a good affinity for the site(s) of thiocarbamate action in corn. Its even more consistent activity in soil, in relation to other antidotes, is an indication that it is not readily adsorbed and made unavailable to the plant. Further indication of this is the fact that in soil-free systems, equal concentrations of R-25788 and herbicide (Tables I and III) are often required for total prevention of herbicide injury, whereas in soil, antidote to herbicide ratios of 1:2 (Table III), 1:10, or less (Pallos et al., 1978) can be totally effective.

Possibly the most interesting aspect of the thiocarbamate dichloroacetamide antagonism in corn is its unique occurrence in corn but not other plant species. Lay and Casida (1978) do not propose that EPTC toxicity via EPTC-sulfoxide production is specific to corn. They explain the selectivity of this antagonism by suggesting that the antidote action of R-25788 via elevation of glutathione levels is unique to corn. It is tempting for the present authors to suggest that competitive inhibition between similar antidotes and thiocarbamates in corn is a possible mechanism; however, in the absence of structure–activity studies with isolated systems, such a suggestion is premature. If competitive inhibition were operative, the sites of action involved in corn must be uniquely accessible to both herbicide and antidote to explain the selectivity of the antagonistic relationship. Also the high activity of different antidotes for each different thiocarbamate herbicide implies that the different thiocarbamate herbicides have slightly different sites of action in corn. Thus while the structure–activity theory for antidotes to EPTC has simplified the search for effective antidotes to vernolate, pebulate, molinate, butylate, cycloate, and possibly other thiocarbamates, it has not clarified our understanding of thiocarbamate action in corn or other plants.

ACKNOWLEDGMENT

We thank E. Pelly for technical assistance and Abbott Laboratories for giving a sample of *N*-ethylcyclohexylamine. G. G. Halliday of Chipman Chemicals Ltd. is also thanked for assistance in preparing various antidote formulations.

Supplementary Material Available: Spectral data used to characterize the antidotes (2 pages). Ordering information is given on any current masthead page.

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Received for review July 13, 1978. Accepted December 7, 1978. This work was supported by the National Research Council of Canada.

Synthesis and Synergistic Activity of Dillapiole Based Pyrethrum Synergists

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Twelve compounds were synthesized by chemical transformation of dillapiole (2,3-dimethoxy-4,5-methylenedioxyallylbenzene), one of the chief constituents of *Anethum sowa* Roxb. (Indian dill) seed oil. All of these compounds exhibit synergism better than piperonyl butoxide toward pyrethrum against flour beetles (*Tribolium castaneum* Herbst.). Isolation of dillapiole, its conversion to the above compounds, and their infrared and nuclear magnetic resonance spectra, R_M values, and factors of synergism are reported in this paper.

Synergists are chemicals capable of enhancing the toxicity of an insecticide. Most of the commercial synergists known for pyrethrum, such as piperonyl butoxide (I; Wachs, 1947, 1951) (see Scheme I); sulfoxide (II; Synerholm et al., 1947); and *n*-propyl isome (III; Synerholm and Hartzell, 1945) are manufactured from safrole (IV), which is available in limited supply. Dillapiole (V), the chief undesirable constituent (up to 35%) of oil of *Anethum Sowa* Roxb. (Indian dill), has already been reported earlier as a synergist for pyrethrum (Gulati and Parmar, 1969a). It has now been tried as an alternative raw material for more potent pyrethrum synergists.

Several new derivatives of V, obtained mostly by modification of the allyl side chain, have shown good synergism for pyrethrum against flour beetles (*Tribolium castaneum* Herbst.).

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MATERIALS AND METHODS

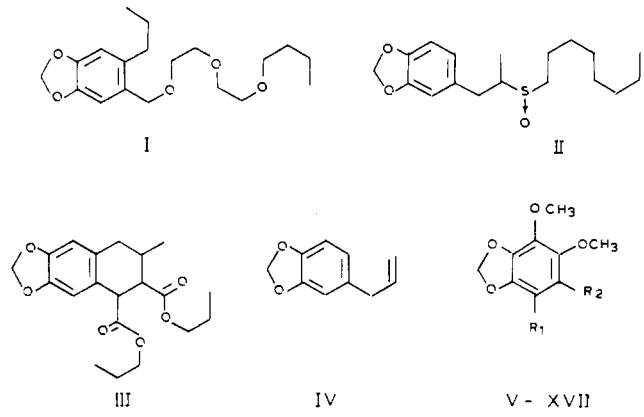
All boiling points are uncorrected. All compounds were finally purified by column chromatography over activated silica gel. Thin-layer chromatography was carried out on silica gel plates impregnated with silver nitrate, and the spots were visualized after warming with H_2SO_4 (20%). Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrometer. NMR spectra were recorded nor-

