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Selective Toxicity of *N,N'*-Thiodicarbamates

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A series of *N*-(alkyl alkylcarbamylosulfenyl) derivatives of methylcarbamate insecticides were prepared and examined for toxicity to house flies, mosquito larvae, and white mice. Compared to the parent methylcarbamate, the derivatives were generally of equal toxicity to the house fly, substantially more toxic to mosquito larvae, and much less toxic to mice. Toxicities to mosquito larvae and white mice were related to octanol–water partition coefficients.

In a previous paper from this laboratory, we described the favorable toxicological properties of a series of N-substituted biscarbamoyl sulfides (Fahmy et al., 1974). These biscarbamoyl sulfide derivatives of methylcarbamate insecticides still retained the good insecticidal activity of the parent methylcarbamate but were substantially less toxic to the white mouse. Based on an earlier study (Black et al., 1973a) of the comparative metabolism in the white mouse and house fly of a related sulfenylated derivative, *N*-(2-toluenesulfenyl)carbofuran, the selective toxicity of the biscarbamoyl sulfides was attributed to differences in rates and routes of metabolism in insects and mammals. High toxicity to insects was ascribed to an activation process which occurred primarily in insects, resulting in the liberation of the toxic methylcarbamate in vivo; low toxicity to the mouse was attributed to preferential degradation of the carbamate ester linkage, possibly by carboxylesterase action, to the nontoxic phenols.

Because of the desired order of selectivity demonstrated by the biscarbamoyl sulfides, it was of interest to examine other derivatives of this type for selective toxicity. This report is concerned with the synthesis and toxicological properties of a series of unsymmetrical *N,N'*-thiodicarbamate derivatives of the general structure I where Ar

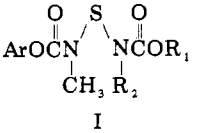

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Table I. Physical Properties of Aliphatic Carbamates and Their *N*-Chlorosulfenyl Derivatives

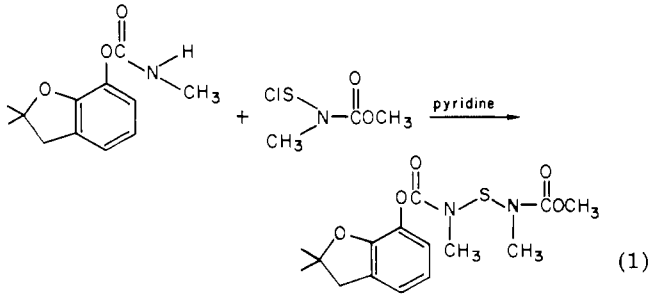
	ROC(O)NHR'				ROC(O)N(R')SCl	
No.	R	R'	Bp/mm or mp, °C	$n^{25}D$	Bp/mm, °C	$n^{25}D$
1	CH_3	CH_3	106/100	1.4158	68-70/9	1.5038
2	CH_3	C_2H_5	78/20	1.4194	52-4/2.8	1.4920
3	C_2H_5	CH_3	72/20	1.4170	54/2.5	1.4782
4	C_2H_5	C_2H_5	74-6/11.5	1.4213	82-4/10	1.4810
5	C_2H_5	$CH(CH_3)_2$	69-70/8.5	1.4220	62-5/3.5	1.4735
6	C_3H_7	CH_3	80/11.5	1.4222	60/1.4	1.4821
7	$CH(CH_3)_2$	CH_3	62-4/7	1.4168	64/5	1.4738
8	$CH(CH_3)_2$	C_2H_5	58-60/2.0	1.4189	44-6/1.25	1.4706
9	C_4H_9	CH_3	65-8/1.8	1.4264	82-4/3	1.4800
10	C_5H_{11}	CH_3	80/2.5	1.4310	76-8/1.0	1.4780
11	C_6H_{13}	C_2H_5	96-8/1.5	1.4346	82-4/.35	1.4731
12	C_7H_{15}	CH_3	74-6/0.1	1.4370	85-6/0.15	1.4752
13	C_8H_{17}	CH_3	75-6/0.05	1.4400	92-5/0.05	1.4750
14	$C_{10}H_{21}$	CH_3	43-44		124-6/0.05	1.4737

is the phenolic moiety of carbofuran, propoxur, carbaryl, *m*-isopropylphenyl methylcarbamate, or oxime of aldicarb, methomyl, and oxamyl, and R_1 and R_2 are aliphatic groups.

MATERIALS AND METHODS

Insecticidal methylcarbamates, carbofuran, propoxur, carbaryl, aldicarb, methomyl, and oxamyl were obtained from their respective manufacturers as technical materials and were purified further by recrystallization from appropriate solvents. *m*-Isopropylphenyl methylcarbamate (MIP) was synthesized from the corresponding phenol and methyl isocyanate. Aliphatic carbamates were prepared in conventional manner by reaction between the appropriate alcohol and alkyl isocyanate or alkyl chloroformate and alkylamine. *N*-Sulfenyl chlorides of alkyl alkylcarbamates [alkyl alkyl(chlorosulfenyl)carbamate] were prepared according to Brown and Kohn (1974) by reaction between the aliphatic carbamate and sulfur dichloride in dichloromethane, using pyridine as the acid acceptor. Boiling or melting points and refractive indices for the various aliphatic carbamates and corresponding sulfenyl chlorides are given in Table I. Compared to aryl- and alkylsulfenyl chlorides the sulfenyl chlorides of aliphatic carbamates were relatively stable compounds and could be stored at room temperature for several months without appreciable decomposition or disproportionation.

