and only one sample of 2,4-D contained measurable amounts of the hexa isomers. The hexa isomers present presumably were there because of tetrachlorophenol impurities which condensed with each other. Higher dioxins were found in some samples of several other pesticides, including erbon, tetradifon, ronnel, sesone, and DMPA.

The dioxin content of the 20 chlorophenol samples is also presented in Table III. No TCDD was detected in any sample at levels above 0.5 ppm. However, the higher dioxins were plentiful. Trichlorophenol contained only small amounts of hexachlorodibenzo-*p*-dioxin and no sample contained over 10 ppm. Tetrachlorophenol contained less than 100 ppm of hexa-, hepta-, and octachlorodibenzo-*p*-dioxins, while six of 20 pentachlorophenol samples contained over 100 ppm of the hepta- and octachlorodibenzo-*p*-dioxin isomers. An infrared spectrum of a pentachlorophenol extract is presented in Figure 2. It is quite obvious that the extract contains octachlorodibenzo-*p*-dioxin when the spectrum is compared to the standard octachlorodibenzo-*p*-dioxin spectrum. Analysis by ec–gc indicated both hepta- and octachlorodioxins were present in the sample. This may account for the peak broadening. The reason for the high amounts of dioxin in chlorophenol is probably due to heat treatment during synthesis. As chlorination of phenol proceeds past the dichlorophenol stage, heat must be supplied in order to keep the reaction mixture in a melt condition. Since heat is being supplied in the presence of chlorophenols, the formation of higher chlorinated dibenzo-*p*-dioxins might be expected. The rate and time of melt heating probably governs the formation and amounts of the various dioxin isomers. If the chlorination temperature is raised too high too quickly, the lower chlorinated dioxins may be formed since the lower chlorophenols would be present and available for reaction with each other. If the temperature is raised too high after nearly all chlorophenol is in the penta form, octachlorodibenzo-*p*-dioxin would be the predominant impurity formed.

In conclusion, TCDD has been present at levels above 0.5 ppm in the past, but was less than 0.5 ppm in the current production samples examined. Higher chlorodioxins are present predominantly in chlorophenols with the highest amounts present in pentachlorophenol. Thirty-eight percent of all samples examined contained at least one chlorodioxin, with many containing more than one.

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The Insecticidal and the Anticholinesterase Activity of *meta*-Acylamidophenyl and *meta*-Thioureidophenyl *N*-Methylcarbamates

R. M. Sacher* and J. F. Olin

Fifty-nine new *N*-methyl and *N,N*-dimethylcarbamates were synthesized and tested as insecticides and as inhibitors of fly and bovine cholinesterases. In spite of the high anticholinesterase activity exhibited by many of these compounds, only few chemicals have shown insecticidal activity. Furthermore, these compounds could not be synergized effectively by 2,3-methylenedioxynaphthalene. Structure–activity correlation revealed that maximal anticholinesterase activity is associated with a definite size of the alkyl substituent on the amide or the thiourea grouping. In all series tested, alkyl substituent with four to six carbon atoms produced the most potent cholinesterase inhibitors.

The insecticidal properties of *N*-methyl and *N,N*-dimethylcarbamic esters of various alcohols and phenols have been demonstrated by several investigators (Gysin, 1954; Kolbezen *et al.*, 1954). A systematic evaluation of the structure–activity correlation of various aromatic carbamates was published in a series of papers by Metcalf, Fukuto, and coworkers (*e.g.*, Metcalf *et al.*, 1960, 1962; Metcalf and Fukuto, 1965). This paper presents a discussion of two new groups of insecticidal carbamates, the *meta*-acylamidophenyl and the *meta*-thioureidophenyl *N*-methylcarbamates.

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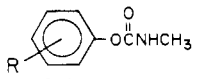
MATERIALS AND METHODS

Chemicals. The *meta*-acylamidophenyl *N*-methylcarbamates were prepared according to Leuckart (1890) by heating the corresponding *meta*-hydroxyacylanilide with methyl isocyanate. Anhydrous alcohol-free ethyl acetate was substituted for toluene as solvent, and triethylamine was used as a catalyst.