0021-8561/79/1427-0547$01.00/0

Table I. Starting Materials and Critical Reaction Conditions for the Synthesis of Ethers X-XVII from Dillapiole/Isodillapiole by "Solvomercuration-Demercuration"

product structure no.	starting compd, g	addition time, min	mercuric acetate, g	alcohol/THF, mL	duration of stirring, h	KOH (g)/ water (mL)	$NaBH_4$, g	yield of product g	yield of product %
X	isodillapiole, 3.31	30	5.19	methanol, 40/40	4	5.5/20	1.45	1.5	40
XI	dillapiole, 2.68	30	4.65	methanol, 30/30	2	3.67/18	0.95	2.4	80
XII	dillapiole, 4.17	35	7.00	ethanol, 50/50	3	6.50/25	1.98	3.4	70
XIII	dillapiole, 3.30	30	5.40	1-Propanol, 40/40	4	5.60/20	1.47	2.9	69
XIV	dillapiole, 4.62	45	7.38	1-Butanol, 50/50	4	7.40/30	2.00	3.5	57
XV	dillapiole, 8.04	90	13.95	*n*-amyl alcohol, 150/150	5	11.2/50	3.1	5.6	50
XVI	dillapiole, 8.10	90	14.1	*n*-hexyl alcohol, 150/150	5	11.5/50	3.2	5.8	50
XVII	dillapiole, 4.42	45	7.20	*n*-butyl carbitol, 20/45	4.5	6.22/25	2.10	1.8	24

Scheme I



mally in CCl_4 solution, unless otherwise stated, on a Varian A-60 spectrometer using Me_4Si as internal reference, and chemical shifts are given in δ values.

Extraction of Dill Oil and Isolation of Dillapiole. Crushed dill seeds (3.5 kg) were extracted with hot petroleum ether (60–80 °C, 5 L), and a greenish-yellow oil (100 g) containing some fatty matter was obtained. This oil was subjected to fractional distillation and the fraction boiling at 115–117 °C (1.5 mm) afforded dillapiole (V) as a light-yellow oil (35 g): ν_{max} (CCl_4) 1615 (aromatic); 945 (OCH_2O); 1000, 985, and 840 cm^{-1} (C=CH_2); NMR 3.15 (d, 2 H, J = 6.5 Hz, $ArCH_2$), 3.59 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.87 (d, 2 H, J = 10 Hz, CH=CH_2), 5.69 (m, 1 H, CH=CH_2), 5.71 (s, 2 H, OCH_2O), 6.05 (s, 1 H, aromatic proton). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3. Found: C, 65.0; H, 6.4.

Synthesis of Test Chemicals. *Isodillapiole (VI).* Dillapiole (22.2 g) in *tert*-butyl alcohol (150 mL) was heated under reflux with potassium *tert*-butoxide (from potassium metal, 4.3 g) for 2 h. The solvent was then removed under vacuum and the residue treated with water. The product, isolated by ether extraction, on recrystallization from petroleum ether yielded colorless needles (22.0 g): mp 44 °C; ν_{max} (CCl_4) 1615 (aromatic), 950 (OCH_2O), 840 cm^{-1} (C=CH); NMR ($CDCl_3$) 1.85 (d, 3 H, J = 6 Hz, =CHCH_3), 3.72 (s, 3 H, OCH_3, 3.98 (s, 3 H, OCH_3), 5.83 (s, 2 H, OCH_2O), 6.15 (m, 1 H, CH=C$H$$CH_3$), 6.61 (s, 1 H, aromatic proton), 6.68 (d, 1 H, J = 15 Hz, ArCH=CH). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3. Found: C, 64.4; H, 6.3.