Synthesis of *N,N'*-Thiodicarbamates. These derivatives of insecticidal methylcarbamates were synthesized by the reaction between the methylcarbamate and alkyl alkyl(chlorosulfenyl)carbamate in pyridine according to a previously described procedure for the synthesis of arylsulfenylcarbamates (Black et al., 1973b). The following procedure for the synthesis of 2,3-dihydro-2,2-dimethylbenzofuranyl-7 *N*-(methyl methylcarbamylosulfenyl)-*N*-methylcarbamate (**1**) according to eq 1 is typical. To a



(1)

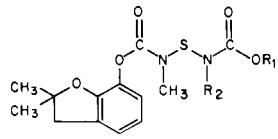
mixture of 11 g (0.05 mol) of 2,3-dihydro-2,2-dimethylbenzofuranyl-7 methylcarbamate (carbofuran) and 30 mL of anhydrous pyridine, chilled to 5 °C, was added in one portion 9.0 g (0.058 mol) of methyl chlorosulfenyl(methyl)carbamate. Pyridine hydrochloride separated within a few minutes after addition. The mixture was allowed to stand overnight at room temperature and poured into water, and the product was extracted into ether. The ether extract was washed with cold 5% hydrochloric acid, water, dried over anhydrous sodium sulfate, and distilled, bp 178–180 °C (0.1 mm), yield 10.5 g (62%). The product was purified further by recrystallization from aqueous ethanol, mp 45–47 °C. ^1H NMR spectrum showed the following absorptions (chloroform-*d*, Me_4Si): δ 6.7–7.4 (m, 3 H, aromatic protons), 3.8 (s, 3 H, OCH_3), 3.5 (s, 6 H, two NCH_3), 3.0 (s, 2 H, CH_2), 1.4 (s, 6 H, *gem*-di-CH_3).

In most cases, the two NCH_3 protons appeared as one singlet of 6 H. However, in a few cases small differences in absorptions (2–7 Hz) between the two N-CH_3 protons were observed (compounds **9**, **16**, **17**, **18**, and **19–24**). Melting or boiling points and elemental analyses for all compounds are presented in Table II. ^1H NMR spectra were obtained with a Varian T-60 spectrometer using chloroform-*d* and Me_4Si.

A modification of the above procedure was later discovered to be a more convenient method for the synthesis of the thiodicarbamates. The aryl or oxime methylcarbamate was dissolved in a minimum amount of dichloromethane (approximately 30–40 mL/0.1 mol of methylcarbamate) and slightly more than 1 equiv of anhydrous pyridine was added. This was followed by the addition of the sulfenyl chloride in an amount equivalent to the pyridine and the mixture was stirred for 12 h. Ether was added, the mixture was washed several times with water and dried over anhydrous sodium sulfate, and the product was purified as described above. This procedure avoided the use of large excesses of pyridine and the subsequent need for a hydrochloric acid wash. The latter had a detrimental effect on yield, particularly in the case of the oxime carbamates. All derivatives of MIP, methomyl, and oxamyl reported in Table II were prepared by this procedure.

Partition Coefficients. The partition coefficients (*P*) between 1-octanol and water of **1**, **13**, **19**, **25**, and **31** were determined at 23 °C. The amount of **1**, **13**, and **19** in each phase was estimated by GLC, using a Varian Aerograph 1400 chromatograph equipped with a flame ionization detector and 6 ft × 0.25 in. glass column packed with 6% OV-210 on Gas-Chrom Q. Temperatures of the injection port, column, and detector were 230, 220, and 250 °C, respectively. Flow rates of helium carrier gas, hydrogen, and air were adjusted to 70, 40, and 300 mL/min, respectively. Owing to the instability of **25** and **31** in the

Table II. Physical Properties and Elemental Analyses of *N,N'*-Thiodicarbamates



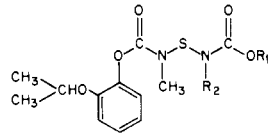
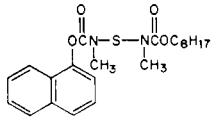
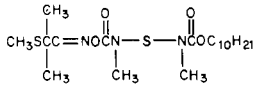
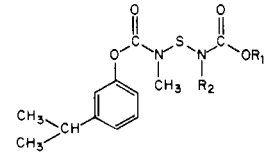
Compd	R_1	R_2	Bp/mm (mp), °C	log *P*	Analysis[a] Calcd	Found
1	CH_3	CH_3	45-47	2.28	C, 52.94 H, 5.93	53.19 6.12
2	C_2H_5	CH_3	90-93	2.78	C, 54.22 H, 6.26	54.30 5.82
3	C_3H_7	CH_3	80-82	3.28	C, 55.42 H, 6.57	55.83 6.43
4	$CH(CH_3)_2$	CH_3	83-85	3.08	C, 55.42 H, 6.57	55.75 6.30
5	C_4H_9	CH_3	178-182/0.05	3.78	S, 8.37 N, 7.32	8.75 8.09
6	C_5H_{11}	CH_3	180-184/0.05	4.28	S, 8.07 N, 7.06	8.72 7.53
7	C_7H_{15}	CH_3	192-196/0.1	5.28	S, 7.54 N, 6.60	7.85 6.94
8	C_8H_{17}	CH_3	187-190/0.01	5.78	S, 7.30 N, 7.64	6.38 6.72
9	$C_{10}H_{21}$	CH_3	220/0.05	6.78	S, 6.86 N, 6.00	6.96 5.82
10	CH_3	C_2H_5	180-182/0.07	2.78	C, 54.22 H, 6.26	55.19 6.41
11	C_2H_5	C_2H_5	176-180/0.07	3.28	C, 55.42 H, 6.57	55.53 6.80
12	C_2H_5	$CH(CH_3)_2$	157-159/0.05	3.58	S, 8.37	8.37
						