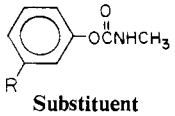
The *meta*-thioureidophenyl *N*-methylcarbamates were prepared *via meta*-hydroxyphenyl isothiocyanate; the latter was synthesized by the procedure of Dyson and George (1924). It is noteworthy that this hydroxyphenyl isothiocyanate reacts exothermically with methyl isocyanate in the absence of a catalyst, a behavior which had not been previously noted with nonalkaline phenols.

Table I. Physical Properties and Biological Activity of Some Substituted Phenyl *N*-Methylcarbamates



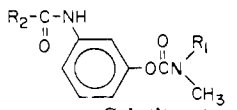
	Substituent	mp °C	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	I_{50} M fly ChE	I_{50} M bovine ChE	Topical LD_{50} μg/♀ fly: Alone	Topical LD_{50} μg/♀ fly: 1:1 synergist
I	*o*-NHCCH$_3$	176–7	57.7	5.8	13.5	57.9	5.9	13.6	5×10^{-5}	4×10^{-4}	>20	>20
II	*m*-NHCCH$_3$	159–61	57.7	5.8	13.5	57.8	5.9	13.6	6×10^{-6}	4×10^{-4}	10	7
III	*p*-NHCCH$_3$	183–5	57.7	5.8	13.5	57.9	6.0	13.4	6×10^{-5}	$>5 \times 10^{-4}$	>20	>20
IV	*o*-NHCC$_2$H$_5$	146–8	59.5	6.4	12.6	59.5	6.5	12.5	1.5×10^{-5}	$>5 \times 10^{-4}$	>20	>20
V	*m*-NHCC$_2$H$_5$	155–6	59.5	6.4	12.6	59.5	6.4	12.5	2×10^{-6}	3×10^{-4}	4	2
VI	*p*-NHCC$_2$H$_5$	160–1	59.5	6.4	12.6	59.7	6.4	12.6	5×10^{-5}	3×10^{-4}	>20	20

Table II. Physical Properties and Biological Activity of *meta*-Acylamidophenyl *N*-Methylcarbamates



	Substituent	mp °C	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	I_{50} M fly ChE	I_{50} M bovine ChE	Topical LD_{50} μg/♀ fly: Alone	Topical LD_{50} μg/♀ fly: 1:1 synergist
VII	H—C—NH—	101–3	55.7	5.2	14.4	55.9	5.4	14.7	7×10^{-6}	9×10^{-4}	7	3
II	CH$_3$—C—NH—	159–61	57.7	5.8	13.5	57.8	5.9	13.6	6×10^{-6}	4×10^{-4}	10	7
V	C$_2$H$_5$—C—NH—	155–6	59.5	6.4	12.6	59.5	6.4	12.5	2×10^{-6}	3×10^{-4}	4	2
VIII	C$_3$H$_7$—C—NH—	151–3	61.0	6.8	11.9	60.9	6.7	11.7	1.2×10^{-6}	1.3×10^{-4}	6	5
IX	C$_4$H$_9$—C—NH—	144–5	62.4	7.3	11.2	62.2	7.2	11.1	1.3×10^{-6}	1.2×10^{-4}	>20	>20
X	C$_5$H$_{11}$—C—NH—	139–40	63.6	7.6	10.6	63.7	7.8	10.8	1.5×10^{-6}	1.1×10^{-4}	>20	>20
XI	C$_6$H$_{13}$—C—NH—	123–4	64.7	7.9	10.1	64.8	7.7	9.9	1.8×10^{-6}	5×10^{-4}	>20	>20
XII	C$_7$H$_{15}$—C—NH—	123–4	65.8	8.3	9.6	65.9	8.4	9.7	2×10^{-6}	7×10^{-4}	>20	>20
XIII	C$_8$H$_{17}$—C—NH—	123–4	66.6	8.5	9.1	66.5	8.5	9.3	3×10^{-6}	$>1 \times 10^{-3}$	>20	>20
XIV	C$_9$H$_{19}$—C—NH—	125–6	67.3	8.8	8.7	67.6	8.9	8.6	7×10^{-6}	$>1 \times 10^{-3}$	>20	>20
XV	C$_{10}$H$_{21}$—C—NH—	125–6	68.2	9.0	8.4	68.4	9.1	8.3	1×10^{-5}	$>1 \times 10^{-3}$	>20	>20
XVI	C$_{11}$H$_{23}$—C—NH—	125–6	68.8	9.3	8.0	69.1	9.5	8.0	2.8×10^{-5}	$>1 \times 10^{-3}$	>20	>20
XVII	C$_{12}$H$_{25}$—C—NH—	125–6	69.5	9.4	7.7	69.8	9.5	7.7	1×10^{-4}	$>1 \times 10^{-3}$	>20	>20

