl is active against the bean aphid (*Aphis fabae* Scopoli), but not against the pea aphid [*Macrosiphum pisi* (Harris)]. Even the stages of the same species often vary widely in their susceptibility. Thus, carbaryl is a moderately effective housefly (*Musca domestica* Linnaeus) larvicide, yet 20 to 40% of a normal population of adults are completely tolerant to it.

The high degree of specificity inherent in the first group of insecticidal carbamates developed commercially (*8*) is often associated with the carbamates as a class. Table I supports our thesis that varying degrees of specificity are common to all three major classes of organic insecticides. The unexpected influence of structure on the specificity of "broad spectrum" compounds is particularly highlighted in the activity of DDT *vs.* *o*-Cl - DDT [1,1,1 - trichloro - 2 - (4-chlorophenyl) - 2 - (2,4 - dichlorophenyl)ethane] and of methyl parathion *vs.* Sumithion [*O,O* - dimethyl *O*-(3 - methyl - 4 - nitrophenyl) phosphorothioate] against the larval stage of the Mexican bean beetle (*Epilachna varivestris* Mulsant). Whether one is screening candidate insecticides, developing practical control measures, or investigating "modes of action," the question, "Why are insecticides specific or selective?" is highly relevant but too often unanswered. To explore some possible answers regarding the carbamate ester insecticides is the purpose of this paper.

Correlation of Cholinesterase I_{50}'s with Toxicities

First, we need some estimate of the intrinsic activity of a compound apart from its over-all effect on living organisms. This, in turn, demands not only a knowledge of the ultimate mode of action, but also a means of measuring it directly. Assuming that cholinesterase inhibition accounts for the mode of action of the carbamate insecticides, there should be a correlation between in vitro anticholinesterase activity and insecticidal potency. As is obvious from the data for houseflies (*5*, *23*), there is none. Carbaryl is somewhat more potent as a cholinesterase inhibitor than Dimetilan (2 - dimethylcarbamoyl - 3-methyl-5-pyrazolyl dimethylcarbamate), yet Dimetilan is a superior housefly toxicant while carbaryl fails even at excessive dosages. The discovery that pyrethrins synergists of the methylenedioxyphenyl type also potentiate the carbamates (*17*) has provided a way around many of these discrepancies. As pointed out by Metcalf, Fukuto, and Winton (*15*), the inherent activity of carbamates for houseflies as indicated by the in vitro fly head cholinesterase (ChE) I_{50}'s can be realized in vivo by the addition of piperonyl butoxide as a synergist. As a rule, our own data support this generalization (Figure 1).

The role of an insecticidal synergist is generally believed to be that of an inhibitor of detoxication processes. We are aware of no data which would suggest otherwise; hence, we shall frequently use this generalization as the basis for interpreting results obtained with carbamate-synergist combinations.

Correlation of Fly Bait with Topical Toxicities

The fly toxicity data in Table I and the synergized toxicities in Figure 1 are based on a bait-feeding method in contrast to the more commonly used topical method. Table II shows that a satisfactory correlation exists between topical toxicities published by Metcalf and coworkers and parallel fly-bait data taken from Union Carbide Corp. screening reports for a variety of substituted phenyl methylcarbamates and this despite differences in holding temperatures and sex of flies used. In fact, the numerical values for the bait LD_{50} in parts per million approximate those for the topical LD_{50} in micrograms per gram weight of fly.

Carbaryl and 3-*tert*-butylphenyl methylcarbamate have been shown to give a nonlinear dosage mortality curve by the topical method with NAIDM flies (*17*). After 60 to 80% mortality, little or no additional kill is obtained with increasing doses. The same phenomenon also occurs in the bait test. LD_{50}'s in these cases are obviously misleading unless reported for both parts of the curve.

Marked failures in bait-topical correlations have been observed among phenyl *N*-methylcarbamates whose ring substituents are not of the types listed in Table II. In these cases, the bait test is much more sensitive, suggesting that the cuticle, a barrier to external penetration, has been effectively bypassed through this method of treatment.

Discrepancies in Housefly ChE I_{50}–Toxicity Correlations

An examination of the data for particular compounds allows us to posit additional toxicological parameters which may explain, qualitatively at least, certain differences between observed and expected activities for the carbamate ester insecticides.

