Alkyl and Halo-phenyl *N*-Methylcarbamates

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A series of multisubstituted alkyl and halo-phenyl alkylcarbamates was synthesized and its toxicity to six species of insects and mites was evaluated. No useful structure-activity relationships were found beyond a confirmation that 2,6-disubstituted compounds were of low activity. 6-Chloro-3,4-xylyl methylcarbamate was promising in extended trials against many arthropod species.

In 1954, Kolbenzen, Metcalf, and Fukuto (*4*) synthesized a number of simple substituted phenyl alkylcarbamates and showed that they had insecticidal properties. Since then, several laboratories have published work along similar lines, which has resulted in the widespread field testing of variously substituted carbamates. At least one of these has found commercial use, 1-naphthyl methylcarbamate. Since both alkyl-substituted (*1–3*, *7*) and halo-substituted (*4*) phenyl alkylcarbamates had been reported to have high insecticidal activity, it was of interest to determine whether multiple substitution would give enhanced biological properties. Since this program was completed, another report covering some of the same compounds (*6*) and a patent covering the same subject matter (*5*) have been published.

Methods and Results

The carbamates synthesized (Table I) were prepared by reaction of the appropriate phenol with either methyl isocyanate to give the methylcarbamate or with ethyl isocyanate to give the ethylcarbamate (*4*). For example, 3,4-dimethyl-6-chlorophenyl methylcarbamate was prepared by adding 5.7 grams of methyl isocyanate to 15.6 grams of 2-chloro-4,5-xylenol dissolved in 200 ml. of diethyl ether containing 2 drops of triethylamine. After standing overnight at room temperature, the solvent was distilled under reduced pressure and the solid residue was crystallized from acetone to give 18.5 grams of the required compound.

The insecticidal and acaricidal activity of the carbamates was determined using an aqueous emulsion containing 500 p.p.m. of the carbamate as a contact spray. The test species were: housefly (*Musca domestica*), southern armyworm (*Prodenia eridania*, third instar), Mexican bean beetle larvae (*Epilachna varivestis*), pea aphid (*Macrosiphum pisi*), and two species of mites (*Tetranychus atlanticus* and *Panonychus citri*). The *P. citri* tests used acetone solutions containing 1000 p.p.m. of the carbamates.

The results are shown in Table II. The carbamates were not outstandingly active against the housefly but several showed enhanced activity in the presence of 1250 p.p.m. of piperonyl butoxide. These results are shown in Table II under the column housefly.

Discussion

Although most of the carbamates described in this paper have activity against at least one species, 2,6-disubstituted compounds 3, 10, 16, 17, and 18 are virtually inert. This structure-activity relationship holds for 2,6-dimethoxy-, 2,6-dimethyl-, and 2,6-dichloro-substitution (*6*) apparently regardless of the rest of the ring substitution.

Compounds 1, 2, 3, and 4 are simple chlorodimethylphenyl position isomers. Compounds 2 and 4, both having a 2, 4, 5 orientation, are highly active, particularly compound 4. Of interest is the striking miticidal activity shown by this compound. On the basis of these and other laboratory tests, larger scale field studies with compound 4 were undertaken.

Compounds 5 and 6 were of interest since they had the 2, 4, and 5 configuration. They had insecticidal properties but lacked the over-all spectrum of activity shown by compound 4. Compound 6 with the side chain *N*-methyl changed to *N*-ethyl confirmed previously published data (*4*) indicating that the optimum *N*-alkyl group in similar cases was methyl. Compound 11, with a methyl replacing the 6-chloro- substituent of compound 4, also had reduced activity.

Compounds 7, 8, and 9 were synthesized and tested in order to assess the

Table I. Analyses and Physical Constants of Alkyl- and Halo-phenyl–Substituted Alkylcarbamates

Compound No.	Carbamates	M.P. or B.P., °C.	Analysis, %, Calculated N	Calculated Cl	Found N	Found Cl
1	2,3-Dimethyl-4-chlorophenyl *N*-methyl	138–140	6.6	16.6	6.8	16.6
2	2,5-Dimethyl-4-chlorophenyl *N*-methyl	124–126	6.6	16.6	6.7	16.5
3	2,6-Dimethyl-4-chlorophenyl *N*-methyl	131–133	6.6	16.6	6.7	16.8
4	3,4-Dimethyl-6-chlorophenyl *N*-methyl	132–133	6.6	16.6	6.6	16.5
5	3-Methyl-4-isopropyl-6-chlorophenyl *N*-methyl	138/0.1 mm.	5.7	14.7	5.4	15.0
6	3,4-Dimethyl-6-chlorophenyl *N*-methyl	96–97	6.1	16.3	6.3	16.0
7	3,5-Dimethyl-4-chlorophenyl *N*-methyl	111–114	6.6	16.6	6.5	16.6
8	3-Methyl-5-ethyl-4-chlorophenyl *N*-methyl	64–66	6.1	15.5	6.0	15.7
9	3,5-Dimethyl-4-bromophenyl *N*-methyl	111–112	5.4	Br: 31.0	5.3	Br: 31.0
10	2-Chloro-3-methyl-6-isopropylphenyl *N*-methyl	90–92	5.8	14.7	6.0	14.6
11	2,4,5-Trimethylphenyl *N*-methyl	112–114	7.3	. .	7.4	. .
12	2,4-Dichloro-3,5-dimethylphenyl *N*-methyl	133–135	5.6	28.6	5.3	28.3
13	2,4-Dichloro-3-methyl-5-ethylphenyl *N*-methyl	118–119	5.3	27.0	5.3	27.1
14	2,4-Dichloro-5-methyl-3-ethylphenyl *N*-methyl	136–138	5.3	27.0	5.4	27.1
15	2,4-Dichloro-3-methyl-5-ethylphenyl *N*-ethyl	91–92	5.1	26.7	5.2	25.7
16	Pentachlorophenyl *N*-methyl	173–175	4.3	54.8	4.4	54.5
17	2,4,6-Trichloro-3,5-dimethylphenyl *N*-methyl	205–209	5.0	37.8	4.9	37.6
18	2,3,5-Trimethyl-4,6-dichlorophenyl *N*-methyl	201–204	5.3	27.1	5.3	27.2
19	1-Naphthyl *N*-methyl	. . .	. .	. .	. .	. .