Table III. Physical Properties and Biological Activities of Some *meta*-Substituted Branched Acylamidophenyl *N*-Methyl and *N,N*-Dimethylcarbamates



	Substituent			Calculated			Found			I_{50} M	I_{50} M	Topical LD_{50} μg/♀ fly	
	R_1	R_2	mp °C	C	H	N	C	H	N	fly ChE	bovine ChE	Alone	1:1 synergist
XVIII	H	$CH(CH_3)_2$	157–9	61.0	6.8	11.9	60.9	6.8	11.7	5×10^{-6}	1×10^{-4}	20	10
XIX	CH_3		120–2	62.4	7.3	11.2	62.2	7.4	11.3	1.5×10^{-4}	$>1 \times 10^{-4}$	>20	20
XX	H	CHC_2H_5 | CH_3	160–1	62.4	7.3	11.2	62.4	7.3	11.3	2×10^{-6}	1×10^{-4}	>20	>20
XXI	H	$C(CH_3)_3$	177–8	62.4	7.3	11.2	62.4	7.1	11.1	5×10^{-6}	1×10^{-4}	>20	15
XXII	CH_3		110–13	63.6	7.6	10.6	63.8	7.7	10.5	1.2×10^{-4}	$>1 \times 10^{-4}$	20	10
XXIII	H	CHC_3H_7 | CH_3	145–6	63.6	7.6	10.6	63.8	7.7	10.6	9×10^{-7}	2×10^{-4}	>20	>20
XXIV	CH_3	CH_3	Viscous syrup	64.8	8.0	10.1	64.5	7.9	9.9	4×10^{-5}	$>1 \times 10^{-4}$	>20	15
XXV	H	CH_3 | $C—C_3H_7$ | CH_3	150–1	64.8	8.0	10.1	64.9	8.0	10.1	4×10^{-7}	1×10^{-4}	20	4
XXVI	CH_3	CH_3	62–3	65.8	8.3	9.6	65.6	8.2	9.4	1.3×10^{-5}	$>1 \times 10^{-4}$	15	7
XXVII	H	CH_3 | $C—CH_2CH(CH_3)_2$ | CH_3	159–60	65.8	8.3	9.6	65.5	8.3	9.5	5×10^{-7}	1×10^{-4}	>20	20
XXVIII	CH_3	CH_3	82–3	66.6	8.6	9.1	66.6	8.6	9.0	1×10^{-5}	$>5 \times 10^{-4}$	>20	15

The physical properties and the analytical data for these chemicals are given in Tables I–VI.

Cholinesterase Determinations. Cholinesterase determinations were done according to Winter (1960) utilizing a Technicon Autoanalyzer. Since all compounds tested were carbamates, the bromine oxidation step, which is required for phosphorothioates, was omitted as unnecessary. Incubation time of the cholinesterase with the various carbamates was kept constant at 12 min. The I_{50} values, the molar concentration giving 50% inhibition of the enzyme under the test condition, was estimated graphically by using from three to five inhibition measurements around this point. The I_{50} values reported are the average of at least two separate determinations. Where a (>) "greater than" estimate is given, little or no inhibition was observed in the highest concentration tested.