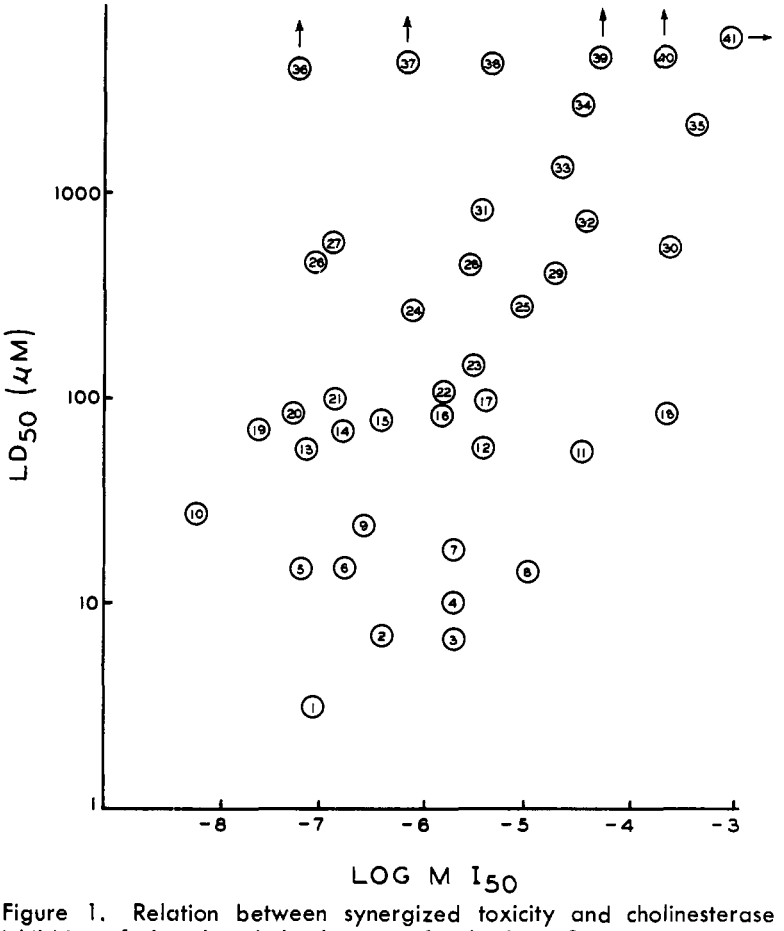

Figure 1. Relation between synergized toxicity and cholinesterase inhibition of phenyl methylcarbamates for the housefly

Methods. Cholinesterase inhibition determined by manometric method with fly heads as source of cholinesterase (*10*). Toxicities determined by combining a constant amount of piperonyl butoxide (1000 p.p.m.) with a dosage series of toxicant. Exposure by bait

Substituents. 1 = 2-$(CH_3)_2CHO$. 2 = 3,5-diCH_3-4-$(CH_3)_2N$. 3 = 3,5-diCH_3-4-$CH_3S(O)$. 4 = 3-$CH{=}CCH_2O$. 5 = 3-CH_3-5-$(CH_3)_2CH$. 6 = 3,5-diCH_3-4-CH_3S. 7 = 3-$(CH_3)_2N$. 8 = 3,5-diCH_3-4-$CH_3S(O_2)$. 9 = 2-$(CH_3)_2CH$. 10 = 2-Cl-5-$(CH_3)_2CH$. 11 = unsubstituted. 12 = 2-C_2H_5. 13 = 2-Br-5-$(CH_3)_2CH$. 14 = 2,4-diCl-3-CH_3-5-C_2H_5. 15 = 3-$(CH_3)_2CH$. 16 = 3-CH_3-4-$(CH_3)_2N$. 17 = 3-CH_3. 18 = 3-isopropylphenyl carbamate. 19 = 3-$(CH_3)_2CH$-4-Br. 20 = 3-$(C_2H_5)_2N$. 21 = 2-Cl-4,5-diCH_3. 22 = 2,4-diCl-5-CH_3. 23 = 2-$CH_2{=}CHCH_2$-4-CH_3. 24 = 3,5-diCH_3-4-Cl. 25 = 4-C_2H_5. 26 = 2-$(C_2H_5)_2NCH_2$. 27 = 2,3,5-triCH_3-4-Cl. 28 = 3-CH_3-4-Cl. 29 = 2,6-di$CH_2{=}CHCH_2$. 30 = 4-Cl. 31 = 2-CH_3-5-$(CH_3)_2CH$. 32 = 2-Cl-6-CH_3. 33 = 2,6-di$(CH_3)_2CH$. 34 = 2,6-diC_2H_5. 35 = 2,6-diCl. 36 = 3-CH_3-4-SCN-6-$(CH_3)_2CH$. 37 = 2,3-diCH_3-4-SCN. 38 = 3-SCN. 39 = 2-$(CH_3)_3C$-5-CH_3. 40 = 2-$(CH_3)_3C$-4-CH_3. 41 = 2,6-diCH_3

