Chemical Structure and Activity of Pyrethrin and Allethrin Synergists for Control of the Housefly

MORTON BEROZA and W. F. BARTHEL

Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Md.

In a study of the relationship between chemical structure and synergism for pyrethrins and the related allethrin, the best unit of structure observed was the 3,4-methylenedioxyphenyl group. More than 200 methylenedioxyphenyl compounds with side chains containing ether, ester, alcohol, acid, acetal, amine, amide, carbamate, phenol, and aldehyde groups were investigated. Compounds with alcohol, carboxylic acid, or acyclic hydrocarbon radicals as side chains did not exhibit appreciable synergism; whereas, those with ether, ester, acetal, sulfoxide, sulfone, or amide substituents were most productive of synergism. Few compounds that did not contain the 3,4-methylenedioxyphenyl group exhibited synergism and most of these were amides. Their activity did not approach the level of activity obtained with the 3,4-methylenedioxyphenyl compounds.

PYRETHRUM is one of the few natural products that still maintain a major place in an insecticide market, which is dominated by synthetics. However, its unique properties of rapid knockdown of insects, broad range of effectiveness, and low toxicity to warm-blooded animals would earn pyrethrum only a limited market at the current price of over $50 per pound for its active ingredients, were it not for the tremendous boosting power of the synergists usually formulated with it. This boost in insecticidal activity is obtained with no apparent increase in mammalian toxicity over that of pyrethrum alone. Repeated usage of the pyrethrum-synergist combinations on insects does not evoke the high degree of resistance commonly encountered with most synthetic insecticides. Because of the emphasis on safe control of insects affecting man and his food supply, especially the enactment of Public Law 518 (Miller Bill), the use of pyrethrum-synergist combinations may be expected to increase.

Background

Judging from the considerable literature on the subject, the study of synergists for pyrethrum is one of the active fields in modern insecticide chemistry. The search for synergists is complicated by the following: Pyrethrum contains four active ingredients, called pyrethrins, each of which may be synergized differently (*24*). Synthetic pyrethroids, such as allethrin and cyclethrin, are also mixtures of compounds each of which may be synergized to a different degree. Effectiveness of a specific combination will depend upon the insect and even upon the stage of the insect. Also important are method of administration, method of testing, compatibility with other ingredients of a formulation, toxicity to warm-blooded animals, plant injury, and effect on beneficial insects. A recent review by Metcalf (*26*) presents an excellent background on the subject.

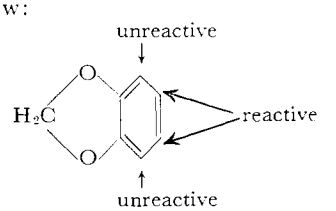
A synergist in combination with pyrethroids should have a low mammalian toxicity, effectiveness against many insects in both knockdown and kill, good solubility characteristics, stability on storage and exposure, inoffensive odor, nonirritating properties, and low cost of production before it can become a commercial reality. Few compounds have met all of these requirements.

The best pyrethrum synergists may be divided into two main categories—amides and the methylenedioxyphenyl derivatives. The first amide synergist, *N*-isobutylundecyleneamide, was introduced by Weed in 1938 (*32*); others have since been introduced, the best known today being MGK-264 (*20*). However, these compounds have not attained the degree of activation obtained with methylenedioxyphenyl derivatives. This discussion will therefore be restricted to methylenedioxyphenyl compounds and be further limited to their effectiveness with pyrethrins or allethrin against the adult housefly, *Musca domestica* (L.). The combinations effective against the housefly may or may not be effective against other insects.

Methylenedioxyphenyl synergists originated in 1942 with the work of Haller and associates (*18*, *19*), when they isolated sesamin from sesame oil and demonstrated its activity as a pyrethrum synergist.

The search for synergists has been more or less empirical. Compounds are prepared from the natural product safrole (or isosafrole), the cheapest source of the methylenedioxyphenyl group, and subjected to test. In this manner the commercial synergists piperonyl butoxide, sulfoxide, piperonyl cyclonene, and *n*-propyl isomer were discovered.