Whole fly homogenates were used to prepare the fly cholinesterase by a method previously described by Darlington *et al.* (1971). Bovine erythrocyte cholinesterase was purchased from Sigma Chemical Co., St. Louis, Mo. For assay the bovine enzyme was diluted to a concentration of 2.5 micromolar units per ml.

Bioassay. Two-day-old susceptible female houseflies (*Musca domestica* L, S_{NAIDM} strain) were utilized for the fly toxicity measurements. One-microliter acetone solutions of the chemicals were applied topically to the thoraces of the flies with the aid of a microsyringe. Treated insects were provided with sugar solution and held in a 26°C, 70% R.H. box for 24 hr. Each dosage was replicated on 3 different days, the average percent mortalities were plotted on a log-probit paper, and the dosage–mortalities regression lines were fitted visually.

For synergism studies flies were treated as above with carbamate-2,3-methylenedioxynaphthalene combinations at 1:1 ratio (w/w). The latter was chosen because of its exceptional synergistic activity with a great variety of carbamates (Metcalf *et al.*, 1966).

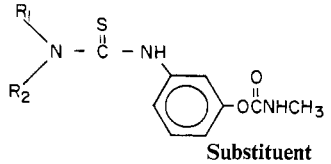
RESULTS AND DISCUSSION

Anticholinesterase Activity. The molar concentration for 50% inhibition of whole fly homogenate and bovine erythrocyte cholinesterases (I_{50}) are given in Tables I–VI.

Table I demonstrates the importance of position isomerism in the acetanilides (Compounds I–III) and the propionanilide (IV–VI) derivatives. Stedman (1926) and Kolbezen *et al.* (1954) found that in simple substituted phenyl *N*-methylcarbamates, meta-substituted compounds were the most active followed closely by ortho isomers while the para isomers were much less active. Subsequently Metcalf *et al.* (1960, 1962) have shown that for alkoxyphenyl, *N,N*-dimethylaminophenyl, and halophenyl *N*-mehylcarbamates the ortho-substituted compounds were the most active cholinesterase inhibitors. From the data in Table I it is evident that meta substituents are the most effective inhibitors in the acylamidophenyl series.

A systematic evaluation of the anticholinesterase activity of a homolog series of *meta*-acylamidophenyl *N*-methylcarbamates is shown in Table II. From the cholinesterase inhibition data, as well as from the corresponding curve in

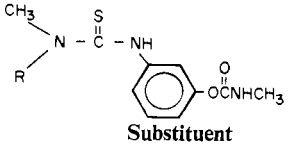
Table IV. Physical Properties and Biological Activities of *meta*-Substituted Mono and Dialkylthioureidophenyl *N*-Methylcarbamates