Table I. Specificity as Demonstrated by Chlorinated Hydrocarbons and Organic Phosphates

	LD_{50}					
					Housefly	
	Bean aphid spray,[a] p.p.m.	2-Spotted mite spray,[a] p.p.m.	Southern armyworm leaf dip,[b] p.p.m.	Mexican bean beetle larva leaf dip,[b] p.p.m.	Bait,[c] p.p.m.	Topical,[d] μg./female
DDT	80	>2500	60	1250	20	0.1
o-Cl-DDT	150	>2500	28	80	...	0.3
Aldrin[e]	200	>1000	14	>1000	20	...
Mirex[e]	>100	ca. 1000	10	>1000	>1000	...
Diazinon[e]	350	...	80	400	15	...
Methyl parathion	5	...	30	150	2	...
Sumithion	2	...	40	15	2	...

[a] Aqueous dispersions applied to infested plants on turntable.
[b] Larvae exposed to bean leaves treated by dipping in aqueous dispersion.
[c] Incorporated in 10% sugar water. [d] In 1 μl. of acetone to dorsal thorax.
[e] Aldrin. 1,2,3,4,10,10-Hexachloro-1,4,4*a*,5,8,8*a*-hexahydro-1,4:5,8-dimethanonaphthalene.
Diazinon. *O,O*-diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl)phosphorothioate.
Mirex. Dodecachlorooctahydro-1,3,4-metheno-2H-cyclobuta(c,d)pentalene.

From the examples cited below there appear to be three major reasons for poor correlation: incomplete or no synergism with piperonyl butoxide, poor penetration of toxicant, and mode of action other than or in addition to ChE inhibition.

Relative Efficiency of Piperonyl Butoxide as a Synergist for Carbamate Insecticides

Although carbaryl is markedly synergized by piperonyl butoxide against the housefly, the full insecticidal potential of this compound as indicated by an I_{50} of $3 \times 10^{-7}M$ is still far from being realized by combination with this synergist. Some other methylenedioxyphenyl compounds such as myristicin (5-allyl-1-methoxy-2,3-methylenedioxybenzene) (*13*), isosafrole, and 1-nitro-3,4-methylenedioxybenzene are much more efficient synergists for carbaryl (Table III); however, this greater efficiency does not necessarily carry over to other carbamates. If a carbamate were susceptible to more than one mode of detoxication, variations in the ability of the synergists to antagonize these different modes could also give rise to such relative synergistic efficiencies. Even when a better synergist is discovered and is used at its optimal ratio, how can we be assured that we have reached maximum activity?

Failure of Piperonyl Butoxide to Synergize Certain Thiocyanate-Substituted Carbamates

The 4-thiocyanophenyl methylcarbamates shown in Table IV are completely refractory to potentiation by piperonyl butoxide in spite of their favorable I_{50}'s. They are also practically devoid of any other insecticidal activity. Recalling that recovery from knockdown is a toxicological characteristic of thiocyanates such as Thanite [a mixture of isobornyl thiocyanate (82%) and related compounds] and Lethane 384 (2-butoxy-2′-thiocyanodiethyl ether), our tentative suggestion is that the thiocyano group is very labile in vivo in a manner not susceptible to antagonism by piperonyl butoxide.

Since the thiocyano group is classified chemically as a halogenoid, it probably is not merely coincidental that some of the more poorly synergized compounds in Figure 1 are halogen-substituted.