13	C_2H_5	C_2H_5	158-160/0.05	1.88	C, 53.93 H, 6.79	53.41 6.78
14	C_5H_{11}	CH_3	150-152/0.02	2.88	C, 56.23 H, 7.34	56.83 7.51
15	C_7H_{15}	CH_3	180-182/0.07	3.88	C, 58.23 H, 7.82	58.08 7.58
16	$C_{10}H_{21}$	CH_3	200-202/0.05	5.38	C, 60.77 H, 8.43	60.41 8.45
17			205-207/0.02		C, 63.14 H, 7.23	62.79 8.55
18			*b*		C, 52.40 H, 8.33	53.45 8.03
						
19	CH_3	CH_3	148-150/0.15	1.49	C, 53.82 H, 6.45	54.31 6.47
20	C_3H_7	CH_3	158-160/0.15	2.49	C, 56.40 H, 7.05	57.38 7.36
21	$CH(CH_3)_2$	CH_3	158-160/0.15	2.29	C, 56.40 H, 7.05	56.42 7.22
22	$CH(CH_3)_2$	C_2H_5	154-156/0.2	2.79	C, 57.56 H, 7.34	57.32 7.15
23	C_4H_9	CH_3	164-166/0.2	2.99	C, 57.56 H, 7.34	57.34 7.20

Table II. (*Continued*)

Compd	R_1	R_2	Bp/mm (mp), °C	log *P*	Analysis[a] Calcd	Found
24	C_7H_{15}	CH_3	175-177/0.1	4.49	C, 60.57 H, 8.14	59.70 8.67
25	CH_3	CH_3	80-2	0.26	C, 34.15 H, 5.37	34.48 5.20
26	C_2H_5	CH_3	69-72	0.76	C, 36.59 H, 5.80	36.62 5.64
27	C_3H_7	CH_3	74-6	1.26	C, 38.82 H, 6.19	39.17 5.98
28	$CH(CH_3)_2$	CH_3	65-7	1.06	C, 38.82 H, 6.19	39.12 6.28
29	$CH(CH_3)_2$	C_2H_5	83-4	1.56	C, 40.85 H, 6.55	41.21 6.58
30	C_6H_{13}	C_2H_5	45-7	3.26	C, 46.00 H, 7.45	46.38 7.37
31	CH_3	CH_3	85-7	−0.07	C, 35.49 H, 5.36	36.26 5.49
32	C_2H_5	CH_3	86-8	0.43	C, 37.49 H, 5.72	37.84 5.84
33	$CH(CH_3)_2$	CH_3	74-6	0.73	C, 39.32 H, 6.05	39.33 6.36
34	$CH(CH_3)_2$	C_2H_5	95-7	1.23	C, 41.03 H, 6.35	42.02 6.92
35	C_6H_{13}	C_2H_5	69-72	2.93	C, 45.48 H, 7.16	46.11 7.34

[a] Elemental analyses were carried out by C. F. Geiger, Ontario, Calif. [b] Purified by preparative TLC.

GLC column, the amounts of these compounds in each phase were determined by means of UV spectrophotometry using a Beckman Model 25 spectrophotometer. Other *P* values for the homologous series of **1**, **13**, **19**, **25**, and **31** were calculated according to additivity principles (Fujita et al., 1964) which showed that each methylene group in a homologous series increases log *P* by about 0.5. Thus, log *P* for **2** is equal to log *P* for **1** plus 0.5 and so forth for all carbofuran derivatives. A branched chain near a functional group decreases log *P* by 0.2, e.g., log *P* for **4** equals log *P* for **3** minus 0.2. All values of log *P* are tabulated in Table II.

Toxicity to Insects and Mice. Insecticidal activities were determined against a susceptible (NAIDM) strain of house flies, *Musca domestica*, and fourth instar mosquito larvae, *Culex pipiens quinquefasciatus*, according to usual procedures (March and Metcalf, 1949; Georghiou et al., 1966). Because of the high lipophilicity of some of the compounds and possible absorption in the wax layer, toxicity tests to mosquito larvae were carried out in glass beakers instead of waxed paper cups. Piperonyl butoxide synergized toxicity to house flies was determined by applying a constant dose of 200 μg/g of piperonyl butoxide prior to application of the test compound. Mammalian toxicity was determined orally on Swiss white mice using corn oil as the carrier according to usual procedure (Hollingworth et al., 1967).