	Substituent			Calculated		Found				Topical LD_{50} μg/♀ fly	
	R_1	R_2	mp °C	N	S	N	S	I_{50} M fly ChE	I_{50} M bovine ChE	Alone	1:1 synergist
XXIX	H	CH_3	144–5	17.6	13.4	17.4	13.6	1×10^{-6}	1×10^{-5}	>10	>5
XXX	H	C_2H_5	125–7	16.6	12.7	16.6	13.0	7×10^{-7}	5×10^{-6}	>10	>5
XXI	H	$CH(CH_3)_2$	130–2	15.7	12.0	15.8	12.2	4×10^{-7}	2.3×10^{-5}		
XXXII	H	$CH(CH_3)CH_2CH_3$	151–2	14.9	11.4	15.1	11.5	1.2×10^{-7}	4×10^{-6}		
XXXIII	H	$C(CH_3)_3$	145–6.5	14.9	11.4	15.1	11.4	1.3×10^{-7}	4×10^{-6}		
XXXIV	H	$C(CH_3)_2CH_2CH_3$	143–4(d)	14.2	10.9	14.3	10.8	5×10^{-8}	5×10^{-7}	>10	>5
XXXV	H	$CH(CH_3)CH_2CH(CH_3)_2$	142–3	13.6	10.4	13.8	10.4	4×10^{-8}	1.2×10^{-6}	>10	>5
XXXVI	H	$C(CH_3)_2CH_2C(CH_3)_3$	140–1	12.5	9.5	12.6	9.7	4.5×10^{-8}	6×10^{-6}		
XXXVII	H	$CH_2CH(CH_2)_3CH_3$ C_2H_5	113–4	12.5	9.5	12.7	9.7	1.7×10^{-8}	1×10^{-6}		
XXXVIII	H	$CH_2CH{=}CH_2$	108–9	15.8	5.7	15.7	5.6	8×10^{-8}	1×10^{-6}		
XXXIX	CH_3	CH_3	151–2	16.6	12.7	16.5	12.9	1.2×10^{-7}	7×10^{-7}	>10	>5
XL	C_2H_5	C_2H_5	131–2	14.9	*a*	14.9	*b*	1.5×10^{-7}	5×10^{-6}	>10	>5
XLI	C_3H_7	C_3H_7	124–5	13.6	10.4	13.7	10.5	6×10^{-8}	1×10^{-6}		
XLII	C_4H_9	C_4H_9	107–8	12.5	9.5	12.5	9.5	6×10^{-8}	1×10^{-6}	>10	>5
XLIII	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	128–9	12.5	9.5	12.4	9.6	1.7×10^{-7}	8×10^{-7}		
XLIV	C_6H_{13}	C_6H_{13}	Straw-colored syrup	10.7	8.1	11.0	8.2	1.5×10^{-6}	5×10^{-4}		
XLV	C_8H_{17}	C_8H_{17}	Straw-colored syrup	9.3	7.1	9.3	7.4	1.0×10^{-5}	$>5 \times 10^{-4}$		

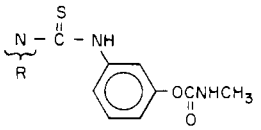
[a] Calcd: C, 55.5; H, 6.8. [b] Found: C, 55.5; H, 6.9.

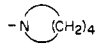
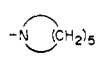
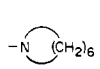
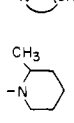
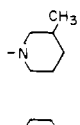
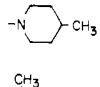
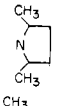
Table V. Physical Properties and Biological Activities of *meta*-Substituted *N'*-Methyl-*N'*-alkylthioureidophenyl *N*-Methylcarbamate



	Substituent	mp °C	Calculated		Found		I_{50} M fly ChE	I_{50} M bovine ChE	Topical LD_{50} μg/♀ fly	
			N	S	N	S			Alone	1:1 synergist
XXXIX	CH_3	151–2	16.6	12.7	16.5	12.9	1.2×10^{-7}	7×10^{-7}	>10	>5
XLV	$CH_2CH{=}CH_2$	134–5	15.0	11.5	15.3	11.5	1.0×10^{-7}	1.1×10^{-5}		
XLVII	C_4H_9	104–6	14.2	10.9	14.3	11.0	2.3×10^{-8}	2×10^{-6}	>10	>5
XLVIII	C_5H_{11}	117–8	13.6	10.4	13.4	10.1	2.1×10^{-8}	9×10^{-7}	>10	>5
XLIX	C_8H_{17}	120–1	12.0	9.1	11.7	9.0	9×10^{-8}	1.2×10^{-6}		
L	$C_{18}H_{37}$	122–3	8.5	6.5	8.3	6.6	2×10^{-5}	$>5 \times 10^{-4}$		

Table VI. Physical Properties and Biological Activities of *meta*-Cyclic Aminothiocarboxylate Derivatives of *N*-Methylcarbamates



