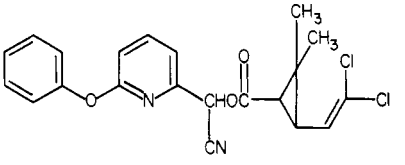
Dowco 417: A Potent Synthetic Pyrethroid Insecticide

Dowco 417, a synthetic pyrethroid insecticide, is a 40:60 mixture of cis and trans isomers of cyano(6-phenoxy-2-pyridinyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. It is a material with low mammalian toxicity and a high level of activity against major foliar insect pests. Its synthesis, biological activity, and physical and toxicological properties are described.

During the past decade great excitement has been generated by synthetic pyrethroids, the photostable analogues of natural pyrethrins (Elliott, 1977). These compounds are among the most effective insecticides known, being characterized by their very rapid knockdown properties and low mammalian toxicity. Because of their high level of activity, they can be applied at extremely low rates. Dowco 417, a new highly potent broad spectrum foliar



Dowco 417

insecticide, belongs to this class of insect control agents. It is a 40:60 mixture of cis and trans isomers of cyano(6-phenoxy-2-pyridinyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate. This preliminary communication describes the preparation, biological activity, and environmental and toxicological properties of this material.

Because of the presence of three asymmetric carbon atoms, Dowco 417 exists as a mixture of eight optical isomers whose insecticidal activities depend markedly on the absolute configuration at the chiral centers. The biological activities and the preparation of these isomers will be reported in a future publication.

MATERIALS AND METHODS

Preparation of 6-Phenoxypicolinaldehyde Cyanohydrin (1). A mixture of 122 g (0.61 mol) of 6-phenoxypicolinaldehyde and 76 g (0.73 mol) of sodium bisulfite was stirred in 750 mL of water until these materials went into solution. The resulting solution was extracted with CH_2Cl_2 to remove water-insoluble material. To this aqueous solution was added 36 g (0.73 mol) of sodium cyanide. After being stirred for 2 h, the reaction solution was extracted with methylene chloride. The extract was washed with aqueous sodium bisulfite and with water. It was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue, a light yellow solid, was stirred in hexane, filtered, and dried to give 112.1 g of a white crystalline solid melting at 84.5 °C: NMR ($CDCl_3$) δ 4.87 (s, 1 H), 5.45 (s, 1 H), 7.17 (m, 8 H). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.78; H, 4.56; N, 12.19.

Preparation of Cyano(6-phenoxy-2-pyridinyl)-methyl 3-(2,2-Dichloroethenyl-2,2-dimethylcyclopropanecarboxylate (Dowco 417). A solution of 27.6 g (0.122 mol) of 6-phenoxypicolinaldehyde cyanohydrin (1) and 28 g (0.123 mol) of 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarbonylic chloride (2; 40:60 mixture of cis and trans isomers) in 300 mL of anhydrous ethyl ether was cooled in an ice bath to 0 °C. To this solution was slowly added 25 mL of triethylamine. The resulting mixture was stirred for 2 h while it gradually warmed to room temperature and was then diluted with water. The organic layer was separated and sequentially washed with water, diluted hydrochloric acid, diluted sodium hydroxide, aqueous sodium bisulfite, and water and then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting concentrate was further heated at 125 °C at 0.05 mmHg for 2 h to remove any low boiling impurities, providing the desired product, a homogeneous yellow oil, in 93% yield: NMR ($CDCl_3$) δ 1.2 (q, 6 H), 2 (m, 2 H), 5.6 (d, J = 8 Hz, 0.6 H, the vinyl proton of the trans isomer), 6.17 (d, J = 8 Hz, 0.4 H, the vinyl proton of the cis isomer), 6.33 (s, 1 H), 7.33 (m, 8 H); n^{25}_D 1.5630. Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_3$: C, 60.44; H, 4.34; N, 6.71. Found: C, 60.43; H, 4.34; N, 6.49.

Biological Methods. For biological testing Dowco 417 was formulated as a 19% emulsifiable concentrate.

The standards used for comparison were cypermethrin [Ripcord 20% E.C. (Shell Chemical Co., Holland)], permethrin [Ambush 2 E.C. (ICI America, Goldsboro, NC) and Pounce 3.2 E.C. (FMC Corp., Middleport, NY)], fenvalerate [Belmark 30.7% E.C. (Shell Chemical Co., Mexico)], and decamethrin [Decis 2.5% E.C. (Procida Pyrethroids Department, Puteaux, France)].