Table II. Biological Activity of Alkyl- and Halo-phenyl–Substituted Carbamates

(% kill of test species)

Compound No.	500 P.P.M. Housefly	Southern armyworm	Mexican bean beetle	Pea aphid	*T. atlanticus* mite	1000 P.P.M., *P. citri* mite
1	33	0	100	0	0	0
2	33	35	98	0	8	0
3	0	0	0	0	0	0
4	100	100	100	90	94	100
5	100	0	100	0	24	. .
6	70	0	85	15	0	0
7	95	0	98	5	20	2
8	97	0	100	0	20	58
9	96	30	100	0	0	0
10	0	0	0	0	0	0
11	100	0	100	0	0	. .
12	100	50	100	80	40	90
13	100	0	100	0	34	100
14	45	0	55	0	0	0
15	50	0	100	0	0	0
16	0	0	0	0	0	0
17	17	0	40	0	0	0
18	0	0	0	0	0	0
19	95	35	100	60	0	0

differences in activity caused by changing from 3-methyl to 3-ethyl or from 4-chloro- to 4-bromo- substitution. Very little change in activity was noted.

Compounds 12, 13, 14, and 15 are examples of tetra-substituted phenylcarbamates and were of interest because of the insecticidal properties of compounds 12 and 13. Again, minor changes in structure—e.g., 14 and 15—adversely affected the over-all activity. We concluded from the foregoing discussion that simple relationships among the number, orientation, and variety of alkyl- and halo-substitution in the phenyl carbamic esters and their biological activity are not immediately evident.

However, compound 4 has been used in field studies and is of promise in many areas. The compound was tested under the code U-12,927, and has the tradename Banol, trivial name carbanolate. Field control of several cotton insects, some mite species, and several beetle, mosquito, and lepidopterous larvae species has been demonstrated; details will be published separately.

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CARBAMATE INSECTICIDES

Alkyl- and Amino-Substituted Phenyl *N*-Methylcarbamate Insecticides

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A new series of phenyl-*N*-methylcarbamates has been prepared which contains various combinations of alkyl and alkylamino groups attached to the aromatic ring. Outstanding insecticidal activity has been found in screening tests with Mexican bean beetles and Southern armyworms with derivatives containing the basic group in the para position and the alkyl groups in the meta position.

THE alkaloid physostigimine (eserine) has long been known to display a complex spectrum of biological activity. The fact that the parent substance eseroline (which is lacking the *N*-methylcarbamate fragment) is biologically inert has led to the study of a large variety of aromatic esters of methylcarbamic acid.

In a series of esters derived from aminophenols and either *N*-methyl or *N*,*N*-dimethylcarbamic acid, Stedman (*18*) observed that a *tert*-amino group ortho, or a quaternary group meta to the phenolic oxygen led to maximum potency as a miotic agent. Subsequently several large series of similar esters were prepared and evaluated (*6*, *19*) to demonstrate relationships between structure and mammalian toxicity. In a study of aromatic *N*-methylcarbamates containing a variety of types of (nonbasic) substituents, Kolbezen, Metcalf, and Fukuto (*11*) demonstrated that both the identity and location of the substituent had a profound effect on its toxicity toward the housefly, *Musca domestica* L., and greenhouse thrip, *Heliothrips haemorrhoidalis* (Bouche). They reported the *N*-methylcarbamate of *m*-*tert*-butylphenol to be the most active insecticide within the series studied. Very few carbamates have been reported, however, which display both basic and alkyl groups in the aromatic ring (*13*).

Through the development of a process in these laboratories for the conversion of benzoic acids to phenols (*7*, *8*), large samples of isomerically pure *m*-*tert*-butylphenol were available. This allowed verification of the observations concerning the *N*-methylcarbamate of *m*-*tert*-butylphenol, and these studies were extended to include nitrogen-containing analogs.