A methylenedioxyphenyl ring is shown below:



The positions ortho to the methylenedioxy are unreactive as compared with the two remaining positions, which are very reactive and may, for instance, be easily halogenated. Synthetic methylenedioxyphenyl synergists are therefore generally substituted in one or both of the equivalent reactive positions.

Current Study

In the past few years, more than 200 methylenedioxyphenyl compounds have been prepared and tested by this laboratory. Data on these compounds, including entomological results, have been reported in eight publications (*1–4*, *9*, *11*, *13*, *16*). These data have been analyzed in an attempt to find relationships between chemical structure and the activity of compounds as pyrethroid synergists. This paper is a report of these findings.

From these data the authors have not been able to derive any simple formula from which they could predict the synergistic effect of a particular compound. Within the framework of a definite chemical structure, such a prediction may be possible, and indeed there are such examples in the literature and in the current work. Nevertheless, many of the data may be tied together

in somewhat broad combinations, so that it is possible on the basis of chemical structure to predict whether a compound has a good chance of being synergistic or, also important, whether it has little chance in this direction. These studies are not complete, but the conclusions, which the authors regard as tentative, should be of value as a basis for future work on housefly synergists.

Test Methods

Tests were usually made at a ratio of 10 parts of synergist to 1 part of pyrethrins or allethrin, and the results are based on a 24-hour kill rather than on knockdown. The solvent or carrier was deodorized kerosine, acetone being added only when necessary to increase the solubility of a compound. The Peet-Grady, turntable, and Orlando (*25*) methods were used. A compound synergistic with either pyrethrins or allethrin was considered synergistic. Tests on the compounds alone—that is, in the absence of pyrethroids—were run to demonstrate synergism, but such tests were sometimes omitted when the joint action of compound plus pyrethroid was weak. From a practical standpoint, the object was to obtain maximum activation of the pyrethroid regardless of whether the synergist itself exhibited toxicity. Usually the synergist candidate itself had little insecticidal activity.

General Findings

In the compounds considered, it is the substituents on the methylenedioxyphenyl group that are being discussed. Table I summarizes most of the general findings.

Compounds containing free carboxyl groups were prepared, but they exhibited no synergism; the authors know of no literature reference to an acid that has appreciable synergistic activity. Furthermore, compounds containing free carboxyl groups are insoluble in the nonpolar solvents usually employed in the dispensing of pyrethrin-synergist combinations. Carboxylic acids are, therefore, of little interest in the present study.

Of 14 compounds containing hydroxyl groups, only three showed some activity, and these effects were weak. Hydroxy compounds also tend to be insoluble in the generally used solvents and are, therefore, considered to be poor candidates for pyrethrum synergists.

With nonpolar groups, if the substituent is an acyclic aliphatic hydrocarbon radical with no functional groups, or if the substituent radical contains only an aldehyde or ketone group, the compound's chances for synergism are poor.

However, if a compound contains an ester group in its side chain, chances for synergism are bright. Of the 100 esters in this study, 57% showed some synergistic activity. Ethers seem to be an even better structural unit contributing toward synergism. Of the 33 ethers prepared, 27, or 82%, showed some activity; also all of the di- or triethers were active.

The best single structural unit to be included in the side chain was the acetal. Of 31 acetals, 30, or 97%, showed some effectiveness as synergists. Prill (*28*) has also reported on 17 cyclic acetals containing the methylenedioxyphenyl radical.

Although the foregoing figures represent a distinction on the basis of being either ineffective or showing some synergism with pyrethrins or allethrin, it is significant that all of the outstanding synergists in this study have fallen into the ester, ether, and acetal categories—the same that gave the highest percentage of effective synergists. Furthermore, the best synergists were polyfunctional—i.e., polyethers, ether-acetals, or ether-esters. These functions all contain oxygen, as do all of the known highly synergistic compounds in their methylenedioxyphenyl substituent.

Carbamates, halides, and nitriles were also prepared, but their activity was either low or nil. The carbamates had the additional disadvantage of being rather insoluble in the solvents generally used. Halides did not seem to contribute to synergism, but rather to detract. Although the few nitriles prepared by the authors had little or no activity, nitriles having activity have been reported (*29*).