All tests were run on laboratory reared strains. The tobacco budworms [*Heliothis Virescens* (F.)] were obtained from the U.S. Department of Agriculture at Brownsville, TX, in 1976. The beet armyworms [*Spodoptera exigua* (Hübner)] were collected in the field near Fresno, CA, in 1978. The codling moths [*Laspyresia pomonella* (L.)] were collected from Fairfield and Davis, CA, in 1974. The aster leafhoppers [*Macrosteles fascifrons* (Ståal)] and green peach aphids [*Myzus persicae* (Sulzer)] were obtained from strains maintained at the University of California, Berkeley. The greenhouse whitefly [*Trialeurodes vaporariorum* (Westwood)] was collected at Walnut Creek, CA, in 1978, while the susceptible NAIDM (National Association of Insecticides and Disinfectant Manufacturers) strain of house flies [*Musca domestica* (L.)] was obtained from the University of California, Riverside.

For the tobacco budworm evaluation, tobacco leaves were dipped in chemical solutions of various strengths and were placed in open petri dishes. When dry, five late second instar larvae were placed on each leaf. Mortality counts were made after 48 h under constant conditions (room temperature maintained at 25–27 °C and relative humidity = 30%).

The beet armyworm test was conducted in a similar manner with the exception that cotton foliage was treated instead of tobacco. The test method used for codling moth measures the early instar contact larvicidal activity of the compounds tested. Newton Pippin apples were treated in duplicate by pouring the formulation over the apple. Egg sheets consisting of wax paper strips containing 50–100 codling moth eggs were then pinned to each apple. The treated apples were incubated in the greenhouse for approximately 12 days, after which counts of the larval

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penetrations in the treated fruit were compared to the untreated check.

The aster leafhoppers were placed on dipped rice foliage after drying. The green peach aphids were preinfested 2 days before treatment, with the chemical solution being sprayed to runoff. Mortality was determined at 48 h in both tests.

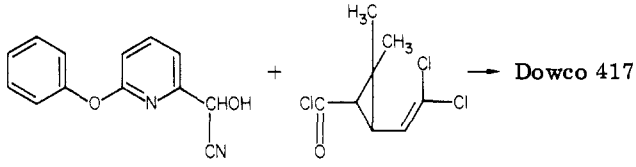
In the greenhouse whitefly test, cotton plants were preinfested with 50–100 whitefly eggs and young larvae. The plants were treated by dipping the infested leaves in the chemical solution, and percent control was recorded at 2 weeks by comparing the adult emergence to the untreated check.

Housefly mortality was evaluated by using a direct contact spray. Cages made from paper cylindrical cartons $3^5/_8$ in. in diameter by $3^1/_4$ in. high, fitted on top and bottom with wire screens, were infested with 10 flies. The chemical solution (1 mL) was sprayed down through the screen lid by using a syringe equipped with a Tee-jet nozzle. Evaluation was made 24 h following treatment and was expressed as a percent control.

The mortality data were adjusted for control mortality by using Abbot's (1925) formula and subjected to probit analysis by a POLO program of Russell et al. (1977).

RESULTS AND DISCUSSION

Dowco 417 is prepared by the esterification of 6-phenoxypicolinaldehyde cyanohydrin (1) with 3-(2,2-dichloroethenyl)-2,2-dimethylcycloprpanecarbonylic chloride (2) using triethylamine as the HCl acceptor:



(1) (2)

Preparation of 6-phenoxypicolinaldehdye is described elsewhere (Malhotra and Ricks, 1979). Synthesis of the acid chloride (2) was carried out according to the procedure of Farkas et al. (1958).

Biological Activity. Table I summarizes the biological activity of Dowco 417 and the standard pyrethroids on selected insects of agricultural importance. The activity of Dowco 417 is quite similar to cypermethrin, with the exception of its greater effect on sucking insect species such as the aster leafhopper and the green peach aphid. Dowco 417 is superior to both permethrin products (Ambush and Pounce) on all insect species tested. Although equivalent to fenvalerate on tobacco budworm, Dowco 417 shows much greater activity toward the other species tested. Dowco 417 also showed considerably better activity on the susceptible NAIDM strain of housefly.

When Dowco 417 was compared to decamethrin, the optically resolved pyrethroid, it was found to be consistently less active on lepidopterous species. However, fairly equivalent activity was noted on housefly, and Dowco 417 was superior on aster leafhopper and green peach aphid.

Environmental Properties. Physical properties of Dowco 417 are described in Table II. Hydrolytic stability studies at 50 °C and pH 7 gave a half-life of 64 h. When aqueous solution at pH 7 was exposed to sunlight at 25 °C, the half-life for the combined photolysis–hydrolysis reaction was 73 h.

Toxicity. Results from preliminary mammalian and fish toxicity studies are reported in Table III. A 90-day dietary study in rats given 50 mg kg^{-1} day^{-1} did not show any adverse effects on tissues examined histopathologically.