Influence of Cuticular Penetration Rates on Topical Toxicities

When measurable rates of detoxication of reversible inhibitors such as the carbamates occur, relatively small differences in external penetration rates could be expected to give rise to marked differences in toxicity. Although we do not have direct evidence in this regard, a comparison of topical and bait toxicities to the housefly suggests that the first

Table II. Comparison of Topical and Bait Methods in Assaying Relative Activity of Phenyl Methylcarbamates to Houseflies

Ring Substituent	Topical LD_{50}, μG./G. Fly	Fly Bait[a] LD_{50}, P.P.M.
3,4-O-CH_2-O	18[c]	17
3,5-DiCH_3-4-CH_3S (Mesurol)	24[d]	25
2-Iso-C_3H_7O (Baygon)	26[c]	21
3-CH_3	50[b]	95
2-C_2H_5-O	55[c]	50
3,5-DiCH_3	60[b]	80
3,5-DiCH_3-4-$(CH_3)_2$N (Zectran)	60[d]	100
2-Br	60[e]	200
3-C_2H_5O	75[c]	105
2-Cl	75[b]	120
3-Iso-C_3H_7 (UC 10854)	90[c]	110
3-CH_3O	90[c]	130
2-I	90[e]	190
2-CH_3-O	93[c]	110
2-C_2H_5	95[e]	70
2-Iso-C_3H_7	100[b]	65
3-*sec*-C_4H_9 (R 5305)	100[d]	150
3-C_2H_5	140[e]	120
3-Br	170[e]	230
3-Iso-C_3H_7O	180[c]	220
3-*sec*-C_4H_9O	220[c]	280
2-F	250[e]	160
4-C_2H_5	250[e]	200
3-DiCH_3N	270[e]	100
3-*n*-C_4H_9O	280[c]	180
Unsubstituted	70[b]; 500[e]	25
3-Cl	100[b]; >500[e]	250; 55
Carbaryl (Sevin)	>500[c]	l-p line not linear
3-*tert*-C_4H_9	>500[d]	l-p line not linear
3-Cl-6-CH_3	>500[f]	500
4-CH_3-O	>500[c]	ca. 600
4-Cl	>500[b]	1000
2-C_6H_{11}	>500[b]	>1000
2,4-DiNO_2	>500[b]	>1000
3-NO_2	>500[b]	>1000
2,6-DiCH_3O	>500[c]	>1000
4-Iso-C_3H_7	>500[b]	>1000
2-CH_3-5-Iso-C_3H_7	>500[b]	>1000
2,4-Di-*tert*-C_4H_9	>500[b]	>1000
2,6-DiCH_3	>500[f]	>1000
2,6-DiCl	>500[f]	>1000
3-CH_3-4-Cl	>500[f]	>1000
3,5-DiCH_3-4-Cl	>500[f]	>1000
3,4-DiCH_3-6-Cl (U 12927)	>500[f]	>1000
2,4-DiCl-5-CH_3	>500[f]	>1000

[a] Mixed sexes, held at 75–80° F. [b] From (*10*). [c] From (*15*). [d] From (*6*). [e] From (*16*). [f] From (*14*).

three compounds listed below penetrate the cuticle more slowly than those listed in Table II.

Substituted Phenyl Methylcarbamates	LD_{50} Topical, μg./g. female fly	LD_{50} Bait, p.p.m.
3-Methylureido	900	23
4-Methylureido	>400	25
3-Methylcarbamoyloxy-5-methyl	ca. 500	29
3-Isopropyl	52	90

Flies topically treated with the standard, 3-isopropylphenyl methylcarbamate, undergo an initial knockdown which is followed by a gradual recovery, the degree depending on the dose. With the three compounds showing poor activity topically, no initial knockdown is observed but kill is gradual, occurring in the latter part of the usual 24-hour holding period and even extending over into the second day.

Compounds More Active than Suggested by Their I_{50}'s

The I_{50}'s for 3,5-dimethyl-4-methylthiophenyl methylcarbamate (Bayer 37344), its sulfoxide, and its sulfone increase about an order of magnitude for each oxidation step, yet they are practically equivalent in their action against the housefly. In contrast to the classical examples among the organophosphates, oxidation of the sulfide side chain does not activate, but actually inactivates, Bayer 37344. Could it be that piperonyl butoxide not only prevents carbamate degradation but also mediates the reduction of the sulfoxide and the sulfone?