Amines were not very productive of synergism, only 1 of 9 showing activity. On the other hand, amides were effective (*14*, *21*, *30*), but few of these compounds have been synthesized in this laboratory, mainly because they are not very soluble in the solvents generally used.

Little work was done with sulfones and sulfoxides; however, the literature shows that such compounds do make good synergists (*12*, *15*, *31*), although the sulfones are rather insoluble in the usual solvents. Thioethers have also been reported to give synergistic compounds (*27*), and several sulfonic acid esters have shown some promise.

A compound with two methylenedioxyphenyl groups in its molecule usually was insoluble in the solvents commonly used to dispense pyrethrum insecticides, and these compounds are of lesser value as practical synergists. Sesamin and sesamolin, which have two such groups, have this defect.

Table I. Effect of Functional Groups in Methylenedioxyphenyl Substituent on Synergism and Solubility Characteristics

Functional Group	Synergism	Solubility
Carboxylic acids	Nil	Poor
Hydroxy compounds	Poor	Poor
Acyclic hydrocarbon	Poor	Good
Acyclic aldehyde or ketone	Poor	Good
Ester	Good, 57%	Good
Ether	Very good, 82%	Very good
Acetal	Excellent, 97%	Very good
Nitriles	Uncertain	Good
Carbamates	Poor	Poor
Halides	Poor	Good
Amines	Poor	Fair
Amides	Good	Fair
Sulfonic acid esters	Fair	Fair
Sulfones	Good	Fair
Sulfoxides	Good	Fair to good

Specific Findings

As some of the compounds were tested at different times, small differences should not be regarded as significant in the following data.

Ester groups offer some interesting comparisons, as shown in Table II. Out of 16 methylenedioxyphenyl esters prepared, having formula I (*4*), only one had any activity and that was weak. For all practical purposes this structure does not give synergists.

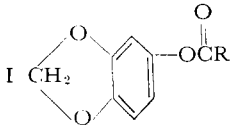
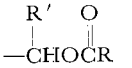
Piperonylic acid esters (formula II) have not been very productive of good synergists; nor have piperonyl alcohol esters (formula III) shown promise. But if the piperonyl alcohol ester is substituted in the alpha position (formula IV), chances for synergism are good. Thus, the last five listings in the table compare the esters of unsubstituted piperonyl alcohols (III) with those of α-allyl substituted piperonyl alcohols (IV). With the first four compounds the boost in synergism caused by the α-allyl substituent is large. Contrary to expectations, the fencholate of the unsubstituted alcohol shows slightly better activity than the one of the substituted alcohol, but this anomaly is believed to be due to experimental error as the compounds were not tested at the same time.

Table III shows the effect of varying the alpha substituent (X) in a series of piperonyl acetates. The first nine com-

pounds are substituted with aliphatic groups. In the next group are phenyl derivatives; the benzyl substituent shows up much better than the phenyl or phenyl propyl group.

In Table IV, the ester of unsubstituted piperonyl alcohol, listed as having hydrogen in the alpha position, showed up unusually well, even better than the esters of most of the alpha-substituted piperonyl alcohols; but this compound was toxic when used without pyrethrins.

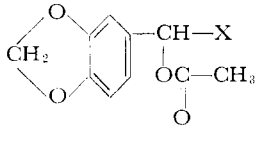
Table II. Synergistic Activity of Esters

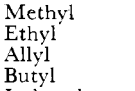
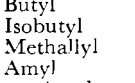
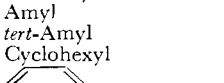
	Ester	Synergism
I		None
II		Slight
III		Slight
IV		Good

Derivative	Piperonyl Alcohol (III), %[a]	α-Allyl Piperonyl Alcohol (IV), %[a]
Hydrocinnamate	+13	+85
Senecioate	+ 5	+36
Phenyl acetate	+ 5	+54
Pivalate	− 1	+75
Fencholate	+15	+ 3

[a] Flies killed in excess of that killed by same amount of allethrin alone.

