Journal of Nematology 21(2):158–163. 1989.

Structure–Activity Studies on Nematicidal Activity of Dialkyl Carbamates and Thiocarbamates[1]

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Abstract: In laboratory tests, 129 dialkyl carbamates of types ROC(O)NHR', RSC(O)NHR', and ROC(S)NHR' were tested in a screening bioassay against *Panagrellus redivivus.* The 10 most active were lethal at concentrations from 5 ppm down to ca. 1 ppm. Eight of these (the only ones active below 2.5 ppm) were thiolcarbamates (RSC(O)NHR'). Decyl *N*-methylthiolcarbamate was also lethal to *Meloidogyne incognita* at approximately 1 ppm in direct contact tests.

Key words: alkyl, carbamate, dialkyl, *Meloidogyne incognita,* nematicide, *Panagrellus redivivus,* structure–activity, thiocarbamate.

Various physical and economic factors have dictated the loss of nematicides, in spite of considerable damage caused by nematodes to various agricultural crops, until very few nematicides are available for use. Omitting specialized and obsolete, but still presumably registered, materials and the gaseous or volatile-liquid soil fumigants, there are only six general-purpose nematicides (Fig. 1) available (3). The environmental fates of five of these (Fig. 1A–C, E, G) have been discussed (10). The three carbamates on this list (Fig. 1A–C) all resemble the structure of acetylcholine (Fig. 1D) rather closely and inhibit the action of acetylcholinesterase. Insecticidal carbamates, as ascertained from references like the Farm Chemicals Handbook (2), are almost exclusively aromatic, derivatives of benzene and naphthalene. The organophosphates (Fig. 1E–G) also inhibit cholinesterase but are outside the scope of this paper.

In view of the dearth of usable nematicidal materials, we have screened compounds prepared in various USDA laboratories for nematicidal activity. These compounds, summarized by Feldmesser and Kochansky (4), include bromoacetates (9), halogenated benzoic acid derivatives (4), alkyl amines and amides (6), and alkanephosphonates (5). The most active compounds in each class were lethal (LC_{95}) to *Panagrellus redivivus* (L.) T. Goodey 1945 in the low-ppm or even sub-ppm range.

A few *O,N*-dialkyl carbamates were synthesized in our laboratory as a part of unpublished research on fire ants. When tested against scabies mites (*Psoroptes* spp.), they showed very high activity, and several hundred related compounds, most previously unreported, were prepared to test their acaricidal activity (11). The compounds, in the three related classes in Figure 2, are of much simpler structure than the carbamates in Figure 1. Few of these compounds have been reported in the literature, and they were mostly of short chain lengths. Analogous compounds, with additional functionality and higher polarity, have been described (8). They were tested against *Heterodera schachtii* Sch. with moderate activity.

With the exception of methyl and ethyl *N*-methylthiolcarbamates (7), reports of activity of dialkyl carbamates as nematicides were not found. When a few compounds were found to be highly active in initial screens against *Panagrellus,* further representatives were tested for nematicidal activity. Those tested provided a general outline of the most active structural areas, which are described here, as is a test of one of these compounds against *Meloidogyne incognita.*

Received for publication 7 December 1987.

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We thank George Wolfhard for technical assistance and Conoco, Stauffer, PPG, Reilly Tar and Chemical Co., Enterprise Chemical Co., and Houdry Process Co. for gifts of chemicals used.

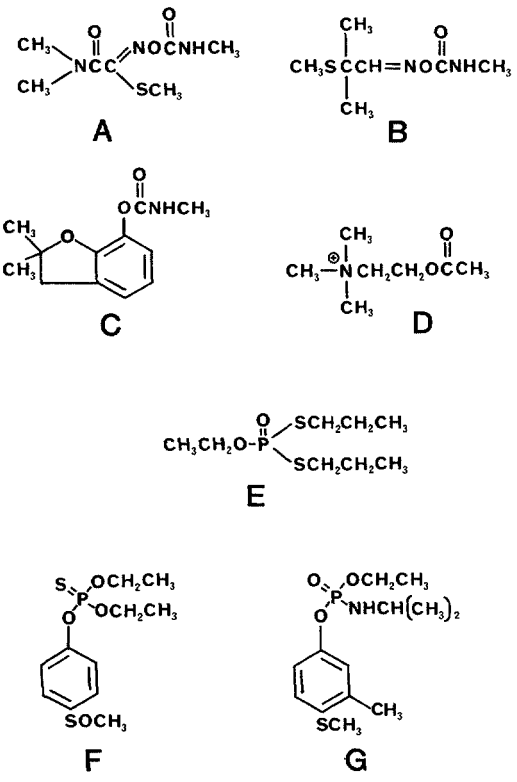

FIG. 1. Broad-spectrum nematicides currently registered. Carbamates, A–C. A) Oxamyl. B) Aldicarb. C) Carbofuran. D) Acetylcholine for comparison. Organophosphates, E–G. E) Ethoprop. F) Fensulfothion. G) Fenamiphos.