Dihydrodillapiole (VII) was obtained by catalytic hydrogenation (Pd–C 10%, 250 mg) of dillapiole (10 g) in ethanol (250 mL) at room temperature and pressure and was purified by vacuum distillation. The product was a colorless liquid (8.5 g): bp 95–97 °C (3 mm); NMR 0.94 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.52 (m, 2 H, CH_2CH_3), 2.5 (t, 2 H, J = 6 Hz, $ArCH_2$), 3.73 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.81 (s, 2 H, OCH_2O), 6.33 (s, 1 H, aromatic proton). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.1. Found: C, 64.3; H, 6.6.

2,3,6-Trimethoxy-4,5-methylenedioxypropylbenzene (IX). Bromination of dihydrodillapiole (2.24 g) in dichloromethane with bromine in dichloromethane (5%, 11.5 mL) at room temperature gave 2-bromo-3,4-methylenedioxy-5,6-dimethoxypropylbenzene (VIII) as a colorless liquid (2.9 g): bp 116.7 °C (0.1 mm). Absence of aromatic protons in its NMR spectrum agreed with the structure. Anal. Calcd for $C_{12}H_{15}BrO_4$: C, 47.5; H, 5.3; Br, 26.4. Found: C, 47.1; H, 4.8; Br, 26.3.

In the next step, a solution of the above bromo compound (VIII, 3 g) in DMF (8 mL) was added slowly to a well-stirred suspension of cuprous iodide (0.6 g) in methanol (20 mL) containing sodium methoxide (from Na, 2 g), and the mixture was heated under reflux for 12 h. The mixture was filtered and, after removal of most of the methanol, was diluted with water and extracted with ether (3 × 100 mL). The washed and dried ether extract on removal of solvent and distillation furnished IX (1.8 g) as a colorless liquid: bp 107–108 °C (0.5 mm); NMR 1.02 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.55 (m, 2 H, CH_2CH_3), 2.5 (t, 2 H, J = 8.5 Hz, $ArCH_2$), 4.05 (s, 3 H, OCH_3), 4.2 (s, 6 H, 2-OCH_3), 6.35 (s, 2 H, OCH_2O). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.0; H, 7.1. Found: C, 61.3; H, 7.3.

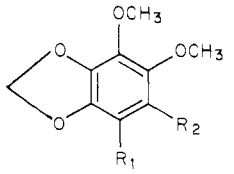
Ethers (X–XVII). The ether derivatives X–XVII reported in Table I along with the experimental details were prepared from isodillapiole and dillapiole by the procedure of Brown and Rei (1969). The general method of preparation is outlined below.

A vigorously stirred suspension of mercuric acetate in the appropriate alcohol was treated with a solution of isodillapiole/dillapiole in THF at 0 °C. After stirring for 2–5 h at room temperature, the mercurial complex was reduced by the addition of an alkaline solution of sodium borohydride. The liberated mercury was filtered and the filtrate extracted with chloroform. The washed and dried extract, on removal of solvent, furnished the ether corresponding to the alcohol used. Further purification was done by column chromatography over silica gel. The NMR spectral and elemental analysis data of these compounds fully agreed with their structures (see Supplementary Material Available paragraph at the end of the article).

Formulation and Bioassay. Purified pyrethrum extract (20%) was used for making a stock solution (2%) in benzene for biological screening. Technical grade piperonyl butoxide was used as standard pyrethrum synergist for comparison.

The synergistic activity of all the test compounds was assessed as pyrethrum based emulsions at insecticide/synergist ratio of 1:5 (w/w). Benzene as solvent (10%) and Tween-80 as emulsifier (0.2%) were maintained throughout in the spray emulsions. The tests were conducted against 2–3-week-old flour beetles (*Tribolium castaneum* Herbst.) reared on fresh wheat flour (free from