Table III. Synergistic Activity[a] of Acetates of Alpha-Substituted Piperonyl Alcohols

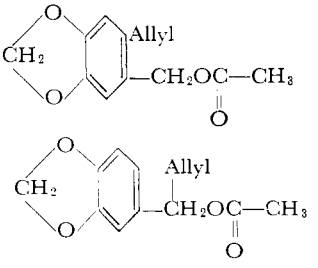


X	With Allethrin, %	With Pyrethrins, %
Methyl	+ 1	− 1
Ethyl	+ 7	+ 9
Allyl	−	+32
Butyl	+36	
Isobutyl	+15	
Methallyl	+23	
Amyl	+16	
tert-Amyl	+20	
Cyclohexyl	+26	
	+ 6	
	+78	
	+14	

[a] Flies killed in excess of that killed by same amount of pyrethrins or allethrin alone.

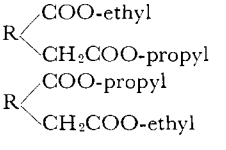
Variation of the alpha substituent with phenyl, benzyl, and phenylethyl groups, shown in the last three compounds of Table IV, shows how small structural variations may affect synergism, and also how alpha substitution on the piperonyl ester may increase synergism.

An interesting situation is shown in the following structures:

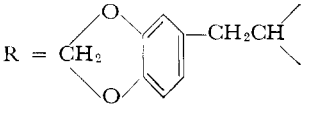


An allyl substitution on the nucleus results in antagonism rather than synergism, whereas an allyl group in the alpha position gives a synergistic compound.

Nine of 11 diesters were synergistic. The formulas of two diesters follow:



where



Here, an ethyl propyl ester boosts the activity of pyrethrins three times as compared with a seven fold increase for the propyl ethyl ester. The authors have no explanation for this effect.

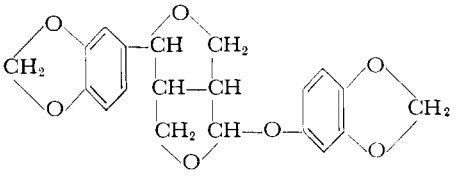
Three piperonyl ethers are listed under the formula in Table V. When X is propyl, the compound is piperonyl butoxide and synergism is very high. It is likewise high for the allyl derivative, but the propenyl derivative is much less effective. Again the striking effects on synergistic activity that may result from small changes in structure are evident.

Hydrogenation may either increase or decrease synergistic action. Synergism is increased if the propenyl derivative under the formula in Table V is converted to the corresponding propyl derivative by hydrogenation. Hedenburg and Wachs (*23*) have shown that hydrogenation of the double bond in piperonyl cyclonene decreases its activity.

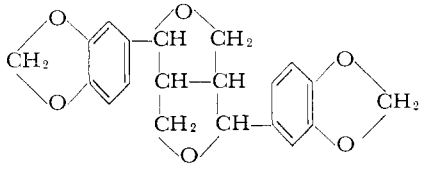
The comparison of two closely related esters illustrates how important the chemical structure adjacent to the methylenedioxyphenyl nucleus may be; the methylenedioxyphenyl ester of benzenesulfonic acid is synergistic, but not the corresponding piperonyl ester.

Natural Products

The authors have also looked to natural products to guide them in their work. Several years ago, Beroza reopened a study of pyrethrum synergists in sesame oil. Sesamin and sesamolin were shown to account for practically all the synergistic activity of the oil (*7*). The formulas of the two compounds follow:



Sesamolin

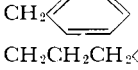
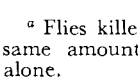


Sesamin

Sesamolin, which had not been known to be synergistic with pyrethrum, proved to be about five times as effective as sesamin against the housefly by the turntable method (*13*). This greater activity of sesamolin made it desirable to determine its chemical structure. This has now been done by this laboratory and by two other independent groups (*5*, *10*, *22*). The racemic forms of sesamin and its stereoisomer asarinin have recently been synthesized by Beroza and Schechter (*8*). Beroza (*6*) has also prepared all six possible optically active stereoisomers of sesamin, two of which were previously unknown. Gersdorff, Piquett, and Beroza (*17*) have found these isomers to be of lesser activity than sesamin.

