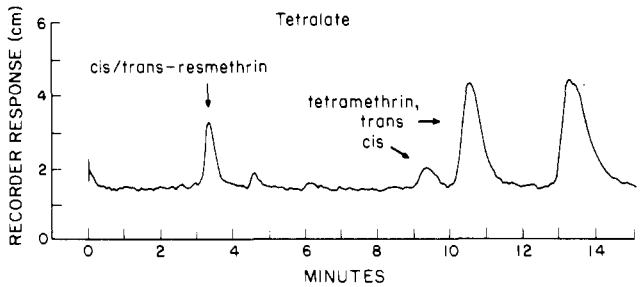


Figure 10. IR chromatogram obtained after a 10-μL injection of a 10% (v/v) Tetralate solution in CCl_4. The detector was operated at 5.80 μm. The mobile phase was 42.5% CCl_4, 42.5% CH_2Cl_2, 14.85% $CHCl_3$, and 0.15% CH_3CN (v/v/v/v).

5.75 μm. Comparison of Figures 7 and 9 indicates the selectivity of the IR detector where response to one compound over another can be enhanced simply by careful selection of the wavelength used.

No data are presented for the UV detector as the mobile phase apparently underwent photodecomposition and gave erratic responses.

When a mobile phase consisting of 50% 1,2-dichloroethane in cyclohexane was used, the two permethrin isomers eluted at 4.0 (cis) and 5.1 (trans) min; the *d*-phenothrin isomers eluted at 5.7 and 6.4 min. Resmethrin also separated into the cis (6.4 min) and trans (7.2 min) isomers.

Tetramethrin. Tetramethrin (phthalthrin) is a good knockdown agent and is usually formulated with other pyrethroids which have greater killing activity. Tetralate is a formulation which contains tetramethrin and resmethrin.

Figure 10 shows the IR chromatogram obtained for Tetralate by using a mobile phase of 42.5% CCl_4, 42.5% CH_2Cl_2, 14.85% $CHCl_3$, and 0.15% CH_3CN. The geometrical resmethrin isomers were unresolved and eluted as a single peak. The HPLC conditions for resmethrin formulation analysis were given by Papadopoulou-Mourkidou et al. (1980). The *cis*- and *trans*-tetramethrin isomers were resolved and eluted at retention times of 9.4 and 10.5 min. It was assumed that the cis isomer eluted before the trans isomer as individual analytical standards were unavailable for confirmation. Two peaks were not identified and are believed to arise from the formulating ingredients.

LITERATURE CITED

AOAC "Official Methods of Analysis of the AOAC", 13th ed.; Horwitz, W., Ed.; AOAC: Washington, DC, 1980; pp 86-87.
Chapman, R. A.; Harris, C. R. *J. Chromatogr.* **1978**, *166*, 513.
Chapman, R. A.; Harris, C. R. *J. Chromatogr.* **1979**, *174*, 369.
Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.
Meinard, C.; Suglia, J. C.; Bruneau, P. *J. Chromatogr.* **1979**, *176*, 140.
Mestres, R.; Chevallier, C.; Espinoza, C.; Cornet, R. *Proc. Int. Soc. Citric., 1977* **1977**, *2*, 429.
Mourot, D.; Delepine, B.; Boisseau, J.; Goyot, G. *J. Chromatogr.* **1979**, *173*, 412.
Nakayama, I.; Ohno, N.; Aketa, K. Suzuki, Y.; Kato, T.; Yoshioka, H. In "Advances in Pesticide Science"; Geissbuehler, H., Ed.; Pergamon Press: New York, 1979; Vol. II, pp 174-181.
Papadopoulou-Mourkidou, E.; Iwata, Y.; Gunther, F. A. *J. Agric. Food Chem.* **1980**, *28*, 1043.

Received for review February 17, 1981. Revised manuscript received July 13, 1981. Accepted August 11, 1981. This research was partially supported by Regional Research Project W-45.