RESULTS AND DISCUSSION

Data for the toxicity of the various *N,N'*-thiodicarbamates to house flies, mosquito larvae, and white mice (oral) are given in Table III. In order to account for differences in molecular weights of the compounds, toxicity data also are expressed on a mole or molar basis as well as on a weight basis, i.e., LD_{50} is given in terms of μmol/kg (mouse) and LC_{50} to mosquito larvae is given as μM solution.

Toxicity to House Flies. Examination of the house fly toxicity data, with and without piperonyl butoxide, reveals that on a mole/gram basis the toxicity of the *N,N'*-thiodicarbamates to house flies was generally equal to the toxicity of the parent methylcarbamate. For example, in the carbofuran series (**1**–**12**) toxicity ranged from 0.023 to 0.031 μmol/g and no discernible trend in toxicity was observed with change in structure. With piperonyl butoxide the LD_{50} range was 0.0017–0.0025 μmol/g. The virtually identical toxicities of these compounds with house flies was somewhat surprising owing to the large change in molecular weights (greater than twofold range) of the derivatives and commensurate change in physical properties. For example, the octanol–water partition coefficient *P* varied from 191 for **1** to 6×10^6 for **9**. The difference in hydrophobic character between **1** and **9** is undoubtedly very large, and, therefore, a large difference in the ability of these compounds to penetrate into the house fly was expected. Also, one would expect a large difference in penetration between water-soluble carbamates such as methomyl and oxamyl and their respective lipophilic derivatives, *e.g.*, **30** and **35**.

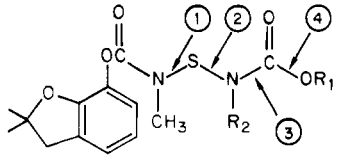
Assuming that in vivo release of the toxic parent methylcarbamate is responsible for the toxicity of the *N,N'*-thiodicarbamate, e.g., carbofuran from compounds **1**–**12**, the nearly equal toxicities observed within a homologous series suggests that nearly equal amounts of parent methylcarbamate are produced from each derivative. Further, since the toxicity of the derivatives are equal or possibly slightly greater than the parent methylcarbamate on a mole basis, it appears that conversion of the derivative to the methylcarbamate is rapid. This may be attributable to the several possible pathways in which the *N,N'*-thiodicarbamates may be cleaved to generate the toxic

Table III. Toxicity of *N,N'*-Thiodicarbamates of House Flies, Mosquito Larvae, and Mice

		House fly LD_{50}							
		Alone		+ PB		*Culex pipiens* LC_{50}		Mouse (oral) LD_{50}	
Compd	Mol wt	μg/g	μmol/g	μg/g	μmol/g	ppm	μM	mg/kg	μmol/kg
Carbofuran	221.3	6.70	0.030	0.36	0.0016	0.052	0.235	2	9
1	340.3	9.25	0.027	0.75	0.0022	0.023	0.0676	45	132
2	354.4	9.0	0.025	0.75	0.0021	0.016	0.0452	72	203
3	368.5	8.5	0.023	0.65	0.0018	0.009	0.0245	88	238
4	368.5	9.0	0.024	0.90	0.0024	0.0088	0.0239	52	141
5	382.5	10.0	0.026	0.77	0.0020	0.0043	0.0113	130	340
6	396.5	10.5	0.027	0.77	0.0019	0.0022	0.0056	140	353
7	424.6	11.0	0.026	0.95	0.0022	0.0010	0.0024	175	412
8	438.6	12.0	0.027	0.85	0.0019	0.0008	0.0019	190	433
9	466.6	14.0	0.030	1.08	0.0023	0.0012	0.0026	250	536
10	354.4	9.0	0.025	0.9	0.0025	0.0160	0.0452	62	175
11	368.5	9.25	0.025	0.77	0.0021	0.0100	0.0272	85	231
12	382.5	12.0	0.031	0.63	0.0017	0.0056	0.0147	125	327
Propoxur	209.2	24	0.115	1.15	0.0055	0.33	1.577	62	
13	356.4	37.5	0.105	2.45	0.0069	0.046	0.129	>1000	
14	384.5	35.0	0.091	1.50	0.0039	0.008	0.021	>1000	
15	412.5	44.0	0.107	1.30	0.0032	0.0008	0.002	>3000	
16	454.6	44.0	0.097	2.5	0.0055	0.009	0.020	>1000	
Carbaryl	201.2	900[a]	4.473	8.5	0.042	1.0	4.967	500[b]	
17	418.5	350	0.836	19.0	0.045	0.08	0.191	1000	
Aldicarb	190.2	5.5	0.029	0.7	0.004	0.16	0.841	0.4	2.1
18	435.5	13.0	0.030	6	0.014	0.0064	0.015	12.5	28.7
MIP	193.2	41	0.207	1.6	0.0083	0.038	0.197	16	83
19	312.4	80	0.256	1.9	0.0061	0.015	0.048	86	275
20	340.4	75	0.220	2.3	0.0068	0.006	0.018	195	573
21	340.4	72.5	0.213	1.6	0.0047	0.0056	0.017	200	588
22	354.4	62.5	0.176	2.1	0.0059	0.000078	0.00022	340	959
23	354.4	80	0.226	2.1	0.0059	0.0001	0.00028	310	875
24	396.6	87.5	0.221	2.7	0.0068	0.000068	0.00017	530	1336
Methomyl	162	3.7	0.023	1.4	0.0086	0.64	3.95	10	62
25	281.4	7.0	0.025	2.4	0.0085	0.92	3.27	160	569
26	295.4	7.3	0.025	2.4	0.0081	0.70	2.37	310	1049
27	309.4	8.8	0.028	2.0	0.0065	0.68	2.19	400	1293
28	309.4	8.5	0.028	2.1	0.0068	0.70	2.26	345	1115
29	323.4	10.5	0.033	2.6	0.0080	0.64	1.98	450	1392
30	365.5	7.5	0.021	3.4	0.0093	0.08	0.22	600	1642
Oxamyl	219	3.6	0.016	1.0	0.0046	0.33	1.51	5[b]	23
31	338.4	3.2	0.010	1.25	0.0037	0.37	1.09	9	27
32	352.4	3.7	0.011	1.35	0.0038	0.41	1.16	10	28
33	366.5	4.2	0.012	1.4	0.0038	0.37	1.01	10	27
34	380.5	4.5	0.012	1.35	0.0035	0.32	0.84	9	24
35	422.6	6.0	0.014	1.65	0.0039	0.08	0.19	12	28