	Substituent R	mp °C	Calculated N	Calculated S	Found N	Found S	I_{50} M fly ChE	I_{50} M bovine ChE	Topical LD_{50} μg/♀ fly: Alone	Topical LD_{50} μg/♀ fly: 1:1 synergist
LI		175–6	15.0	11.5	15.1	11.4	3×10^{-8}	5×10^{-5}	>10	>5
LII		154–5	14.3	*a*	14.5	*b*	5×10^{-8}	4×10^{-6}	>10	>5
LIII		167–8	13.7	10.4	13.6	10.3	5×10^{-8}	4×10^{-6}	>10	>5
LIV		165–7	13.1	10.0	13.2	10.0	3.2×10^{-8}	2.7×10^{-6}	>10	>5
LV		144–5	13.7	10.4	13.7	10.4	6×10^{-8}	1×10^{-5}		
LVI		135–6	13.7	10.4	13.7	10.5	3×10^{-8}	8×10^{-6}	>10	>5
LVII		148–9	13.7	10.4	13.7	10.2	3×10^{-8}	3×10^{-5}		
LVIII		127–8	13.7	10.4	13.7	10.6	6×10^{-7}	2.5×10^{-5}	>10	>5
LIX		112–3	13.1	10.0	13.2	10.2	5×10^{-6}	$>1 \times 10^{-4}$		

[a] Calcd: C, 57.3; H, 6.5. [b] Found: C, 57.5; H, 6.6.

Figure 1, it was determined that the optimal chain length for maximal anticholinesterase activity in this series is four carbons. Metcalf *et al.* (1962) noted a gradual increase in relative affinity for cholinesterase, with an increase in the number of methyl groups in the *meta*-alkyl and *ortho*-alkoxyphenyl *N*-methylcarbamate derivatives. However, they did not increase this number beyond three carbons. Table III summarizes the activity of some branched acylamidophenyl carbamates. These compounds have shown a substantial increase in the anticholinesterase activity as compared to the normal alkyl counterparts. This is consistent with data reported by Kolbezen *et al.* (1954) on the superior anticholinesterase activity of isopropyl *vs.* propyl and *sec*-butyl *vs. n*-butyl phenyl *N*-methylcarbamates, respectively. Figure 1 suggests that the optimum number of carbons in the branched side chain has been shifted from four to six; however, even in this series the main carbon skeleton of this side chain is approximately four carbon atoms long at its optimum.

The comparison between mono- and dimethylcarbamates in Table III shows, as expected, that simple phenyl *N*-methylcarbamates are between 20 and 45 times more effective than their *N*,*N*-dimethyl counterparts (XXIII *vs.* XXIV and XXVII *vs.* XXVIII, respectively).

Tables IV, V, and VI summarize the activity of *meta*-thioureidophenyl *N*-methylcarbamates. These derivatives are among the most potent carbamates ever evaluated as anticholinesterase inhibitiors. Figure 1 shows the correlation between the variation in the alkyl substituents on the thiourea group and the anticholinesterase activity. There is striking similarity in these correlations between these chemicals and the previously discussed acylamido derivatives. It is interesting to note that the optimal side chain length did not change appreciably in a variety of chemical structures even though as much as 60-fold difference in activity was noted between the different series. Again, the four carbons and the six carbons gave the best cholinesterase inhibition in the normal and branched alkyl derivatives, respectively.

Of special interest are the pyrrolidine, piperidine, and the higher cyclic aminothiocarboxylate derivatives (Compounds LI–LIX, Table VI). These compounds were found to be more active than the corresponding dialkyl-substituted thioureas (*e.g.*, LI *vs.* XL and LII *vs.* XLI). Monomethyl substitution on the piperidinethiocarboxylates (LV, LVI, and LVII) did not alter greatly the anticholinesterase activity; however, dimethyl substitution in the pyrrolidine (LVIII) and in the piperidine (LIX) decreased the fly cholinesterase inhibition by 50- and 100-fold, respectively.

