Benzo[*b*]thienyl Carbamate Insecticides

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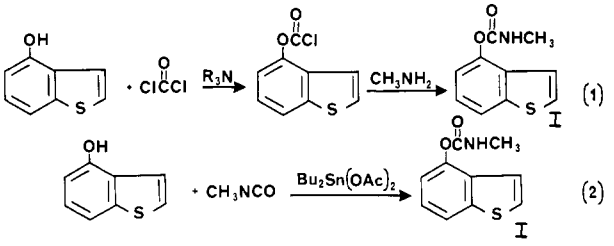
A new series of heterocyclic carbamates based on benzo[*b*]thiophene has been synthesized and the toxicity to three species of insects evaluated. One of these, benzo[*b*]thien-4-yl methylcarbamate (Mobam), exhibited a favorable combination of broad spectrum insecticidal activity coupled with low mammalian toxicity (acute oral LD_{50} rat, 234 mg. per kg.; acute dermal LD_{50} rabbit, >6230 mg. per kg.). In all cases reported, the effectiveness of the various carbamates corresponded generally to the fly-head cholinesterase inhibition values.

The biological effect of carbamates was recognized by Salway (1912), Stedman (1924), and Stedman and Barger (1925). Wiesmann (1951) and Wiesmann *et al.* (1951) synthesized one of the first heterocyclic carbamate insecticides, 1-phenyl-3-methyl-5-pyrazolyl *N,N*-dimethyl carbamate. Other analogs were found to be insecticidal. Generally these *N,N*-dialkyl carbamates were effective against a narrow range of insects, as reported by Gysin (1952, 1954a,b). Kolbezen *et al.* (1954) investigated the insecticidal activity of a variety of substituted phenyl carbamates and in particular showed that the *N*-methylcarbamates exhibited maximum toxicity.

In succeeding years, the broad insect activity and economic potential were developed as described by Fukuto (1961), Metcalf (1961), O'Brien and Matthysse (1961), and Casida (1963). Following the review by Weiden and Moorefield (1964), Kilsheimer *et al.* (1965) described a new class of broad-spectrum heterocyclic based *N*-methylcarbamates derived from benzothiophene. One compound, benzo[*b*]thien-4-yl methylcarbamate (Mobam), one of the more active members of this class, was selected for further development by Mobil Chemical.

SYNTHESIS

Two general methods were used to prepare Mobam as well as the other benzothienyl carbamates. The first (Equation 1) involved the reaction of 4-hydroxybenzo[*b*]thiophene with phosgene in the presence of a base such as a tertiary amine. The resulting chloroformate then reacted with methylamine or any other desired primary or secondary amine to give the *N*-alkyl, or *N,N*-dialkylcarbamates, respectively. A far more convenient method, however, was to treat a toluene solution of the hydroxybenzo[*b*]thiophene with methyl isocyanate or other suitable isocyanates in the presence of a catalyst, preferably dibutyltin diacetate (Equation 2). Methyl, *m*-chlorophenyl, and *p*-chlorophenyl isocyanate were obtained in high purity from the Ott Chemical Co. Butyl and phenyl isocyanate were obtained from the Carwin Co. Propyl isocyanate was obtained from Matheson, Coleman and Bell.



A number of hydroxybenzo[*b*]thiophene intermediates employed in this work have been discussed and reviewed by Hartough and Meisel (1954).

4-Hydroxybenzo[*b*]thiophene, the key phenolic intermediate in the synthesis of Mobam, was first prepared by Biedermann (1886). In our hands, Biedermann's method proved difficult for preparing suitable quantities of the desired 4-hydroxybenzo[*b*]thiophene; a more convenient synthetic scheme was described by Fieser and Kennelly (1935).

3-Hydroxybenzo[*b*]thiophene was synthesized by ring closure of 2-carboxymethylmercaptobenzoic acid with acetic anhydride according to the method of Friedlander (1906).

5,6- and 7-Hydroxybenzo[*b*]thiophene were prepared by a similar multistep operation starting from the corresponding *m*-, *p*-, or *o*-anisidine by a procedure of Sunthanker and Tilak (1951).

Benzo[*b*]thien-4-yl 1,1-dioxo-methylcarbamate (XVI) was synthesized by oxidizing benzo[*b*]thien-4-yl methylcarbamate (I) with 30% hydrogen peroxide in acetic acid. This technique was first used by Lanfry (1912) to oxidize benzothiophene to its sulfone.

2,3-Dihydro-4-hydroxybenzo[*b*]thiophene-1,1-dioxide was obtained by oxidizing 4-methoxybenzo[*b*]thiophene to the sulfone in the manner just described. The thiophene ring was best reduced by palladium on charcoal catalyst, by the technique of Bordwell and Stange (1955). Demethylation to the desired phenol required heating with pyridine hydrochloride at 275° C. for 12 hours.