[a] Extrapolated value. [b] Value obtained on rats.

methylcarbamate in vivo, exemplified by II with the carbofuran derivative. Bond cleavage at 1 results directly



II

in carbofuran formation and cleavage of 2, 3, or 4 results in derivatives which eventually are converted to carbofuran (Fahmy and Fukuto, 1972; Fukuto et al., 1975; Chiu et al., 1975).

On the basis of piperonyl butoxide synergized toxicity data, it appears that an oxidative process is not responsible for the in vivo generation of the toxic methylcarbamate. The high degree of synergism obtained with piperonyl butoxide probably resides in the ability of the synergist to protect the methylcarbamate ester from detoxication after its formation from the *N,N'*-thiodicarbamate. The synergized toxicity data indicate that carbofuran and its derivatives are all synergized to about the same degree with an average LD_{50} value of 0.0021 μmol/g. This value is virtually identical with the amount of carbofuran (0.0022 μmol/g) previously found to be present in internal extracts of house flies treated with approximately the LD_{50} dosage of a related carbofuran derivative, *N*-(2-toluenesulfenyl)carbofuran (Black et al., 1973a). Thus, it appears that the synergized LD_{50} values in Table III are approaching the actual amounts of carbofuran required in the house fly to produce an LD_{50} effect.

The difference in house fly toxicity of carbaryl and its derivative 17 is noteworthy. Carbaryl is notoriously ineffective against house flies, and this ineffectiveness has been attributed to poor penetration of carbaryl into the fly, allowing metabolic detoxication to occur as it was being absorbed. The fivefold greater toxicity of 17, which contains an *n*-octyl methylcarbamylosulfenyl moiety attached to carbaryl, suggests that it is able to penetrate house fly cuticle more readily than carbaryl. Carbaryl and 17 were equitoxic to house flies in the presence of piperonyl butoxide.

Toxicity to Mosquito Larvae. Sulfenylated derivatives of insecticidal methylcarbamates are generally more effective against mosquito larvae than the parent methylcarbamate (Fahmy et al., 1974; Black et al., 1973a; Schaeffer and Wilder, 1970). This was also true with the *N,N'*-thiodicarbamates. The data in Table III show that, in contrast to house flies, toxicity to mosquito larvae

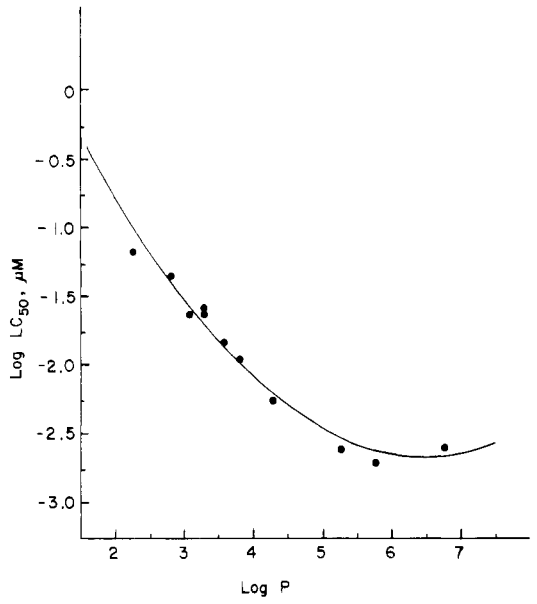


Figure 1. Relationship between toxicity of sulfenyl carbofuran derivatives to mosquito larvae (log LC_{50}, μM) and logarithm of the octanol–water partition coefficient (log P).

systematically increased with increase in carbon atoms in the aliphatic carbamate moiety. Maximum toxicity was observed when the total number of carbon atoms was eight or nine and further increase in carbons resulted in a gradual decrease in toxicity. These results suggest that hydrophobicity of the molecule plays an important role in mosquito larvae intoxication by the derivatized methylcarbamates. In the aqueous habitat of the larvae, the carbamate derivative must partition between water and the hydrophobic epicuticular wax layer of the larvae and derivatives of greater hydrophobicity should move more readily into the larval cuticle. However, when the number of carbon atoms becomes too large, the molecules become too insoluble in water and either are present in aggregates which are less available to the larvae or are trapped in the larval wax, resulting in reduced subsequent movement.