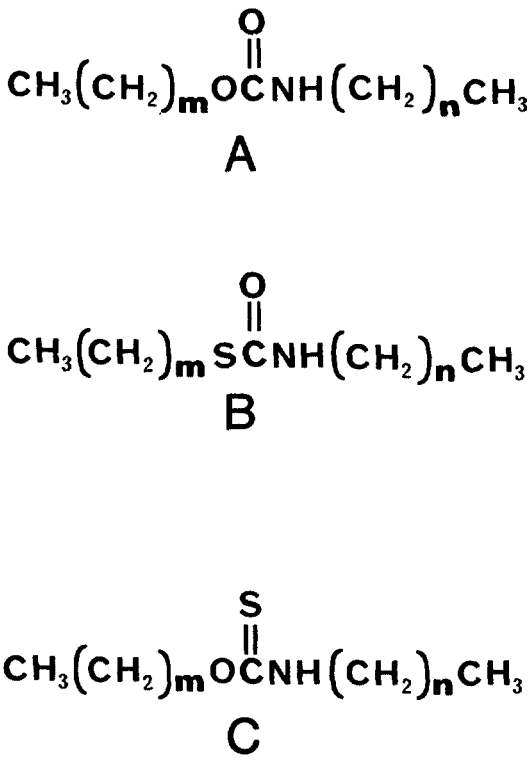

FIG. 2. General formulae for carbamates reported in this paper.

MATERIALS AND METHODS

The carbamates (Fig. 2A) were synthesized from the appropriate alcohols and isocyanates or from long-chain amines and alkyl chloroformates. The thiolcarbamates (Fig. 2B) were prepared analogously from thiols and isocyanates or from amines and chlorothiolformates; the thionocarbamates (Fig. 2C) were prepared from alcohols and alkyl isothiocyanates. They were synthesized and named as described by Kochansky and Wright (11); also given were references for preparation of intermediates. Carbamates of type C are unstable (unpubl.), rearranging spontaneously to isomers of type B at 25 C. The half life has not been measured accurately, but it seems to be approximately 2–3 years.

The compounds were evaluated in a standard direct contact test (5). *Panagrellus redivivus,* a saprophytic nematode and a sensitive indicator of nematicidal activity, was immersed for 48 hours in mixtures containing water, quartz sand, and the toxicant in solubilized form. Each compound was tested at concentrations ranging from 100 ppm to 5 ppm, or lower when 5 ppm was lethal. The compounds were solubilized in a solvent–surfactant–water medium with the following composition: one part acetone and one part of an aqueous solution containing 5% Tween 20 (polyoxyethylated sorbitan monolaurate) and 5% Triton X-100 (polyoxyethylated octylphenol). Solvent–surfactant concentrations were 0.5% or less (vol:vol), of each formulated solution containing a candidate nematicide. Approximately 400 nematodes in all developmental stages were exposed in each test.

Effects were determined during the day immediately after exposure by microscopic examinations. Normal unstressed *Pana-*

TABLE 1. Minimum lethal concentrations of dialkyl carbamates, ROC(O)NHR', to *Panagrellus redivivus*.

	Minimum lethal concentration (ppm) in R' groups 1–12											
R group	1	2	3	4	5	6	7	8	9	10	11	12
1								10–20		10–20		> 20
2								10–20		10–20		> 20
3												
4	> 80											
5												
6	> 100		> 20	20								
7	40–80		10	10								
8	10–20											
9	5–10	5–10										
10	2.5–5†	5–10	> 40	> 40				> 100				
11	> 100	> 100										
12	> 100	> 40	> 20	> 20								
13												
14	> 100	> 20		> 20								

Row and column numbers refer to the numbers of carbon atoms in the respective alkyl groups. All alkyls are straight chain and saturated. Aldicarb and carbofuran were lethal at 5 ppm.