Compound	LD_{50}, P.P.M. Aphid	Mite adult	Southern armyworm	Mexican bean beetle larva	Fly Bait Alone	Fly Bait + PB[a]	I_{50}, Fly Head ChE × 10^{-6}M
37344	50	50	125	4	25	3.3	0.2
Sulfoxide	50	45	325	20	15	1.6	2
Sulfone	100	1000	1000	100	65	3.5	10

[a] 1000 p.p.m. piperonyl butoxide.

3 - Isopropylphenyl carbamate (UC 12765) is a poor inhibitor of fly head ChE ($I_{50} = 2.4 \times 10^{-4}$ *M*) compared to its *N*-methyl derivative ($I_{50} = 4 \times 10^{-7}$ *M*). The piperonyl butoxide–synergized fly-bait toxicities of 15 and 8 p.p.m., respectively, certainly belie the difference in I_{50}'s. Sensitivity to the *N*-unsubstituted carbamate ester is not a peculiarity of the housefly, since many other insect species are equally susceptible to these two compounds. In a study of the pharmacology of alkylphenyl carbamates, Barnes *et al.* (*2*) pointed out that although some of these compounds were toxic to mice, they were extraordinarily poor inhibitors of mammalian pseudocholinesterase. For carbamoyl choline, a poor anticholinesterase agent, "its cholinergic action on effector cells is probably a direct one unrelated to its anticholinesterase activity" (*7*). Some caution must be used, therefore, in attributing the insecticidal action of carbamate esters only to their anticholinesterase activity. The 3-isopropylphenyl carbamate may provide a pharmacological tool for studying the acetyl choline receptor protein (*20*) in insects.

Role of Dioxole Ring in Synergism of Carbamates by Methylenedioxyphenyl Compounds

As has been shown for the pyrethrins, maximum synergism of carbaryl depends on the presence of the intact 1,2-methylenedioxy group (*19*). Substitution by 1,2-dimethoxy, 1-methoxy-2-hydroxy, or 1,2-ethylenedioxy groups extinguishes or greatly reduces synergistic activity. The synergism of carbaryl by methyl eugenol (1-allyl-3,4-dimethoxybenzene), an exception for the pyrethrins too, appears to be associated with the allyl group, since the *n*-propyl analog is inactive.

Of a wide variety of methylenedioxyphenyl derivatives (Table V), only those possessing a carboxy or a phenolic group are completely inactive. Poor penetration to the site of action and/or rapid excretion may be responsible. Cuticular penetration is probably the limiting factor for those compounds active by bait feeding but not by topical application.

Compounds Other than Methylenedioxyphenyl Derivatives as Synergists against the Housefly

Moorefield and Tefft (*18*) have described the synergistic effect of the drug potentiator, 2-(3,5-dichloro-2-biphenyl-

Table III. Relative Efficiencies of Several Methylenedioxyphenyl Derivatives in Synergizing Carbaryl against Housefly

Synergist + Carbaryl (1 to 1 Ratio)	Topical LD_{50} in Terms of Carbaryl, μG./Female Fly
Isosafrole	0.45
Myristicin	0.20
1-Nitro-3,4-methylenedioxybenzene	0.45
Piperonyl butoxide	1.05
Carbaryl alone	>10.00

yloxy)triethylamine (Lilly 18947), with carbamates. This compound does not synergize the pyrethrins.

By the bait-feeding method, alkyl and aryl boronic acids are another interesting type of carbamate synergist. As a class, they do not appear to be as efficient as the methylenedioxyphenyl compounds nor do they synergize pyrethrins. These compounds are not active topically, again suggesting that cuticular penetration may be a limiting factor.

With DDT, the solvent used in topical tests can markedly affect toxicity to houseflies (*1*). Dioctyl phthalate has been suggested as an alternative to Risella oil for topical tests (*3*). When the former compound is used in combination with acetone—e.g., in a ratio of 1 to 3—the topical activity of Sevin is significantly increased and the dosage-mortality (l-p line) curve becomes linear. Whether this is caused by increased penetration or inhibition of detoxication is unknown.

Synergism of Carbamates against Insects Other than Housefly

Systematic studies of the anticholinesterase activity of carbamate esters have been generally limited to the housefly enzyme for technical reasons and as a matter of convenience. Consequently, we have no gage for estimating the potential toxicity of this class of compounds to other insects. The use of synergists to develop this intrinsic insecticidal activity provides another means of attacking the problem. Unfortunately, synergists active against the housefly when combined with either the carbamates or the pyrethrins show little or no activity against most other species. This does not mean that the housefly is unique in its reaction to synergists, but probably reflects the fact that screening for synergists has been done more extensively with the housefly than any other insect. Our experience suggests that synergists, like toxicants, also exhibit species specificity.