Figure 1 provides a graphic relationship between the logarithm of the toxicity of the various sulfenylated derivatives of carbofuran (log LC_{50}, μM) and logarithm of the octanol–water partition coefficients (log P). The circles represent actual values of log LC_{50} and log P for each compound and the solid line is the best parabolic fit of the points according to eq 2, obtained by multiple regression analysis

$$\log LC_{50} = 1.24 - 1.19 \log P + 0.09 (\log P)^2 \qquad (2)$$
$$n = 12 \qquad r = 0.988$$

where n is the number of compounds and r is the multiple linear regression coefficient. Neither the position of the alkyl chain, i.e., on nitrogen or oxygen, nor branching had any effect on the correlation.

A similar relationship between log P and mosquito larvicidal toxicity was observed for other N,N'-thiodicarbamates such as the homologous series of propoxur (**13–16**), MIP (**19–24**), methomyl (**25–30**), and oxamyl derivatives (**31–35**), as shown graphically in Figure 2. The plots show that the curves tend to become parabolic as the log P values increase beyond 2. An increase in partition coefficient from 1 to 100 (log P from 0 to 2) had a smaller effect on larvicidal activity than an increase from 100 to 1000. In the case of highly water-soluble methomyl and oxamyl, most of the derivatives showed log P values less than 2 and a significant increase in activity was not observed until log P was increased to around 3. Extrapolation of the curves for the propoxur and MIP derivatives to low log P values indicates a similar relationship for these compounds. Since the toxicity of the derivatives is doubtlessly attributable to the parent methylcarbamate, on a molar basis the intrinsic toxicity of each derivative in a given series should be the same. The results depicted in Figure 1 and 2, therefore, indicate that activity is largely dependent on the partitioning of the derivative between the larvae and aqueous phase. Hence, the plots shown in Figures 1 and 2 probably approximate the relationship between amount absorbed by the mosquito larvae and the partition coefficient of the derivative.

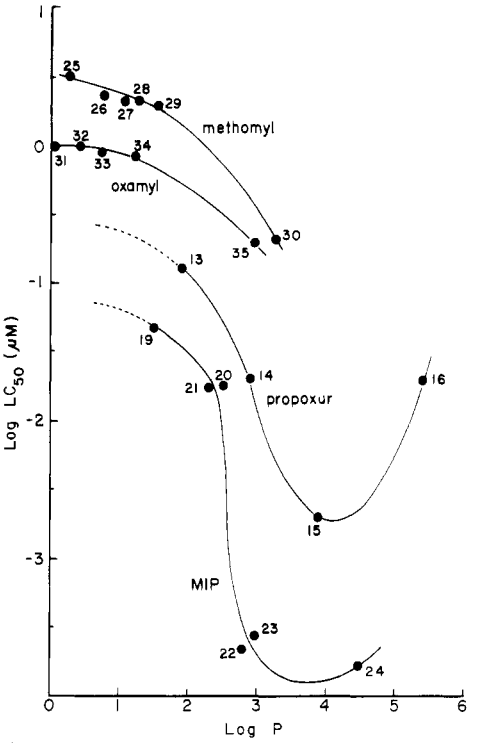


Figure 2. Relationship between toxicity of sulfenyl MIP, propoxur, methomyl, and oxamyl derivatives to mosquito larvae (log LC_{50}, μM) and logarithm of the octanol–water partition coefficient (log P).

Compared to propoxur and MIP, two of their sulfenylated derivatives **15** and **24**, were astonishingly effective against mosquito larvae. Compound **15** or n-heptyl methylcarbamylosulfenyl derivative of propoxur is almost 800-fold more toxic to mosquito larvae than propoxur and **24** is almost 1200-fold more toxic than MIP. The LC_{50} value of 0.000 068 ppm for **24** makes it one of the most effective mosquito larvicides ever tested in this laboratory. By using 1.76 mg for the average weight of a larva and assuming complete absorption of the test material in the aqueous medium (Leesch and Fukuto, 1972), an LD_{50} value of 0.0057 μmol/g of larvae was calculated for **15**. This makes **15** 17.5-fold more toxic to mosquito larvae than to house flies. In contrast, propoxur is eightfold more toxic to house flies than to mosquito larvae by a similar calculation.

