Benzothiadiazoles, A Novel Group of Insecticide Synergists

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Attempts to extend the activity of the methylenedioxybenzene synergists to other similar heterocyclic systems have always shown that slight modifications of the dioxole ring give appreciable or complete loss of synergistic activity. We now report another heterocyclic synergist system, the 1,2,3-benzothiadiazoles. Tests on houseflies, *Musca domestica*, with pyrethrum, one organophosphate, and two carbamate insecticides have revealed appreciable synergistic activity, particularly of the latter three materials both with the parent compound, 1,2,3-benzothiadiazole, and more markedly with chlorinated derivatives—notably 5,6-dichloro-1,2,3-benzothiadiazole. Both the methylenedioxybenzene and benzothiadiazole compounds are inhibitors of a mushroom phenolase system, when tested with catechol as substrate. When two similarly substituted materials were examined, the benzothiadiazole derivative was found to be a better inhibitor than the methylenedioxybenzene.

Synergists of insecticides are of both fundamental and practical significance. Their practical use has recently been reviewed by Hewlett (1968). They have also been used as research tools in the study of the structure/activity relationships of both chlorinated hydrocarbon insecticides (Brooks, 1966) and carbamates (Felton, 1968).

Although several types of chemicals are known to act as synergists of insecticides, the most important group commercially is the methylenedioxybenzene derivatives. Piperonyl butoxide is the best known member of this series, but recently much simpler compounds have been found to be active as carbamate synergists (Felton, 1967; Wilkinson *et al.*, 1966; Wilkinson, 1967). In the bicyclic methylenedioxybenzene system, very little modification can be made to the dioxole ring without appreciable or total loss of activity. The only change made by Wilkinson *et al.* (1966) that was not too disadvantageous was the replacement of one oxygen atom by sulfur. Replacement of one oxygen by a methylene group to give a 2,3-dihydrobenzofuran reduced activity greatly, and similar replacement of the second oxygen to give an indane produced complete inactivity. The same workers confirmed the earlier findings of Moore and Hewlett (1958) that substitution on the methylene group of the dioxole ring removed activity.

The present paper describes a group of bicyclic compounds, the benzothiadiazoles, with similar synergistic properties to those of the methylenedioxybenzenes, but lacking oxygen or a methylene group in the five-membered ring.

EXPERIMENTAL

A preliminary account of the synthesis, physical properties, and analytical data of the benzothiadiazoles has already been published (Kirby, Soloway, and Haddock, 1970) and a full paper has been prepared (P. Kirby, S. B. Soloway, J. H. Davies, and S. B. Webb, to be submitted to *J. Chem. Soc. C.*). Pyrethrins were used as the standard 25% extract, dicrotophos as technical material containing 78% α-isomer, and the two carbamates as technical material of better than 95% purity.

The compounds have been evaluated as synergists of insecticides using a simple topical application technique with 2- to 3-day old female houseflies, *Musca domestica*, as test insect (Felton, 1967). Activity is expressed as synergism factor derived from the following formula: synergism factor = LD_{50} of insecticide alone/LD_{50} of insecticide in synergist/insecticide mixture.

All the synergists discussed proved to be nontoxic to houseflies at twice the highest dosage used in synergist/insecticide mixtures.

RESULTS

The synergistic activity of some simple benzothiadiazoles is compared to that of similar methylenedioxybenzene derivatives in Table I.

The data in Table I reveal several features of the synergistic activity of benzothiadiazoles. First, the parent compound is appreciably active in synergizing dicrotophos and the two carbamates. This contrasts with the extremely low activity of unsubstituted methylenedioxybenzene reported by Moore and Hewlett (1958) and Wilkinson (1967). Substitution with one chlorine increases activity with carbamates slightly and with two chlorines more definitely, so that the dichloro compound is more active than the analogous methylenedioxybenzene derivative. These compounds are not active pyrethrum synergists, but introduction of polyether side chains into the benzothiadiazoles does increase their activity with pyrethrins, just as in the case with methylenedioxybenzenes, although activity at the level of piperonyl butoxide has not yet been achieved with a benzothiadiazole.

The benzothiadiazole nucleus, unlike that of methylenedioxybenzene, is not bilaterally symmetrical, and some data on the activity of isomer pairs are given in Table II.

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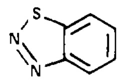
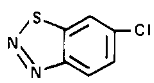
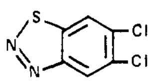
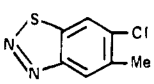
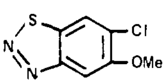
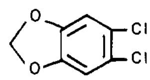
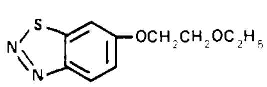
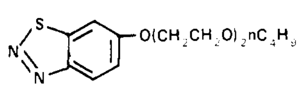
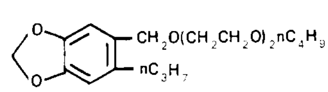
Table I. Synergistic Activity of Simple and Disubstituted Benzothiadiazoles by Topical Application to Houseflies

Synergist	Synergism Factor at a 5:1 Synergist/Insecticide Ratio with: Pyrethrins	Dicrotophos[a]	3,4,5-trimethyl phenyl-*N*-methyl carbamate	Isolan
	2.0	4.4	2.7	6.7
	1.6	5.0	4.3	7.9
	2.3	5.8	6.0	16
	2.8	6.1	8.9	16
	3.3	5.0	7.7	18
	1.0	3.2	2.7	11
	4.1	3.6	2.7	4.2
	4.2	3.0	3.4	4.5
	11	1.2	2.2	4.1

[a] Approved British Standards common name for *cis*-dimethyl 1-dimethylcarbamoyl-prop-1-ene-2-yl phosphate; Bidrin.