Sesamolin differs from sesamin in

Table IV. Synergistic Activity of Chrysanthemumates of Alpha-Substituted Piperonyl Alcohols with Allethrin[a]

Alpha Substitution	Synergism, %
Hydrogen	+70 (toxicant)
Ethyl	+16
Allyl	+60
Propyl	+14
Isopropyl	+36
Methallyl	+37
Butyl	+18
Amyl	+ 8
tert-Amyl	+23
	+36
	+85
	+77

[a] See footnote [a] to Table II.

having one of its methylenedioxyphenyl groups attached to the central nucleus through an oxygen atom. In other words, it has a methylenedioxyphenoxy group in place of one of the methylenedioxyphenyl groups of sesamin. Because this difference resulted in such a marked increase in synergism, a series of methylenedioxyphenoxy compounds or sesamol (3,4-methylenedioxyphenol) derivatives were prepared as candidate synergists (*4*). Five classes of these derivatives were synthesized—ethers, esters, arylsulfonates, carbamates, and acetals.

Methylenedioxyphenoxy Derivatives

As shown in Table VI, many ethers of sesamol were prepared, and almost all of them were synergistic to some degree (*16*). Compounds were tested at the same time and under controlled conditions so that the results might be compared. In the 12 compounds making up the first group, R is an alkyl or a hydrocarbon radical. The propyl, butyl, amyl, and allyl ethers exhibited weak synergism; the 2-ethylhexyl and octyl ethers exhibited somewhat greater activity; and cyclopentyl, cyclohexyl, and cyclohexylethyl ethers even greater activity. This effect with cyclic hydrocarbon radicals was noted with a number of other series.

The next group in Table VI contains seven benzyl ethers. The benzyl ether itself shows slightly greater activity than the straight-chain ethers. The addition of a chlorine atom on the benzyl group diminishes activity, and two chlorine atoms cause greater loss. The bromine addition causes an increase in effectiveness with allethrin but not with pyrethrum. The nitro compound is less effective than the benzyl.

The third group of Table VI shows the polyethers, which are all very effective synergists. The chloro compound is again less effective than those without the chlorine.

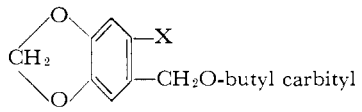
The last compound in Table VI, which is an ether ester, is not synergistic; it illustrates that two functional groups in the substituent do not ensure that a compound will be synergistic.

Various methylenedioxyphenyl esters have been described (*4*). Except for the chrysanthemumate, which demonstrated weak activity, none of these showed synergism. In a negative sense, this effect again demonstrates the importance to synergism of the groups adjacent to the methylenedioxyphenyl nucleus.

Although the carboxylic acid esters were practically devoid of activity, four arylsulfonic acid esters (Table VII) did show activity, especially the benzenesulfonate. Five carbamates (Table VII) showed no appreciable synergism.

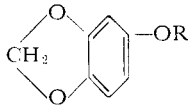
Finally, a series of acetals were prepared (Table VIII), and they proved to be the best of the sesamol derivatives. Included were alkyl, alkoxyalkyl, polyalkoxyalkyl, and heterocyclic acetals. The difference between the ethyl and chloroethyl derivatives shows that the chlorine atom again diminishes synergism. The acetals with ether linkages (alkoxy groups) are better than those with hydrocarbon radicals. The heterocyclic acetals are excellent synergists, but data, not shown in the table, indicate that the ether acetals are better.