The inhibition of bovine erythrocyte cholinesterase followed

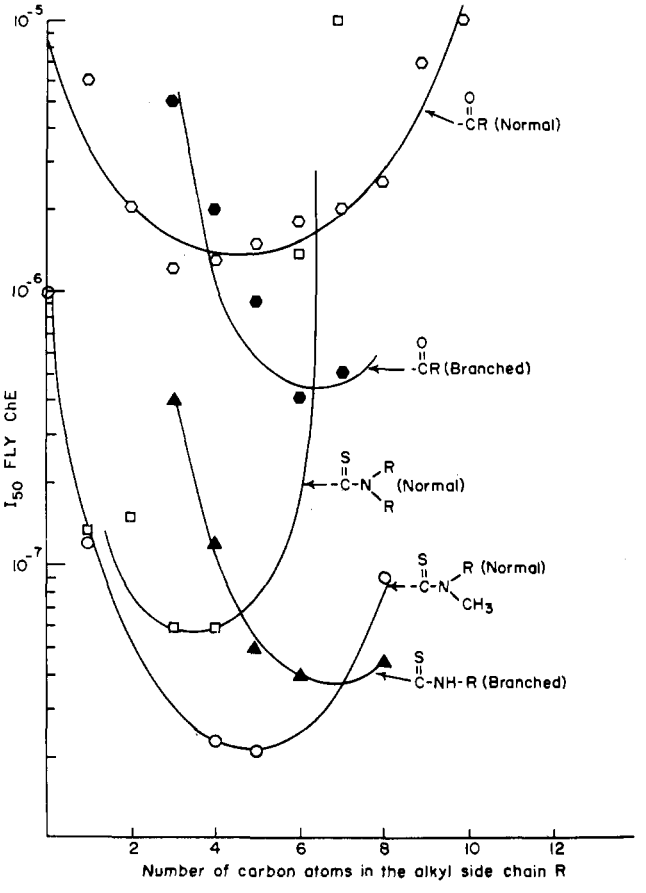


Figure 1. Correlation between structure and anticholinesterase activity for five series of meta-substituted acylamido and thioureidophenyl *N*-methylcarbamates, m-$C_6H_4(OOCNHCH_3)(NHC(=X)Y)$

the same general pattern of the fly enzyme inhibition. However, because of the overall weak anticholinesterase activity against the bovine enzyme, the structure–activity correlations were not as obvious as with the housefly enzyme. Most compounds were between 10- and 800-fold less effective against the bovine cholinesterase. Notable was Compound LI (Table VI), which has shown a selectivity ratio of 1700!

This enzyme selectivity might be a very important factor when searching for a selective organophosphate or carbamate insecticide.

The changes in the alkyl moiety in all the series discussed did not result in large variations in the Hammett substituent (σ) constant. Therefore, differences in the inhibition power of members of a homolog series can be attributed to their relative affinity to the "anionic site" of cholinesterase or their relative "fit" to the enzyme surface.

Insecticidal Activity. In spite of the good anticholinesterase activity of the *meta*-acylamidophenyl and the *meta*-thioureidophenyl *N*-methylcarbamates, most of these compounds were not highly effective as housefly insecticides. Activity (last two columns in Tables I–VI) seems to be sporadic with no apparent pattern, making it difficult to correlate it with structural requirements.

Even at the high doses of 10 and 20 μg/♀ (500 and 1000 μg/g, respectively), only 20% of the chemicals have shown appreciable activity. Furthermore, attempts to synergize these chemicals with 2,3-methylenedioxynaphthalene did not improve their performance in most cases. The inability to enhance the insecticidal activity of these chemicals with a synergist suggests that oxidative metabolism does not play a major role in their detoxification. Other factors that might be responsible for their inactivity are slow rates of penetration, chemical instability, nonoxidative detoxification, or internal adsorption. No evidence to support these alternatives is available at this time.

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