An insect such as the southern armyworm [*Prodenia eridania* (Cramer)], which is highly susceptible to but few carbamates (*23*), is capable of rapidly metabolizing carbaryl. Using fly head ChE inhibition as an assay method, the half life of a 50-μg. dose injected into 0.3 to 0.8 gram larvae is less than 1 hour. Anerobic conditions completely arrest this degradation, suggesting an oxidative detoxication mechanism, yet the typical methylenedioxyphenyl synergists provide no potentiation of carbaryl against this species. We have found, however, that 1-naphthyl *N*-hydroxy-*N*-methylcarbamate (UC 22708) is effective in this regard, but fails against the housefly.

Although phenyl and naphthyl carbamates are very active against the Mexican bean beetle, the Geigy heterocyclic enol carbamates, Dimetilan and Pyrolan (3-methyl-1-phenyl-5-pyrazolyl dimethylcarbamate), are practically inactive (*23*). Phenyl dimethylcarbamate at a constant, nontoxic dosage of 1000 p.p.m. reduces the LD_{50} (leaf dip method as per Table I) for Dimetilan against Mexican bean beetle larvae from 620 to 66 p.p.m.; for Pyrolan, from 560 to 100 p.p.m. The phenyl dimethylcarbamate is inactive by itself. With the 1-naphthyl dimethylcarbamate, observed kill was not greater than additive.

Significance of Species Specificity and Synergism to Development of Carbamate Insecticides

Insect toxicity–chemical structure correlations by themselves fail to provide adequate knowledge of the structural requirements of the critical biochemical or biophysical lesion responsible for insecticidal activity. Not only must we have a way of independently verifying the assumed mode of action, but the parameters for penetration and detoxication must also be incorporated into any such scheme.

The terms "broad spectrum" and "selective" when applied to the carbamates represent a practical point of view—viz., the control of most of the important pest species in major crop or public health categories; and safety to man, domestic animals, and beneficial forms of the fauna, respectively. From the taxonomic viewpoint such distinctions are still so haphazard that the development of better and safer compounds will remain highly empirical for some time to come.

Specificity is the other side of the coin called "resistance," be it natural or acquired. Cases of natural tolerance are previews of types of resistance that might be expected to develop in other species under conditions of practical usage. The poor activity of DDT against the Mexican bean beetle, which results from detoxication by dehydrohalogenation (*22*), is a classical example of such a natural tolerance.

Undoubtedly a more detailed knowledge of detoxication processes particularly at the in vitro level will be obtained in the next decade. Hopefully, synergists may be discovered or, less optimistically, designed to extend the utility of current pesticides effectively to resistant species

Table V. Effect of Substituents on Synergism of Carbaryl by 1,2-Methylenedioxybenzene Derivatives

4-Substituent	Synergism: Topical[a]	Synergism: Bait[b]
Unsubstituted	KD[c]	?
Br	Yes	Yes
OH	No	No
CHO	KD[c]	?
CH_2OH	No	Yes
$CH{=}NOH$	Yes	Yes
COOH	No	No
$CH{=}CHCOOH$	No	No
$CH_2CH{=}CH_2$	Yes	Yes
$CH{=}CHNO_2$	Yes	Yes
$OCONHCH_3$	Toxic	Toxic
$CH{=}NOCONHCH_3$	Yes	Toxic
$CH_2OCONHCH_3$	Yes	Yes
NO_2	Yes	Yes
$NH_2.HCl$	No	Yes
$CH_2OCOOCH_3$	No	?
$CH(OH)C{\equiv}CH$	Yes	Yes
$COOC_2H_4OC_2H_5$	Yes	Yes
$CH_2NH_2.HCl$	No	Yes
CH_2NH_2	Yes	Yes
$CH_2NHCONHCH_3$	No	Yes

[a] 5 μg. of synergist plus 0.5 μg. of carbaryl per female fly.
[b] 1000 p.p.m. of synergist plus 50 p.p.m. of carbaryl in 10% sugar water bait given to mixed sexes.
[c] Knockdown synergism observed with these compounds at standard dosage.