Table V. Effect of Double Bond



X	Synergism
—$CH_2CH_2CH_3$ (piperonyl butoxide)	Very high
—$CH_2CH{=}CH_2$	Very high
—$CH{=}CH{-}CH_3$	Fair

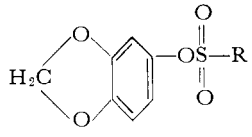
Table VI. Synergistic Activity[a] of 3,4-Methylenedioxyphenyl Ethers



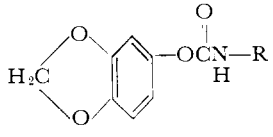
R	With Pyrethrins	With Allethrin
Propyl	3	2
Butyl	3	2
Amyl	3	2
Isoamyl	3	2
2-Ethylhexyl	5	3
2-*n*-Octyl	4	2
Allyl	2	2
2-Chloroallyl	2	2
3-Chloroallyl	2	2
Cyclopentyl	6	3
Cyclohexyl	9+	3.5+
Cyclohexylethyl	9+	3.5+
Benzyl	5	2
o-Chlorobenzyl	3	2
p-Chlorobenzyl	3	2
2,4-Dichlorobenzyl	2	2
3,4-Dichlorobenzyl	2	2
p-Bromobenzyl	2	3
p-Nitrobenzyl	3	2
2-Butoxyethyl	9+	3.5+
2-(2-Ethoxyethoxy)ethyl	9+	3.5+
2-(2-Chloroethoxy)ethyl	7	3
2-(2-Butoxyethoxy)ethyl	9+	3.5
Acetic acid, butyl ester	1	1

[a] Number of times activity of pyrethrins or allethrin was increased.

Table VII. Synergistic Activity of 3,4-Methylenedioxyphenyl Sulfonates and Carbamates with Pyrethrins or Allethrin



R	Synergism
Phenyl	Good
2-Naphthyl	Fair
2-Tolyl	Fair
p-Chlorophenyl	Fair

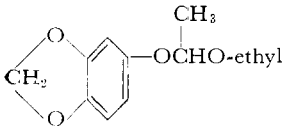
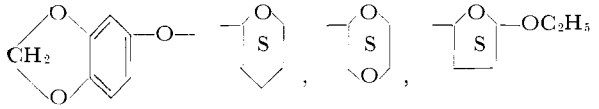


R	Synergism
Phenyl	Very poor
o-Tolyl	Very poor
m-Tolyl	Very poor
p-Tolyl	Very poor
1-Naphthyl	Very poor

Acknowledgment

The authors gratefully acknowledge the valuable contributions of the entomological staff of the Entomology Research Division at Beltsville, Md., and Orlando, Fla.

Table VIII. Synergistic Activity[a] of Acetals

	With Pyrethrins	With Allethrin
	9+	3.5+
-chloroethyl	7	3
-butyl	4	2
-isobutyl	4	2
-2-ethylhexyl	3	3
-2-methoxyethyl	9+	3.5+
-2-butoxyethyl	9+	3.5+
-2-(2-ethoxyethoxy)ethyl	9+	3.5+
-2-(2-butoxyethoxy)ethyl	9+	3.5+
	9+	3.5+

[a] Number of times the activity of pyrethrins or allethrin was increased.

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ACTION OF RUMEN FLUID ON PESTICIDES

In Vitro Destruction of Some Organophosphate Pesticides by Bovine Rumen Fluid

J. W. COOK

Division of Food, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D. C.

Parathion and three other compounds containing *p*-nitrophenol and the thiono isomer of Systox were rapidly destroyed—as measured by an anticholinesterase method of analysis and by paper chromatography—when 100 p.p.m. each of parathion and nine other phosphate pesticides were added to aliquots of bovine rumen fluid. The *p*-nitrophenol moiety of the parathion molecule was reduced to *p*-aminophenol. Paper chromatography of extracts of incubation mixtures revealed that thiol isomers are not destroyed like thiono isomers. Evidence indicates that metabolism of parathion in the rumen can account for its apparent lack of toxicity to cattle as reported in the literature.

USE OF PESTICIDES in control of insects on forage and other dairy feed crops creates the possibility of incurrence of residues of these pesticides by milk. Studies in feeding of chlorinated pesticides such as DDT and lindane, (γ - 1,2,3,4,5,6 - hexachlorocyclohexane) have shown that residues of this type of pesticide are stored to varying degrees in animal fat and excreted in milk (*4, 14–16*).

Considerably less has been reported on the feeding of organophosphate pesticides. Development of the facts is important, not only because of the current trend toward increased use of this type of pesticide on feed crops, but also because of the potential value of organo-