Toxicity to Mice. LD_{50} values for the toxicity of the N,N'-thiodicarbamates to mice are given in Table III in terms of both mg/kg and μmol/kg. With the exception of the oxamyl derivatives, the results clearly indicate that, in addition to their high insecticidal activity, the N,N'-thiodicarbamates are remarkably less toxic to the white mouse than the parent methylcarbamate. For example, on a micromole basis, **9** was 60-fold less toxic to the white mouse than carbofuran. In fact, **7**, **8**, and **9** were safer to

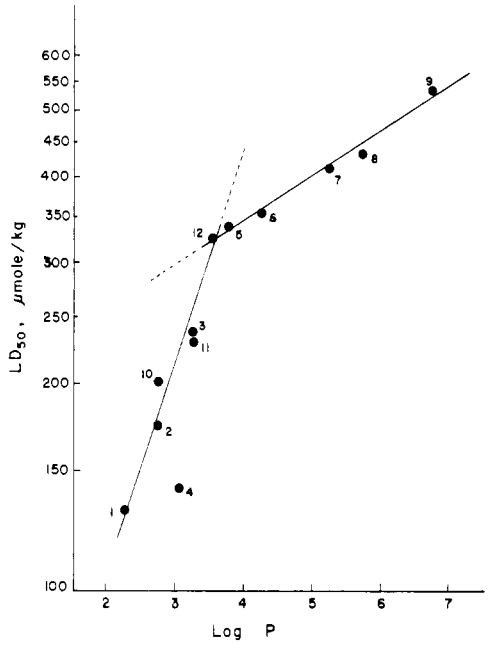
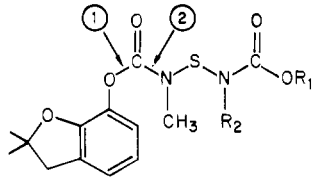


Figure 3. Relationship between toxicity of sulfenyl carbofuran derivatives to white mice (log LD_{50}, μmol/kg) and logarithm of the octanol–water partition coefficient (log P).

mice than any other sulfenylated derivative of carbofuran previously examined in this laboratory (Fahmy et al., 1974; Black et al., 1973b; Fukuto et al., 1975). Further, the *N,N'*-thiodicarbamates prepared from propoxur (**13–16**) were extremely safe to mice, e.g., **15** failed to produce mortality in mice at dosages up to 3000 mg/kg. Derivatization of aldicarb resulted in a thiodicarbamate (**18**) which was significantly less toxic to the mouse than aldicarb, but because of the exceptionally high toxicity of aldicarb, **18** was still undesirably toxic.

Earlier studies (Black et al., 1973a; Miskus et al., 1969; Krieger et al., 1976) on the metabolism and mode of action of derivatized methylcarbamate esters have shown that their low mammalian toxicity is attributable to preferential metabolic detoxication of the derivative to nontoxic phenols. It is reasonable that this also is the explanation for the mammalian safety of the *N,N'*-thiodicarbamates. Cleavage at points 1 or 2 in structure III would result in



III

non-toxic products.

As in the case of mosquito larvicidal activity, mouse toxicity also appeared to be dependent on the hydrophobic character of the derivative. Figure 3 shows the relation between mice toxicity (LD_{50} μmol/kg) and log P for the homologous series of carbofuran derivatives (**1–12**). Evidently, toxicity decreases with increasing log P in two distinct linear relationships. By means of linear regression analysis, 3 and 4 were computed to give best fit to the data:

$$\log LD_{50} = 1.503 + 0.272 \log P \qquad r = 0.968 \qquad (3)$$

$$\log LD_{50} = 2.273 + 0.066 \log P \qquad r = 0.994 \qquad (4)$$

Log P for the point at which the two lines intersect was

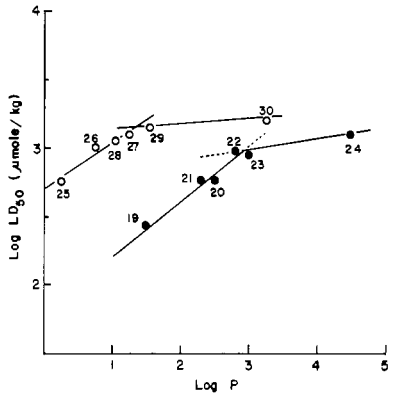


Figure 4. Relationship between toxicity of sulfenyl MIP (●-●) and methomyl (O-O) derivatives to white mice (log LD_{50}, μmol/kg) and logarithm of the octanol–water partition coefficient (log P).

calculated to be 3.74; this corresponds to a P value of 5500. While the biphasic nature of the relationship in Figure 3 is not understood, it raises the possibility of a change-over in intoxication process which depends upon the hydrophobic properties of the molecule. This biphasic relationship between mammalian toxicity and log P also was evident for the other carbamates such as the MIP derivatives **19–24** and methomyl derivatives **25–30**, and, therefore, may be of a general nature (Figure 4).

The sulfenylated oxamyl derivatives, **31–35**, were unusual in that they, and oxamyl itself, were all equally toxic to the white mouse and no improvement in toxicity was noted with derivatives containing up to eight carbon atoms in the attached carbamylosulfenyl moiety. Compared to the methomyl derivatives the log P values of the corresponding oxamyl derivatives are smaller (see Table II) but partition coefficients evidently have little to do with the toxicity of the oxamyl derivatives. For example, **27** and **34** have about the same log P values (1.26 and 1.23, respectively) but **27** (methomyl derivative) is 54-fold less toxic to mice than **34** (oxamyl derivative). On a mole basis, oxamyl is about threefold more toxic to mice than methomyl. While lipophilicity of the derivative is an important contributing factor in reducing mammalian toxicity, results obtained with the oxamyl derivatives indicate that factors, e.g., availability of alternative routes for detoxication, also must be taken into account.