From the data in Table II it is apparent that the pairs of isomers do differ between themselves in activity as synergists. With mono-chloro and mono-nitro substitution, the 6-position is preferred over the 5. In disubstituted compounds there are fewer data, but again it seems that chlorine should occupy the 6-position. As the data in Table I show, the nature of the 5-substituent does not seem to affect the activity greatly.

In view of the interesting synergistic activity found in the benzothiadiazoles, representatives of a number of other bicyclic compounds containing a five-membered heterocycle have been examined. The dichloro- derivatives have been chosen where available in view of the activity of this member of the benzothiadiazole and methylenedioxybenzene series; otherwise the mono-chloro- derivative has been tested. The data obtained are given in Table III. None of the four types of heterocycle evaluated showed appreciable synergistic activity.

In their paper on the mode of action of carbamate synergists, Metcalf *et al.* (1966) discuss the inhibition of phenolase detoxifying systems by methylenedioxybenzene synergists, and they show some correlation between synergistic activity and ability to inhibit a purified tyrosinase system. In view of the general similarity shown above between benzothiadiazoles and methylenedioxybenzenes, it was of interest to compare the effects of both on a similar enzyme system. The data given in Table IV were obtained by Popjak and Clifford (1966) with a mushroom (*Psalliota* sp.) phenolase using catechol as substrate and a simple spectrophotometric assay system. The data in Table IV indicate that benzothiadiazoles do inhibit the phenolase system used. Dichlorobenzothiadiazole is both a better inhibitor and a better synergist than the analogous methylenedioxybenzene derivative.

DISCUSSION

Enough work has already been done to establish the benzothiadiazoles as an interesting group of insecticide synergists. They represent the first major deviation from the methylenedioxybenzene nucleus to give other heterocyclic compounds with such activity. Table III illustrates that no synergistic activity is exhibited by several other aromatic heterocyclic systems, including the isomeric 2,1,3-benzothiadiazoles.

Table II. Synergistic Activity of Pairs of Isomers of Benzothiadiazoles by Topical Application to Houseflies

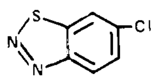
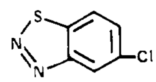
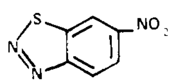
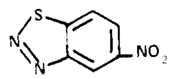
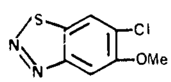
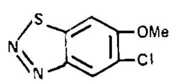
Synergist	Synergism Factor at a 5:1 Synergist/Insecticide Ratio with: Pyrethrins	3,4,5-trimethyl phenyl-N-methyl carbamate	Isolan
	...	4.3	...
	...	3.1	...
	2.0	...	8.0
	1.0	...	6.0
	...	7.7	...
	...	4.4	...

Table III. Synergistic Activity of Certain Bicyclic Compounds by Topical Application to Houseflies

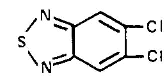
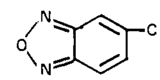
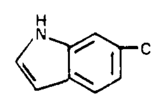
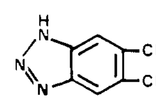
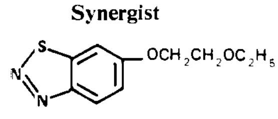
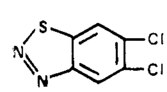
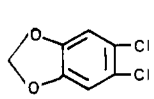
Synergist	Synergism Factor at a 5:1 Synergist/Insecticide Ratio with: Pyrethrins	Dicrotophos	3,4,5-trimethyl phenyl-N-methyl carbamate	Isolan
	1.1	1.8	1.5	2.8
	1.7	1.4	1.0	1.5
	2.3	1.7	1.0	2.1
	1.5	1.0	0.9	<2.3

Table IV. Correlation of Inhibition of Mushroom Phenolase and Synergistic Activity

Synergist	Inhibition of Mushroom Phenolase at: 10^{-3}M	10^{-4}M	Synergism Factor at a 5:1 Synergist/Insecticide Ratio with: Pyrethrins	3,4,5-trimethyl phenyl-N-methyl carbamate
	...	26%	4.1	2.7
	...	69%	2.3	6.0
	53%	...	1.0	2.7

It has been postulated for some time that synergists exert their efforts by interfering with normal oxidative processes within the insect (Sun and Johnson, 1960). This and the thesis that synergists act by inhibiting detoxification enzymes, typified by phenolases, propounded in its most recent form by Metcalf *et al.* (1966), is of course supported by the data reported in Table IV.

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Received for review December 22, 1969. Accepted April 6, 1970.