2,3-Dihydro-4-hydroxybenzo[*b*]thiophene was prepared through a series of steps starting with the reaction of 4-hydroxybenzo[*b*]thiophene with dimethyl sulfate in base to give 4-methoxybenzo[*b*]thiophene. The methyl ether

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Table I. Physical Properties and Biological Activity of Benzo[*b*]thienyl Carbamates

No.	Carbamate	M.P. (B.P.), ° C.	Elemental Analysis Calculated %C	%H	%N	Found %C	%H	%N	% Mortality at 1000 P.P.M.[a] Bean beetle	Army-worm	Pea aphid	Molar I_{50}CHE
I	Benzo[*b*]thien-4-yl methyl-carbamate	129–131	57.9	4.4	6.8	57.8	3.8	6.8	100 (2)	100 (75)	68 (750)	3×10^{-8}
II	Benzo[*b*]thien-3-yl methyl-carbamate	134			6.8			6.8	90 (100)	0	15	1×10^{-7}
III	Benzo[*b*]thien-5-yl methyl-carbamate	126			6.8			6.8	100 (8)	0	0	9×10^{-7}
IV	Benzo[*b*]thien-6-yl methyl-carbamate	128			6.8			6.8	100 (50)	13	0	4×10^{-7}
V	Benzo[*b*]thien-7-yl methyl-carbamate	139			6.8			6.9	100 (7)	40	90	3×10^{-7}
VI	Benzo[*b*]thien-4-yl methyl-thiocarbamate	168–71	53.9	4.1	6.3	53.5	4.1	6.3	0	0	0	4×10^{-5}
VII	Benzo[*b*]thien-4-yl propyl-carbamate	73–75			6.0			5.9	100 (~50)	30	50	4×10^{-6}
VIII	Benzo[*b*]thien-4-yl cyclo-propylcarbamate	94–97	61.7	4.8	6.0	61.7	5.1	5.9	100	87	13	8×10^{-7}
IX	Benzo[*b*]thien-4-yl propargyl-carbamate	93–95	62.3	3.9	6.1	62.4	3.9	6.0	100	...	90	9×10^{-7}
X	Benzo[*b*]thien-4-yl butyl-carbamate	78–81			5.6			5.8	7	0	6	1×10^{-5}
XI	Benzo[*b*]thien-4-yl dimethyl-carbamate	(165° C. at 1.4 mm.)			6.3			6.2	100 (50)	0	100 (50)	3×10^{-7}
XII	Benzo[*b*]thien-4-yl phenyl-carbamate	173			5.2			5.2	0	0	0	$>1 \times 10^{-1}$
XIII	Benzo[*b*]thien-4-yl (*m*-chloro-phenyl) carbamate	115–17			4.6			4.6	100 (750)	0	17	$>1 \times 10^{-1}$
XIV	Benzo[*b*]thien-4-yl (*p*-chloro-phenyl) carbamate	165–66			4.6			4.7	53	0	0	$>1 \times 10^{-1}$
XV	2,3-Dihydrobenzo[*b*]thien-4-yl methyl carbamate	114–17	57.4	5.3	6.7	57.3	5.7	6.6	100 (20)	93 (500)	100 (50)	5×10^{-8}
XVI	Benzo[*b*]thien-4-yl 1,1-dioxo methylcarbamate	158–59	50.2	3.8	5.9	50.0	3.9	5.9	53	0	7	2×10^{-6}
XVII	2,3-Dihydrobenzo[*b*]thien-4-yl 1,1-dioxo methyl-carbamate	132–34	49.8	4.6		50.2	4.6		100	0	53	4×10^{-6}

[a] Approximate LD_{50} shown in parentheses.

reacted with 30% hydrogen peroxide in acetic acid to give 4-methoxybenzo[*b*]thiophene 1,1-dioxide, which in turn was reduced to 2,3-dihydro-4-methoxybenzo[*b*]thiophene-1,1-dioxide with hydrogen in the presence of palladium on charcoal. By using Bordwell and McKellin's (1951) method we were able to effect reduction with lithium aluminum hydride to produce 2,3-dihydro-4-methoxybenzo[*b*]-thiophene, a compound readily demethylated at 275° C. in the presence of pyridine hydrochloride to 2,3-dihydro-4-hydroxybenzo[*b*]thiophene.

4-Mercaptobenzo[*b*]thiophene (b.p. 117–18° C. at 0.58 to 0.6 mm, $n_D^{24.5}$ = 1.6918–21) was isolated as a by-product in the vapor phase synthesis of 4-chlorobenzo[*b*]thiophene from the reaction of 2,6-dichlorostyrene and hydrogen sulfide described by Kaufman and Foster (1967).