Insecticidal Phosphoramidothio Derivatives of the Carbamate Methomyl

Fred E. Dutton, Edwin G. Gemrich II, B. Lamar Lee, Stephen J. Nelson,* Price H. Parham, and William J. Seaman

The insecticidal activities of a number of phosphoramidothio derivatives of methomyl were investigated. The derivatives demonstrated activity comparable to that of methomyl in feeding tests against southern armyworm (*Spodoptera eridania*, Cramer), cabbage looper (*Trichoplusia ni*, Hubner), and tobacco budworm (*Heliothis virescens*, Fabricius). The topical activities were generally equal or superior to methomyl while ovicidal activities were less than those of methomyl against the same species. The derivatives demonstrated longer residual activity and reduced phytotoxicity relative to methomyl. Toxicological evaluation of one of the compounds (methyl *N*-[[[[[(diethoxyphosphinothioyl)isopropylamino]thio]methylamino]carbonyl]oxy]ethanimidothioate, U-47319) showed a substantial improvement in acute mammalian safety toward male and female rats when compared to that of methomyl.

The modification of carbamate insecticides by substitution of the carbamate nitrogen with moieties which alter the ancillary properties of the parent compound, particularly toxicity toward nontarget organisms, has been the object of intensive research in both academia and industry. Noteworthy among the substitutive groups employed for this purpose are *N*-thio derivatives. Arylthio (Black et al., 1973a), aminothio (Fukuto et al., 1975), and *N*-carbamylthio (Fahmy et al., 1978) derivatives of a number of carbamate insecticides show reduced mammalian toxicity. Aminothio derivatives of methomyl are reported to have reduced phytotoxicity and longer residual effectiveness as well as reduced mammalian toxicity (Gemrich et al., 1978). The increased selectivity of *N*-thio carbamates has been attributed to differential metabolism (Black et al., 1973b; Krieger et al., 1976). We report here the results of our investigations of phosphoramidothio derivatives of methomyl.

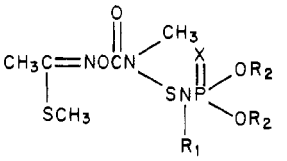
Agricultural Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001.

EXPERIMENTAL SECTION

Synthesis of Compounds. The phosphoramidothio derivatives (Table I) were obtained by the reaction of an *N*-chlorothiophosphoramide (NCP) with methomyl in the presence of a catalytic amount of cuprous chloride (Figure 1). The chlorothiophosphoramides were prepared by the reaction of sulfur dichloride with the phosphoramides

0021-8561/81/1429-1111$01.25/0

Table I. Chemical[a] and Insecticidal Properties[b] of Phosphoramidothio Derivatives of Methomyl



compd	R_1	R_2	X	mp, °C	foliar feeding SAW[c]	foliar feeding CL[d]	foliar feeding TBW[e]	topical, TBW	ovicidal TBW	ovicidal CL
1	$-CH(CH_3)_2$	$-CH_2CH_3$	S	72-73	++±−	+±−−	+±±−	+++±±	+±±±	++−−
2	$-CH(CH_3)_2$	$-CH_2CH_3$	O	71-72	++−−	++−−	++±−	±±±±−	+±±−	+±−−
3	$-CH_3$	$-CH_3$	S	55-56	++−−	+−±−	++±−	+++++±	++±±	+±−−
4	$-CH_3$	$-CH_3$	O	67-69	++±−	+±±−	++±±	+±±±±	++±±	+±−−
5	$-CH_2CH_3$	$-CH_2CH_3$	S	oil	+++−	+±−−	+±±−	++±±−	++±±	++−−
6	cyclohexyl	$-CH_2CH_3$	S	89-90	++±−	+−±−	+−−−	++±−−	+−−−	++−−
7	cyclohexyl	$-CH_2CH_3$	O	oil	+−−−	+±−−	++−−	±±−−−	+±±−	+±−−
methomyl					+++−	++−−	++±±	+±±−−	++++	++++

[a] Satisfactory elemental analyses (±0.4%) were obtained for all compounds. [b] (+) 71-100% corrected (Abbott's formula) mortality; (±) 36-70% mortality; (−) 0-35% mortality. Rates for foliar feeding: SAW,[c] 50, 16.7, 5.6, and 1.9 ppm; CL,[d] $^1/_8$, $^1/_{16}$, $^1/_{32}$, and $^1/_{64}$ kg/ha; TBW,[e] $^1/_{16}$, $^1/_{32}$, $^1/_{64}$, and $^1/_{32}$ kg/ha. Rates for topical: 50, 25, 12.5, 6.3, and 3.1 μg/g. Rates for ovicidal: 100, 33, 11, and 3.7 ppm. [c] Southern armyworm. [d] Cabbage looper. [e] Tobacco budworm.