Table II. R_M Values, LC_{50} Values, and Factors of Synergism for Various Test Chemicals



compd	R_1	R_2	R_M values	LC_{50} for pyrethrum alone	LC_{50} for pyrethrum plus chemical	factor of synergism
I		piperonyl butoxide	−0.27	0.090	0.045	2.0
V	H	$CH_2CH{=}CH_2$	−0.55	0.090	0.046	2.0
VI	H	$CH{=}CHCH_3$	−0.55	0.085	0.030	2.8
VII	H	$CH_2CH_2CH_3$	−0.35	0.090	0.042	2.2
VIII	Br	$CH_2CH_2CH_3$		0.091	0.052	1.7
IX	OCH_3	$CH_2CH_2CH_3$	−0.45	0.080	0.017	4.7
X	H	$CHCH_2CH_3$ | OCH_3	−0.63	0.081	0.026	2.9
XI	H	CH_2CHCH_3 | OCH_3	−0.66	0.080	0.018	4.4
XII	H	CH_2CHCH_3 | OCH_2CH_3	−0.50	0.085	0.018	4.7
XIII	H	CH_2CHCH_3 | $OCH_2CH_2CH_3$	−0.37	0.081	0.016	5.0
XIV	H	CH_2CHCH_3 | $OCH_2CH_2CH_2CH_3$	−0.23	0.080	0.017	4.7
XV	H	CH_2CHCH_3 | $OCH_2CH_2CH_2CH_2CH_3$	−0.10	0.076	0.019	4.0
XVI	H	CH_2CHCH_3 | $OCH_2CH_2CH_2CH_2CH_2CH_3$	+0.30	0.077	0.024	3.2
XVII	H	CH_2CHCH_3 | $OCH_2CH_2OCH_2CH_2OC_4H_9$	−0.75	0.090	0.045	2.0

pesticide), in three replications of 15 insects each, as reported earlier by Mukerjee et al. (1973) using direct spray (Potter, 1941). The data after correction (Abbot, 1925) were subjected to probit analysis (Finney, 1971), and factors of synergism were calculated as ratios of LC_{50} of pyrethrum alone to LC_{50} of pyrethrum in combination with various test synergists (Chadwick, 1963).

Lipophilicity of the Dillapiole Derivatives. Lipophilicity of the test compounds was determined by finding out the R_f values by reverse-phase thin-layer chromatography and calculating the R_M values by using the equation $R_M = \log [(1/R_f) - 1]$ (Boyce and Milborrow, 1965). Silica gel plates after activation for 2 h at 110 °C were coated with paraffin (10% liquid paraffin in hexane, 24 h). The coated plates were spotted with the test chemicals and developed in an acetone/water mixture (75:25). The positions of ethers were visualized by heating after spraying with dilute sulfuric acid, and R_f values were measured. The mean of three R_f values of each compound was used for calculation of its R_M values.

RESULTS AND DISCUSSION

Isodillapiole (VI) and dihydrodillapiole (VII) were prepared in this work by improved modifications of earlier methods (Talwar et al. 1966; Gulati and Parmar, 1969b). The nuclear methoxy derivative of dihydrodillapiole (IX) was prepared from the corresponding bromo derivative VIII by CuI induced diplacement reaction employed earlier by Mckillop and co-workers (1974) for the conversion of 2,4,6-trimethoxybromobenzene to 1,2,3,5-tetramethoxybenzene. This reaction failed to give higher alkoxyl homologues of IX. Other new compounds were prepared by the mercuration–demercuration reaction (Brown and Rei, 1969) on the allyl side chain of dillapiole. This reaction was much slower with isodillapiole and methanol and failed altogether with higher alcohols. Even in the case of dillapiole, the reaction was very sluggish with alcohols of longer chain lengths such as butyl carbitol.

None of the test chemicals showed any significant toxicity up to 1% concentration against the test insect (*T. castaneum*), but all of them showed different degrees of synergism toward pyrethrum against the same test insect. The factors of synergism along with LC_{50} values for pyrethrum in combination with the test chemicals and their R_M values are given in Table II. It will be seen from the table that the synergistic factor of the test chemicals ranges from 1.7 to a high value of 5. It is known in general that a good methylenedioxyphenyl synergist for pyrethrum like piperonyl butoxide (I) should have two or three ether linkages in the side chain attached to the methylenedioxyphenyl group. A perusal of the structures having high synergistic factors in Table II shows that when some ether linkages are present in the benzene ring only one additional such linkage in the side chain enhances greatly the synergistic activity of the molecule. Thus compounds (X–XVI) having only one ether linkage in the side chain but two or more in benzene ring are all very potent synergists.