BIOLOGICAL SCREENING METHODS

The biological activity of the subject carbamates was evaluated against three orders of insects: *Lepidoptera* (Southern armyworm, *Prodenia eridania*), *Coleoptera* (Mexican bean beetle, *Epilachna varivestis*), and *Homoptera* (pea aphid, *Illinoia pisi*). The compounds were formulated as wettable powders and diluted with water to the concentrations of actual chemical indicated. Reference standards such as DDT, etc., were formulated in a similar manner.

In the Southern armyworm and Mexican bean beetle tests, cranberry bean plants were dipped in the appropriate concentrations of the respective formulations and then allowed to dry. Third instar larvae were then caged on the treated plants and maintained under greenhouse conditions for 48 hours, following which mortality counts were made. Three replicates were used for each level of application and the LD_{50} was calculated from the dosage mortality figures.

In the aphid evaluation, wingless pea aphids (*Illinoia pisi*) confined in spherical wire-mesh cages, were sprayed for 5 seconds with appropriate concentrations of the respective wettable powder formulation. Treated aphids were transferred to and caged on untreated broad bean plants, maintained under greenhouse conditions for 72 hours; a mortality count was made and percentage mortality calculated. Three replicates were used for each level of application.

CHOLINESTERASE DETERMINATION

The molar concentrations for 50% inhibition of fly-head cholinesterase (I_{50}) were determined using the colorimetric

procedure described by Robbins *et al.* (1958) for measuring bovine red-blood-cell cholinesterase activity. The housefly acetylcholinesterase used was prepared from female houseflies (Rutgers Wilson strain). The percentage inhibition for each inhibitor concentration was obtained by the expression $\%I = (S-A)/(B-A) \times 100$, where S is the absorbance value for an inhibitor concentration, A is the absorbance value for the maximum enzyme activity control, and B is the absorbance value for the nonenzymatic hydrolysis control. The I_{50} was determined by plotting the per cent inhibition values obtained *vs.* in vitro inhibitor concentration. At least four concentrations were run and replicated at least twice. The results are given in Table I.

RESULTS AND DISCUSSION

The isomeric benzothienylcarbamates (I to V) were compared for their effectiveness and revealed a generally high order of insecticidal activity, in agreement with the in vitro cholinesterase data (Table I). Benzo[*b*]thien-4-yl methylcarbamate, however, is one of the more active members of this family, as illustrated by its control of Coleoptera and Lepidoptera. A very dramatic loss of broad spectrum activity was noted when the *N*-methylcarbamate of 4-mercaptobenzo[*b*]thiophene was prepared (VI). Insecticidal activity can be seen for the compounds containing an *N*-*n*-propyl (VII), *N*-cyclopropyl (VIII), and *N*-propargyl (IX) group, although these analogs are less active than the corresponding *N*-methyl compound (I). This activity is consistent with their I_{50} values. A reduction in activity relative to I can be seen when the alkyl group is increased in size, as shown for the *N*-butyl (X). When both hydrogen atoms on the carbamate group are replaced by methyl (XI), the compound remains an effective cholinesterase inhibitor. Table I illustrates the relatively good control of bean beetle and pea aphid afforded by XI. A decrease in the effectiveness of inhibition relative to I resulted with the introduction of *N*-aryl substituents (XII to XIV). This effect was observed in the study of *N*-substituted carbamates of phenols by Kolbezen *et al.* (1954). XIII gave complete control of bean beetle at the initial rate.

Metcalf *et al.* (1965) observed from model studies that maximum fit of alkylthiophenyl *N*-methylcarbamates to the theoretical cholinesterase enzyme site occurs when the alkylthio group is in the ortho position of the aromatic ring. The most active anticholinesterases were found by these workers to be the ortho-substituted compounds. Compound V exhibits higher anticholinesterase activity than ortho-substituted alkylthiophenyl *N*-methylcarbamate reported by Metcalf *et al.* (1965). This is consistent with the speculation of Metcalf. The explanation of effectiveness of cholinesterase activity becomes less consistent when a comparison is made of the 4 and 7 isomers, I and V. It would appear that although sulfur is important for bonding at an anionic site as suggested by Metcalf, the steric relation of the thiophene ring is also a considerable factor in determining anticholinesterase activity.

ACKNOWLEDGMENT

The insect data reported were obtained at the Crop Protection Institute by Robert J. Norton. Cholinesterase values from the modified Hestrin method were furnished by Andrew Forgash, Department of Entomology, Rutgers, The State University, New Brunswick. Elemental analyses were performed under the direction of A. G. Chasar, Mobil Chemical, Research and Development Laboratory, Analytical Department.

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Received for review May 29, 1968. Accepted September 5, 1968.