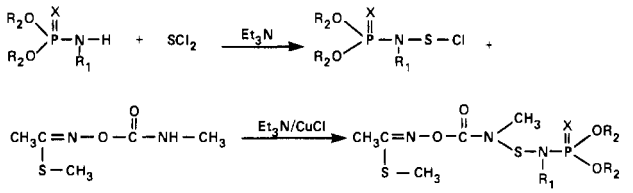


Figure 1. Synthesis of phosphoramidothio derivatives of methomyl.

which, in turn, were obtained by standard procedures (Sasse, 1964). The preparation of methyl *N*-[[[[[(diethoxyphosphinothioyl)isopropylamino]thio]methylamino]carbonyl]oxy]ethanimidothioate (1, Table I) is typical.

A solution of diethyl *N*-isopropylphosphoramidothioate (26.18 g, 0.124 mol) and triethylamine (12.5 g, 0.124 mol) in hexane (250 mL) was added dropwise to a solution of sulfur dichloride (15.4 g, 0.149 mol) in hexane (250 mL) cooled to 0° C over 30 min. After the addition, the mixture was stirred for 30 min at 0 °C and then filtered under nitrogen. The filtrate was concentrated under reduced pressure at less than 30 °C to leave the crude NCP as a pale yellow oil. Attempts to purify this material by distillation resulted in decomposition. The crude NCP in THF (100 mL) and triethylamine (12.5 g, 0.124 mol) in THF (100 mL) were added dropwise and simultaneously to a mixture of methomyl (20.1 g, 0.124 mol) and cuprous chloride (0.5 g) in THF (100 mL) at 0 °C. After the additions, the mixture was stirred at 0 °C for 30 min and then diluted with water (1000 mL). The mixture was extracted with hexane, and the combined organic phases were washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure to leave a brown oil. Trituration with hexane and recrystallization from ethyl acetate–hexane gave 1 (23.5 g, 47%) as white needles: mp 72–73 °C; NMR ($CDCl_3$) δ 4.05 [m, 5 H, $(OCH_2—)_2$, N-CH], 3.40 (s, 3 H, N-CH_3), 2.37 (s, 3 H, S-CH_3), 2.29 (s, 3 H, CH_3C=), 1.32 [t, 12 H, $(OCCH_3)_2$, N-$C(CH_3)_2$]; IR (Nujol) 1730 cm^{-1}. Other compounds were purified by crystallization or, when appropriate, chromatography on silica gel eluting with ethyl acetate–hexane.

Biological Test Methods. *Formulation.* All compounds were dissolved in acetone for direct topical application to larvae. The compounds were formulated for spray or dip application to leaves, plants, and ova by dissolving them in acetone and diluting with an aqueous solution of Lignosol SFX (0.01%), Lignosol Chemicals Ltd., Quebec, Canada, and Nekal BA77 (0.01%), GAF Corp., New York, NY. Chemicals were prepared as aqueous technical suspensions by using Tween 20 (0.5–10%), ICI Americas, Inc., Wilmington, DE, and methylcellulose (0.125–0.25%) for administration to rats.

Insecticidal Assays. The compounds were evaluated in laboratory screening tests to determine their contact ovicidal and larvicidal as well as their foliar feeding toxicities to cabbage looper (CL), *Trichoplusia ni*, tobacco budworm (TBW), *Heliothis virescens*, and southern armyworm (SAW), *Spodoptera eridania*. Regardless of the species or type of larval evaluation, 20 uniformily sized third instars were examined per dosage, including appropriate controls. Insects in all tests were held at 20–22 °C for 72 h at which time mortality was recorded.

In topical application studies, the desired amount of test chemical was applied in 0.1-μL of acetone to the dorsal thoracic segments of the TBW larvae growing individually in portion cups on an artificial TBW diet (BioServ Inc., Frenchtown, NJ). SAW larvae were placed on dip-treated pairs of lima bean, *Phaseolus vulgaris*, cv. Henderson bush, leaves in Petri dishes according to the method of Gemrich et al. (1978). TBW and CL larvae were placed onto sprayed cotton, *Gossypium hursutum*, cv. Delta Pine 16, leaves in Petri dishes. Cotton seedlings were sprayed such that chemical was applied to the upper leaf surfaces at 300 L of spray volume/ha.