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Overcrowding Factors of Mosquito Larvae. 10. Structure–Activity Relationship of 3-Methylalkanoic Acids and Their Esters against Mosquito Larvae

Yih-Shen Hwang,* H. A. Navvab-Gojrati,[1] and Mir S. Mulla

To study structure–activity relationships, 3-methylalkanoic acids, and methyl, ethyl, and isopropyl 3-methylalkanoates having 14–21 carbon atoms in their main chains were synthesized and evaluated for their larvicidal activity against first-instar larvae of *Culex pipiens quinquefasciatus* Say. Those carboxylic acids and esters having 17–20 carbon atoms in their main chains generally showed a high level of activity. Especially, the C-19 carboxylic acid and esters, i.e., 3-methylnonadecanoic acid and methyl, ethyl, and isopropyl 3-methylnonadecanoates, exhibited the greatest activity. The more active compounds possessed larger slopes of probit regression lines than the less active compounds. In general, alkyl 3-methylalkanoates were less active than their corresponding 3-methylalkanoic acids, and the activity declined in the order of acids, methyl, ethyl, and isopropyl esters.

Previously, we reported that substituted aliphatic carboxylic acids, major components of the overcrowding factors of mosquito larvae, possessed larvicidal activity against several species of mosquitoes (Hwang et al., 1974a; Ikeshoji and Mulla, 1974). Of these acids, some 2-alkylalkanoic acids and 3-methylalkanoic acids showed a high level of activity. Based on these findings, 2-ethyl-, 2-butyl-, and 2-hexylalkanoic acids were synthesized and evaluated for their biological activity against young larvae of the southern house mosquito *Culex pipiens quinquefasciatus* Say (Hwang et al., 1974b). As a result of these studies, it was found that 2-alkyltetradecanoic acids, 2-alkylhexadecanoic acids, and 2-alkyloctadecanoic acids generally exhibited good activity. Their methyl esters also showed a high level of larvicidal activity (Hwang et al., 1976b). As an extension of these investigations, a series of 2-bromoalkanoic acids and methyl 2-bromoalkanoates was evaluated (Hwang and Mulla, 1976). The biological activity of 7-methyloctadecane and 8-methylnonadecane, minor components of the overcrowding factors of mosquito larvae, was studied (Hwang et al. 1976a).

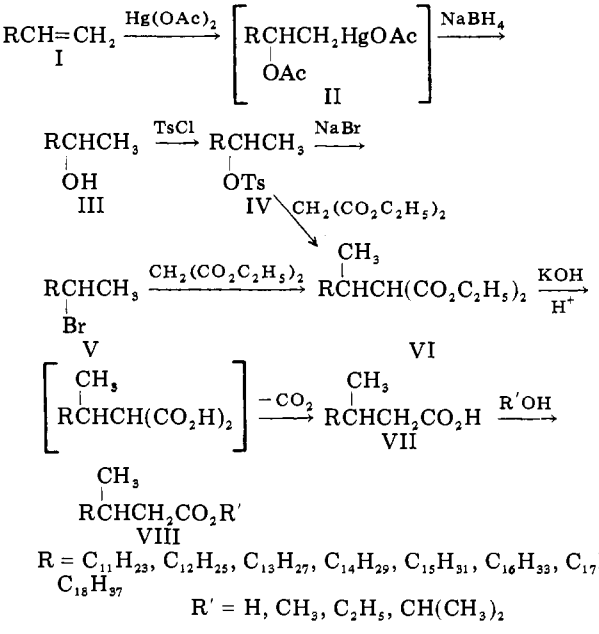
Among the compounds investigated thus far, some 3-methylalkanoic acids, such as 3-methyloctadecanoic acid and 2,3-dimethyloctadecanoic acids, exhibited the greatest larvicidal activity. It therefore became necessary to systematically study this series of compounds. Here we report the synthesis and evaluation of 3-methylalkanoic acids having 14–21 carbon atoms in the main chains and their methyl, ethyl, and isopropyl esters. Based on the evaluation, structure–activity relationships of these acids and their esters are studied and discussed.

EXPERIMENTAL SECTION

Synthesis. Previously, a 2-alkanol (III) (Scheme I) was synthesized by treating a methyl alkanoate with methylsulfinyl carbanion, hydrogenolyzing the resultant methylsulfinylmethyl alkyl ketone with aluminum amalgam, and subsequently reducing the 2-alkanone thus formed with lithium aluminum hydride (Hwang et al., 1974a). Despite the high yield, this procedure involved lengthy and laborious operations. A more convenient method using oxymercuration and demercuration of olefins (Brown and Geoghegan, 1967) was adopted for synthesizing the 2-alkanols (III) in the present work. Thus, a 1-alkene (I) was treated with mercuric acetate in aqueous tetrahydrofuran. The intermediary oxymercurial (II), without isolation, was then reduced with sodium borohydride in an alkaline medium to give the desired 2-alkanol (III).

Following the procedures similar to those reported previously (Hwang et al., 1974a), the 2-alkanol (III) was tosylated with *p*-toluenesulfonyl chloride in dry pyridine,

Scheme I. Synthesis of 3-Methylalkanoic Acids and Their Esters



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