Table I. Contact Toxicity of Pyrethroids to Various Insect Species (in ppm)

product	active ingredient	tobacco budworm		beet armyworm		codling moth		aster leafhopper		green peach aphid		greenhouse whitefly		NAIDM strain housefly	
		LC_{50}	LC_{90}	LC_{50}	LC_{90}	LC_{50}	LC_{90}	LC_{50}	LC_{90}	LC_{50}	LC_{90}	LC_{90}	LC_{90}	LC_{50}	LC_{90}
Dowco 417	Dowco 417	10.8	32.2	3.5	12.2	2.0	2.8	1.7	5.0	1.0	2.3	39.2	60.8	2.7	6.9
Ripcord	cypermethrin	11.5	30.4	3.3	12.5	2.4	14.3	7.1	20.7			37.4	80.4	2.2	13.5
Ambush	permethrin	38.0	128.0	42.5	118.0	8.3	25.6	5.4	14.7						
Pounce	permethrin	33.2	96.6	45.7	150.0										
Belmark	fenvalerate	16.6	32.0	31.5	110.2	6.8	11.4	8.0	53.0	6.4	26.6	70.7	135.8	4.7	26.8
Decis	decamethrin	1.2	6.1	0.9	4.6	0.7	2.5	2.8	6.2	2.4	7.9	5.4	17.5	1.7	7.5

Table II. Physical Properties of Dowco 417

physical state	light yellow oil
vapor pressure	1.54×10^{-6} mmHg at 26 °C[a]
solubility (water)	0.2 ppm at 26 °C[b]
1-octanol-water distribution coefficient	640 000[c]
average soil adsorption coefficient (K_{oc})	46 000[d]

[a] Determined by the effusion method (Hamaker and Kerlinger, 1969). [b] Determined by the nephelometric method (Davis and Parke, 1942). [c] Determined by the method of Fujita et al. (1964). [d] Based on soil-water slurry measurements in 20 soils with an organic carbon content of 0.0976–1.3%; determined by the method of Grover et al. (1979).

Table III. Toxic Properties of Dowco 417

acute oral LD_{50} (rat)	460 mg/kg[a]
acute oral LD_{50} (mouse)	100–200 mg/kg[a]
dermal LD_{50} (rabbit)	>625 mg/kg[a]
skin and eye (rabbit)	nonirritating[a]
TLM_{48} (goldfish)	4.8 ppb[b]

[a] Keeler and Lockwood (1978). [b] Kurihara and Larson (1980).

When the method of Ames (1971) was used, Dowco 417 was found to be nonmutagenic (Brusick, 1977). Some individuals with known "sensitive skin" may experience a skin reaction if exposed to Dowco 417. The phenomenon is common to synthetic pyrethroids (World Health Organization, 1979). Its high fish toxicity is not much different from that of commercial pyrethroids (Kurihara and Larson, 1980), and in light of extremely low effective dosage for crop pest control and its immobility in soil, Dowco 417 should present a minimal hazard to fish.

Conclusion. Dowco 417 belongs to a new and extremely important generation of insecticides which possesses low mammalian toxicity and offers a large number of other significant advantages over conventional insecticides. It is highly active against important foliar pests, especially sucking insects, and because of its lower application rates, plants do not show any foliar injury, thus resulting in higher crop yields. In view of its low use rates and relatively rapid breakdown in the environment, this material would involve little risk of environmental contamination.

ACKNOWLEDGMENT

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Specific Toxicity of Paralytic Shellfish Poisons

The specific toxicity of six paralytic shellfish toxins, neosaxitoxin and gonyautoxins-I, -II, -III, -IV, and -V, in mice was established in an equivocal manner, and their relative toxicity to saxitoxin was calculated. The method used is based on determinations of the nitrogen content of a toxin solution with a known number of mouse units and is not affected by isomerization, degradation, or the hygroscopic nature of the toxin. No clear structure–activity relationship was observed.

Paralytic shellfish poisoning, PSP (Figure 1), has been a serious problem for a long time in many parts of the world. The sporadic and unpredictable outbreaks usually cause serious health hazards and great losses to the seafood industry. The toxins accumulate in shellfish as a result of ingestion of toxic dinoflagellate. Saxitoxin (STX), first isolated from Alaska butter clams, *Saxidomus giganteus*, and later from California mussels, *Mytilus californianus* (Schantz et al., 1957), was thought to be the only toxic principle produced by the causative organism *Gonyaulax catenella* (Schantz et al., 1966). Recent studies, however, have shown that the toxicity is caused by a group of closely related compounds and that saxitoxin did not even constitute the major component in many cases (Shimizu et al., 1978a). Toxins of *Gonyaulax tamarensis*, the causative organism of PSP in the North Atlantic region, was also studied in our laboratory and was found to contain more than seven toxins, including saxitoxin (Shimizu et al., 1975; Oshima et al., 1977; Hsu et al., 1979).

The toxicity of saxitoxin was assigned to be 5500 mouse units (mu)/mg of the dihydrochloride or 1 mouse unit is equivalent to 0.18 μg of saxitoxin dihydrochloride (Schantz et al., 1958). Regarding other toxins, there is no description of their specific toxicity except for two toxins isolated from toxic scallops (Boyer et al., 1978b), but there is no complete list of specific toxicity of all the toxins determined under

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