Table IV. Bioassay of Some 4-Thiocyanophenyl Methylcarbamates and Related Compounds

Substituent	LD_{50}'s, P.P.M.[a]: Bean aphid	Southern armyworm	Mexican bean beetle	Fly bait	Fly bait + P.B.	I_{50}, Fly Head ChE × 10^{-6}M
4-SCN	>100	>1000	>1000	>1000	ca. 1000	5.0
4-Cl	600	>1000	320	. . .[b]	100	240.0
Unsubstituted	>100	1000	200	25	8	35.0
3-CH_3-4-SCN	>1000	>1000	750	>1000	1000	0.3
3-CH_3-4-Cl	200	440	47	>1000	90	3.0
3-CH_3	140	750	130	95	16	7.2
2,3-DiCH_3-4-SCN	>100	>1000	250	>1000	>1000	0.8
3-CH_3-6-IsoC_3H_7-4-SCN	>1000	>1000	>1000	>1000	>1000	0.1

[a] See Table I for method outline.
[b] l-p line not linear.

without increasing the hazard to man, domestic animals, and the beneficial fauna. Such knowledge may also be used to modify certain toxicants so that they will be activated by the very detoxicative mechanisms responsible for resistance to other insecticides, thus utilizing the principle of "negative correlation."

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CARBAMATE INSECTICIDES

Photodecomposition of Carbamate Insecticides

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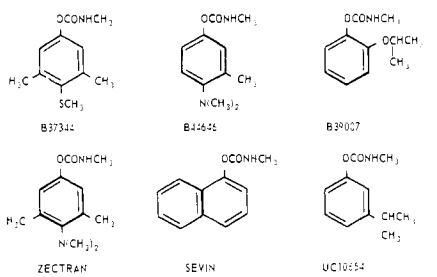
The effect of sunlight and of laboratory ultraviolet light on six *N*-methylcarbamate insecticides has been determined by an improved method which combines thin-layer chromatography and enzyme inhibition. With the exception of Bayer 39007, each of the compounds decomposed to give unidentified cholinesterase inhibitors as well as other substances.

During the past five years *N*-methylcarbamate esters have become an important class of insecticides. Although, like the organophosphorus insecticides, the carbamates are inhibitors of the enzyme acetylcholinesterase, they generally exhibit much lower mammalian toxicities than most of the phosphates. In 1955, Cook (*1*) developed a method for the detection of acetylcholinesterase inhibitors on paper chromatograms. With it, he was able to demonstrate that several phosphate insecticides were decomposed in the presence of ultraviolet light to unidentified products which themselves inhibited the enzyme to a significant degree.

Although several other investigators (*2, 4*) have improved on Cook's procedure, paper chromatographic methods are not readily applied to the isolation of most organic substances because of limited adsorptive capacity and the introduction of impurities during elution. We have developed a variation of Cook's method which employs thin-layer chromatography (TLC) and have demonstrated that the carbamates, too, decompose under the influence of ultraviolet light to series of inhibitors.

Experimental

Materials and Methods. CARBAMATES. 3,5-Dimethyl-4-(methylthio)-phenyl *N*-methylcarbamate (Bayer 37344), 3-methyl-4-(*N,N*-dimethylamino)phenyl *N*-methylcarbamate (Bayer 44646), and 2-isopropoxyphenyl *N*-methylcarbamate (Bayer 39007) were analytical reference standards provided by the Chemagro Corp., Kansas City, Mo. 1-Naphthyl *N*-methylcarbamate (Sevin), 3-isopropylphenyl *N*-methylcarbamate (UC 10854), and 3,5-dimethyl-4-(dimethylamino)phenyl *N*-methylcarbamate (Zectran) were supplied as technical products by the Union Carbide Corp. Chemicals Division and the Dow Chemical Co., their respective manufacturers; they were purified by repeated recrystallization from ethanol and from benzene until sharp melting points were attained.



IRRADIATION. Solutions of the carbamates in absolute ethanol or redistilled hexane were subjected to irradiation in the laboratory for 1 to 3 hours. Two types of ultraviolet source were used, both of which produced peak radiation at about 254 mμ: (1) a Multiray short wavelength laboratory lamp (G. W. Gates and Co., Franklin Square, N. Y.)