† Active at ≤ 5 ppm.

grellus redivivus were in continuous rapid motion and the esophageal areas were hyaline. Exposure to nematicides resulted in reduced motility, immotility, and death, and when the nematodes were moribund or dead the esophageal structures disintegrated and darkened. When reduction or cessation of motility appeared to be the sole or major effect of exposure, nematodes were held for 24 hours or longer after the end of the exposure period to determine recovery of motility, if any, and to determine mortality rates. Untreated checks were run along with all experimental compounds. Check mortality was < 10% (typically 3–4%), and mortalities were corrected by Abbott's formula (1).

In this assay, concentration ranges were such that the lower concentration usually caused 80–90% mortality, whereas the higher one killed all exposed nematodes. Treatments were replicated at least three times, and additional tests were done in questionable cases. Since this was a rapid screening bioassay to determine a minimum LC_{100}, further tests to determine LC_{50} by probit analysis were not conducted.

In the *Meloidogyne* assay, also described in (5), *Meloidogyne incognita acrita* (Kofoid & White, 1919) Chitwood, 1949 juveniles were exposed in vials to a range of concentrations of the test compound, in the same solvent–surfactant medium as used in the *Panagrellus* test, for 48 hours and then washed free of the candidate toxicant. Visual examinations showed darkened disintegrated structures in the esophageal areas of many of the exposed juveniles. Final viability determinations were made by using exposed juveniles to inoculate small nematode-free tomato seedlings (*Lycopersicon esculentum* Mill. cv. Rutgers) growing in nematode-free soil in small containers. One thousand exposed nematode juveniles were placed in three or four small holes in the soil around the stem of each tomato seedling. The holes were closed and the plants were watered lightly and thereafter were maintained on a regular greenhouse schedule. Control plants were inoculated with unexposed juveniles. The inoculated tomato seedlings were examined after 3 weeks to determine the viability of the nematode inocula expressed as root infections. Root-knot nematode infections were indexed visually, and the roots were examined microscopically after staining with hot cotton blue-lactophenol and differential destaining with lactophenol to show possible nematodes in roots lacking visible

TABLE 2. Minimum lethal concentrations of dialkyl thiolcarbamates, RSC(O)NHR', to *Panagrellus redivivus*.

R group	Minimum lethal concentration (ppm) in R' groups 1–10									
	1	2	3	4	5	6	7	8	9	10
1	> 100	> 100	> 100	> 100	80–100	10		> 100		> 100
2	> 100	> 100	> 100	10–20	10–20	5–10		5–10		> 100
3	> 100	20–40	> 100	40–80	20–40	5–10	10–20	> 100	> 100	> 100
4	5–10	20–40	40–80	10–20	10–20	80–100	> 100	> 10	> 100	> 40
5	2.5–5†	5–10	10–20	5–10	5–10	40	40	40		
6	5†			20–40	20–40	> 100	> 100			
7	2.5–5†	0.625–1.25†	5	10–20	> 100	> 100	> 100	> 100		
8	1.25–2.5†	5–10	10	> 80	> 100	> 100				
9	1.25–2.5†	40		> 40						
10	0.625–1.25†		> 100	> 100						
11	2.5†	> 40	> 40	> 100						
12	> 20	> 10	> 20	> 100						
14	> 40									

Row and column numbers refer to the numbers of carbon atoms in the respective alkyl groups. All alkyls are straight chain and saturated. Aldicarb and carbofuran were lethal at 5 ppm.
† Active at ≤ 5 ppm.

galls (12). The arbitrary root-knot index describes extent of infection as follows: 0 = 0%, trace = < 5%, 1 = 6–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100% infection.

RESULTS

The most active dialkyl carbamate, ROC(O)NHR', was decyl *N*-methylcarbamate (Table 1). It was lethal at 2.5–5 ppm; three others were active at 5–10 ppm. By comparison, aldicarb and carbofuran were lethal at 5 ppm in this assay.

The thiolcarbamates, RSC(O)NHR', were the most active materials (Table 2). Two thiolcarbamates, decyl *N*-methyl and heptyl *N*-ethyl, were lethal at 0.625–1.25 ppm, and octyl and nonyl *N*-methylthiolcarbamates were lethal at 1.25–2.5 ppm. Fourteen others were active at 5–10 ppm.

Few thionocarbamates, ROC(S)NHR', were tested (Table 3). Octyl *N*-methylthionocarbamate was lethal at 2.5–5 ppm, but none of the others was active below 10 ppm.