TBW and CL ova were treated by the method of Gemrich et al. (1978). Small pieces of paper toweling on which ova (less than 24 h old) had been deposited were dipped into emulsions of the test chemical, allowed to dry, and then placed in Petri dishes. Sixty or more eggs were treated per concentration.

The foliar residual activity of the compounds was monitored in a greenhouse trial. Cotton seedlings were dip treated in 50-ppm emulsions of the test compounds. After the deposits dried, plants were held in the greenhouse (20–43 °C), and leaves were removed at various time intervals for up to 3 weeks. The leaves were placed in Petri dishes and infested with CL larvae as described above for the foliar feeding test except that only 15 larvae were examined per chemical residual interval for mortality determinations.

Phytotoxicity. The chemicals were tested for their abilities to produce plant injury to cotton, eggplant, *So-*

Table II. Plant Safety of Phosphoramidothio Derivatives of Methomyl

	av % phytoxicity index[a] for compd								
crop	1	2	3	4	5	6	7	methomyl	LSD (0.05)
eggplant	0	0.8	1.8	1.3	1.0	0	0.5	5.0	0.68
soybean	0	1.0	1.5	1.8	2.5	0	5.0	5.3	1.09
cotton	0	1.0	2.3	5.3	3.3	0	0.8	6.7	1.09

[a] 0 = no damage; 10 = complete kill.

lanum melongena, cv. Black Beauty, and soybean, *Glycine max*, cv. Amsoy 71, in a greenhouse trial. Four seedling (at least two fully expanded noncotyledonary leaves per plant) plants were sprayed twice 7 days apart by using full coverage applications. Chemicals were applied at 1200 ppm, and injury (0 = no injury to 10 = plant dead) was recorded 6 days following the second application. Significance was determined by the LSD test ($P = 0.05$).

Acute Oral Rat Studies. Five male Sprague–Dawley white rats per dosage were utilized in defining preliminary acute oral LD_{50} values. Ten males and ten females were treated per dosage to examine differences in susceptibilites of the sexes and to define the LD_{50} values more precisely. Animals weighed between 190 and 220 g, and 1 mL of the technical chemical suspension was administered per 100 g of body weight. A minimum of four dosage levels per compound was administered once by gastric intubation. Animals were housed individually at 20–22 °C, and mortality was recorded after 7 (preliminary studies) or 14 (refined studies) days. Spearman-Karver statistics were utilized in calculating approximate LD_{50} values.

RESULTS AND DISCUSSION

Results of the insecticidal assays are summarized in Table I. On the basis of the feeding studies, all of the compounds with the exception of compound **7** demonstrated activity approximately equal to that of methomyl on at least one species. The activity of compound **4** equaled that of methomy on all three species, while the overall activity of compounds **1**, **2**, **3**, **5**, and **6** was slightly lower. TBW larvae proved more sensitive to the action of all the compounds than did CL.

This differential sensitivity between the two species was also apparent in the ovicidal evaluations, but in the latter case methomyl proved to be more toxic than any of the derivatives. Inspection of the feeding and ovicidal data in Table I indicates no clear structure–activity relationships among the derivatives when comparing corresponding phosphoramide (P=O) and thiophosphoramide (P=S) analogues.

In contrast to the feeding and ovicidal activities, the topical toxicities of the derivatives to TBW larvae were generally equal or superior to that of methomyl, and in this case the P=S derivatives were consistently more active than their corresponding P=O derivatives.

The results of the insecticidal tests demonstrated that several of the derivatives had activities comparable to that of methomyl. As they have molecular weights on the order of twice that of methomyl, their toxicities are increased on a molar basis assuming the parent carbamate is the toxic agent being generated from the derivatives in a manner similar to that reported for other derivatized carbamates (Black et al., 1973a). It is possible that the phosphoramide moiety may directly contribute to the toxicity of the compounds. In screening tests, however, they proved to demonstrate no toxicity at much higher levels than those cited in Table I. It is likely that the increase in activity on a molar basis is due to factors such as penetration, transport, and protection from premature detoxication.

Table III. Residual Effectiveness of Phosphoramidothio Derivatives of Methomyl

compd	% act.[a]	compd	% act.[a]
1	100	5	54
2	100	6	96
3	78	7	71
4	13	methomyl	0

[a] Percent of original activity maintained 21 days postapplication for the various compounds.