The results further indicate that a long polyalkoxy side chain as in piperonyl butoxide (I) or a long alkyl chain as in sulfoxide (II) is not a must for a good pyrethrum synergist. Compound XVII having the same alkoxy side chain as piperonyl butoxide (I) is a poorer synergist. Amongst the synergistic compounds derived from dillapiole, the optimum structural requirement seems to be a side chain of four to five carbon atoms with one ether linkage as in XII and XIII.

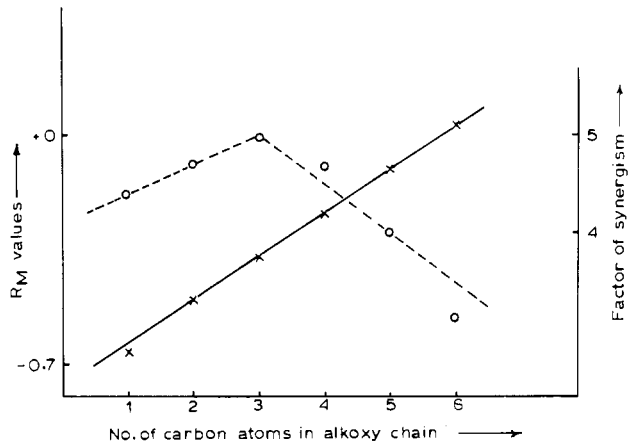


Figure 1. Relationship among the length of alkoxy substituent of dillapiole side chain, R_M values, and factors of synergism. R_M value (x–x); factor of synergism (O--O).

The plot of R_M values against the number of carbon atoms of the alkoxyl substituent in the dillapiole side chain in Figure 1 reveals a linear relationship, implying that lipophilicity of these molecules increases with increasing chain length, but Table II reveals that lipophilicity alone is not the criterion for enhanced synergistic activity. Thus compound IX whose R_M value is less than that of dihydrodillapiole is a better synergist. The same is also true in the case of compound XI, having a methoxyl group more than that of dillapiole. In a homologous series as in compounds XI–XVI, the synergistic activity increased with increasing lipohilicity up to a maximum of three carbon atoms in the side chain. Similar results have been observed recently in other homologous series (Vaidyanathaswamy et al., 1977). Further increase in chain length actually leads to a decrease in synergism.

Supplementary Material Available: A listing of data from NMR spectrometry and elemental analyses of ethers X–XVII (2 pages). Ordering information is given on any current masthead page.

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Received for review June 1, 1978. Accepted November 22, 1978. Contribution No. 143.

Metabolism of [^{14}C]Fosamine Ammonium in the Rat

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The active ingredient in DuPont Krenite Brush Control Agent is ammonium ethyl carbamoylphosphonate (fosamine ammonium salt, formerly known as DPX-1108). When carbonyl-labeled [^{14}C]fosamine ammonium was administered as a single oral dose to preconditioned rats by intragastric intubation, the radioactivity was rapidly eliminated in the feces (87%) and urine (13%). Trace amounts of radioactivity were found in the gastrointestinal tract, hide, and exhaled air (0.1–0.2%). Less than 0.05% radioactivity was found in the body tissues after 72 h. Total recovery of applied radioactivity was nearly 100%. The eliminated carbon-14 in both urine and feces was 87% intact fosamine and about 13% carbamoylphosphonic acid. The synthesis of these compounds is described.

Fosamine ammonium salt (formerly known as DPX-1108) is the active ingredient in DuPont Krenite Brush Control Agent. This water soluble, nonflammable, nonvolatile compound is diluted with water and applied as a foliar spray for control and/or growth suppression of many woody species. When applied in late summer or early fall, fosamine ammonium acts as a bud break inhibitor and has minimum effect on existing foliage except for certain pines which may show a response soon after application (Weed et al., 1974). Susceptible plants fail to refoliate in the spring and subsequently die or their growth is severely retarded.

Fosamine ammonium is relatively nontoxic to mammals, e.g., LD_{50} = 24000 mg/kg in male rats (Weed et al., 1974), and no cumulative toxicity or adverse effects in offspring has been noted.

This paper describes the synthesis of ammonium ethyl [^{14}C]carbamoylphosphonate ([^{14}C]fosamine ammonium) and its metabolism in the rat.

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0021-8561/79/1427-0550$01.00/0