Compounds related to the three primary classes of carbamates were also tested. Decyl methyl carbonate was inactive at 20 ppm. Octyl, decyl, and dodecyl carbamates (unsubstituted on N) were inactive at 20 ppm. Decyl and dodecyl *N,N*-diethylcarbamates were inactive at 100 ppm, as were the do-

TABLE 3. Minimum lethal concentrations of dialkyl thionocarbamates, ROC(S)NHR', to *Panagrellus redivivus*.

R group	Minimum lethal concentration (ppm) in R' groups 1–7						
	1	2	3	4	5	6	7
6						> 100	
7				20–40			
8	2.5–5†	> 100	> 100		> 100	20–40	
9	10–20	10–20	> 20				
10	10–20	> 100	> 100	> 100	> 100		
11	> 20						
12	> 20	> 100	> 100	> 100		40–80	

Row and column numbers refer to the numbers of carbon atoms in the respective alkyl groups. All alkyls are straight chain and saturated. Aldicarb and carbofuran were lethal at 5 ppm.
† Active at ≤ 5 ppm.

TABLE 4. Comparative nematicidal effectiveness of decyl N-methylthiolcarbamate and ethoprop against root-knot nematodes (*Meloidogyne incognita*).

ppm	Root-knot indices for replicated tests		
	1	2	3
	Decyl *N*-methylthiolcarbamate		
40	trace	0	trace
20	0	0	trace
10	trace	trace	trace
5	trace	0	0
2.5	0	trace	0
1.25	trace	trace	1.0
0.625	trace	0	0.5
0.312	3–3.5	2–2.5	3–3.5
Control	2.5–3	2	3.5–4
	Ethoprop		
80	0	0	0
40	trace	0	0
20	1.0	trace	1.5–2

Replicates used 800–900 larvae each with a contact time of 48 hours followed by 6 weeks exposure of treated inoculum to tomato roots. The arbitrary root-knot index describes extent of infection as follows: 0 = 0%, trace = < 5%, 1 = 6–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100% infection.

decyl carbamates having cyclic amide groups with four, five, or six methylene groups. Alkyl *N*-phenylcarbamates having 6, 8, 10, 12, or 14 carbons in the alkyl groups were inactive at 20 ppm. Several *N,N'*-dialkyl ureas and thioureas were also inactive at 20 ppm. 3,7-dimethyloctyl *N*-methylthiolcarbamate was inactive at 100 ppm.

When decyl *N*-methylthiolcarbamate was tested against *M. incognita* in a direct-contact test followed by inoculation of tomato roots with the treated nematodes, there was at most trace infection of the tomato roots at concentrations above 1.25 ppm (Table 4). Ethoprop, a commercial nematicide, was not effective at 20 ppm.

DISCUSSION

The results of the *Panagrellus* assay clearly indicate that nematicidal activity of these compounds is distributed less widely than the acaricidal activity previously reported (11), but the basic requirements are similar. Activity requires one and only one alkyl group on nitrogen and one on the oxygen or sulfur. Presence of two alkyls or two hydrogens on nitrogen destroys activity. Apparently, branching of the alkyl groups on oxygen or sulfur is detrimental to activity, since 3,7-dimethyloctyl *N*-methylthiolcarbamate was inactive, whereas the *n*-octyl or *n*-decyl analogs were highly active compounds.

Carbamates and thionocarbamates (Fig. 2A, C) were generally less active than thiolcarbamates (Fig. 2B), as the only compounds active at ca. 1 ppm were thiolcarbamates. Although the most active materials were *N*-methyl or *N*-ethyl derivatives, there was a trend similar to that seen for the acaricidal activity where activity was characteristic of a given total molecular size without regard to the position of the functional group within the molecule. This was apparent in various thiolcarbamates with alkyl groups R and R' such that compounds whose lethal concentrations were ≤ 10 ppm had 7–12 carbons in R and R' combined (Table 2). Lethality at this level is as good as the best of the amines and amides reported by Feldmesser et al. (6).

Except for methyl and ethyl *N*-methylthiolcarbamates (7) (inactive in our assay), this is the first report on the nematicidal activity of these compounds. All of these compounds are easily synthesized. For example, decyl *N*-methylthiolcarbamate can be prepared in > 95% yield on a 2-kg scale. When administered by stomach tube as a 10% solution in propylene glycol, decyl *N*-methylcarbamate showed no toxic effect in rabbits at single oral doses of 300 mg/kg (Kochansky and Herlech, unpubl.). Because of their high activity, ease of preparation, and anticipated low mammalian toxicity, these materials have promise as new nematicidal agents.

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