As the insecticidal assays failed to provide any clear rational for selection of a compound for continued evaluation, we turned to an examination of some of the ancillary properties of the derivatives.

The phosphoramidothio derivatives demonstrated a marked reduction in phytotoxicity to eggplant, soybeans, and cotton (Table II) compared to that of methomyl. The P=S derivatives were less phytotoxic than the corresponding P=O derivatives, and two of the compounds, **1** and **6**, produced no measurable injury.

The residual insecticidal toxicity of the compounds 21 days after treatment is presented in Table III. There is a strong suggestion that the P=S compounds are more residual than their P=O counterparts. Also, a high correlation (0.96) was observed between phytotoxicity produced and that loss in residual insecticidal toxicity on cotton.

Three compounds, **1**, **2**, and **6**, which demonstrated the best overall bioactivities, i.e., insecticidal activity, plant safety, and residual toxicity, were subjected to preliminary toxicological investigations. On the basis of acute oral male rat studies, compound **2** proved to have an LD_{50} below 100 mg/kg, while **1** and **6** were above this value. The potential for formation of cyclohexylamine in the metabolism of compound **6** was considered as posing a finite risk from chronic exposure. Therefore, compound **1** was selected for continued evaluation in more refined toxicology studies.

The studies showed a surprisingly large difference in acute oral toxicity between sexes (LD_{50} values of 325 and 832 mg/kg for females and males, respectively). Although the cause of this more than 2-fold difference in toxicity is unknown, a substantial level of safening was afforded over methomyl [LD_{50} values of 24 and 17 mg/kg for females and males, respectively (Meister, 1980)].

The results reported here suggest the potential utility of phosphoramidothio derivatives of methomyl as insect control agents. On the basis of several considerations, compound **1** (U-47319) was chosen for further evaluation in toxicological and field studies. Results from acute and subacute toxicological investigations suggest limited user handler and chronic safety hazard (The Upjohn Company, 1979) while field data (Hofmaster and Francis, 1979, 1980; Pieters and Pitts, 1979) have demonstrated the utility of the compound in controlling certain lepidopterous pests.

The studies reported here prompted the preparation and evaluation of closely related phosphorinanylaminothio

derivatives of methomyl. Results of those investigations are reported in the following paper (Dutton et al., 1981).

ACKNOWLEDGMENT

We acknowledge the assistance of L. H. Hope and P. A. Timmons in the biological evaluations and P. K. Brown in the toxicological investigations.

LITERATURE CITED

Black, A. L.; Chiu, Y. C.; Fahmys M. A. H.; Fukuto, T. R. *J. Agric. Food Chem.* **1973a**, *21*, 747.
Black, A. L.; Chiu, Y. C.; Fukuto, T. R.; Miller, T. A. *Pestic. Biochem. Physiol.* **1973b**, *3*, 435.
Dutton, F. E.; Gemrich, E. G., II; Lee, B. L.; Nelson, S. J.; Parham, P. H.; Seaman, W. G. *J. Agric. Food Chem.* **1981**, following paper in this issue.
Fahmy, M. A. H.; Mallipudi, N. M.; Fukuto, T. R. *J. Agric. Food Chem.* **1978**, *26*, 550.
Fukuto, T. R.; Black, A. L.; Chiu, Y. C.; Fahmy, M. A. H. "Environmental Quality and Safety"; Coulston, F.; Korte, F., Eds.; George Thieme: Stuttgart, 1975; Supplement Vol. III, pp 394–400.
Gemrich, E. G.; Lee, B. L.; Nelson, S. J.; Rizzo, V. L. *J. Agric. Food Chem.* **1978**, *26*, 391.
Hofmaster, R. N.; Francis, J. "Insecticide and Acaricide Tests, Vol. 4"; Sorensen, K. A., Ed.; Entomological Society of America: College Park, MD, 1979; pp 75–76.
Hofmaster, R. N.; Francis, J. A. "Insecticide and Acaricide Tests, Vol. 5"; Sorensen, K. A., Ed.; Entomological Society of America: College Park, MD, 1980; p 71.
Krieger, R. I.; Lee, P. W.; Fahmy, M. A. H.; Chen, M.; Fukuto, T. R. *Pestic. Biochem. Physiol.* **1976**, *6*, 1.
Meister, R. T., Ed. "Farm Chemicals Handbook, 1980"; Meister Publishing Co.: Willoughby, OH, 1980; p D197.
Pieters, E. P.; Pitts, D. L. "Insecticide and Acaricide Tests, Vol. 4"; Sorensen, K. A., Ed.; Entomological Society of America: College Park, MD, 1979; pp 136–137.
Sasse, K. "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Thieme: Stuttgart, 1964; Vol. XII, Part 2, pp 413, 759.
The Upjohn Company "U-47319 Technical Brochure"; The Upjohn Company: Kalamazoo, MI, 1979; pp 1–5.

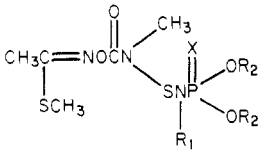
Received for review March 25, 1981. Revised manuscript received July 6, 1981. Accepted August 17, 1981.

Insecticidal Phosphorinanylaminothio Derivatives of the Carbamate Methomyl

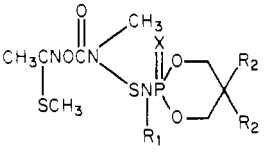
Fred E. Dutton, Edwin G. Gemrich II, B. Lamar Lee, Stephen J. Nelson,* Price H. Parham, and William J. Seaman

The insecticidal activities of phosphorinanylaminothio derivatives of methomyl were examined. The derivatives demonstrated activity comparable to that of methomyl in feeding tests against southern armyworm (*Spodoptera eridania*, Cramer), cabbage looper (*Trichoplusia ni*, Hubner), and tobacco budworm (*Heliothis virescens*, Fabricius) but had reduced topical and ovicidal activities against the same species. Of the compounds tested, none were phytotoxic toward cotton, eggplant, and soybean and demonstrated significantly greater residual effectiveness than did methomyl. Mammalian toxicity was shown to be substantially reduced relative to that of methomyl, and three of the compounds had acute oral LD_{50} values of over 8000 mg/kg to male rats. These compounds perhaps demonstrate the greatest selectivity yet achieved through N-substitution of pesticidal carbamates.

In the preceding paper (Dutton et al., 1981), we reported results of our investigations of phosphoramidothio derivatives (1) of methomyl. These compounds demonstrated



1



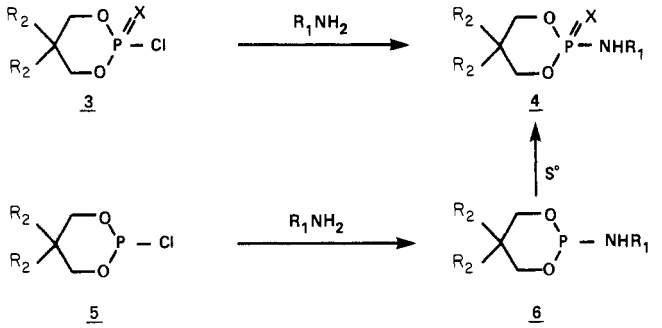
2

insecticidal activity toward lepidopterous larvae approximately equal to that of methomyl but showed reduced phytotoxicity, longer residual activity, and substantially reduced mammalian toxicity. As part of our continuing effort to modify carbamate insecticides having high activity but which suffer shortcomings in their ancillary properties, we have investigated the closely related phosphorinanylaminothio derivatives (2) of methomyl.

EXPERIMENTAL SECTION

Synthesis of Compounds. The phosphorinanamines 4 required for the preparation of the derivatives were obtained by reaction of a primary amine with the appropriate chlorophosphorinane 3 (Sasse, 1964), as outlined in Scheme I. In those cases where X is sulfur and the primary amine is hindered, it proved much more convenient to react the phosphorochloridite 5 with the amine (Cogne et al., 1974), followed by treatment with elemental sulfur.

Scheme I. Synthesis of Phosphorinanamines



The phosphorinanamines 4 were coupled with methomyl through the *N*-chlorothio or -bromothio intermediates 8 which were obtained by reaction of the corresponding disulfides 7 with elemental halogen (Scheme II). Although bromothio compounds and their chemistry are reported (Kuhle, 1970), this is to our knowledge the first example of their use in the preparation of *N*-thiocarbamates. In

Agricultural Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001.

0021-8561/81/1429-1114$01.25/0