Quantitative Structure–Activity Relationships in Insecticidal Oxathiolane and Dithiolane Oxime Carbamates and Related Compounds

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The insecticidal and acaricidal activities and the mammalian toxicity of a series of 28 oxathia and dithia heterocyclic oxime methylcarbamates have been related to certain of their physicochemical properties. Multiple regression studies have shown that fly head acetylcholinesterase inhibition and housefly, buckthorn aphid, two-spotted spider mite, southern armyworm, Mexican bean beetle, and rat toxicities are enhanced by increased steric requirement of ring substituents (Taft E_s). Increasing lipophilicity (log P) uniformly diminishes activity against the arthropods and the rat while the presence of a β-sulfur as compared to a β-oxygen is associated with increased activity against all test organisms. These correlation studies suggest that further synthesis in this series is unlikely to yield effective insecticides in which the arthropod/mammal selectivity is improved over that of compounds already in hand.

The syntheses and the insecticidal properties of carbamate esters of 4-oximino-1,3-oxathiolanes (Ia), 3-oximino-1,4-oxathianes (Ib; Kurtz et al., 1987), 4-oximino-1,3-dithiolanes (Ic), and 3-oximino-1,4-dithianes (Id; D'Silva et al., 1985) have been reported separately (Chart I).

These materials are broad-spectrum insecticides having excellent activity against the buckthorn aphid, Mexican bean beetle, southern armyworm, and the housefly. The dithia compounds and selected members of the oxathia series in addition exhibit good acaricidal potency. The more insecticidally active monomethylcarbamates in both series of compounds, however, possess significant levels of toxicity to warm-blooded animals as measured by acute toxicity to the rat. As part of the examination of these compounds we sought to define which structural and physicochemical features of the monomethylcarbamates in the series are significant in controlling toxicity to both insect and mammalian species. With the role of such physicochemical features defined, the activities of synthesis candidates could be predicted. Should features leading to biological selectivity be identified, structures could be devised to improve the insect/mammalian toxicity ratio.

This report is concerned with development of quantitative structure–activity relationships (QSAR) required to reach these goals. Multiple-regression analyses following the approach developed by Hansch (Tute, 1971) are presented.

An examination of the data given for I in companion reports (D'Silva et al., 1985; Kurtz et al., 1987) reveals that the N-monomethylcarbamate compounds (I: $R_1 = CH_3$, $R_2 = H$) are the most potent toxicants in the series. In order to focus on the role of various structural features *in the oxime moiety*, the compound data bank was limited to N-monomethylcarbamates in the present study. In Table I are presented chemical structures, dose/response activity data, and physicochemical parameters for the 15 oxathia (compounds 1–15) and 13 dithia (compounds S16–S28) heterocyclic oxime methylcarbamates examined in this work. (The prefix S on a compound number designates the material as a member of the dithia series.)

Compounds in these series can exist as syn (oximino oxygen cis to the thiohydroximate sulfur) or anti isomers. All data reviewed in the present report are for syn isomers. Methods used to establish configuration are given in the companion reports (D'Silva et al., 1985; Kurtz et al., 1987).

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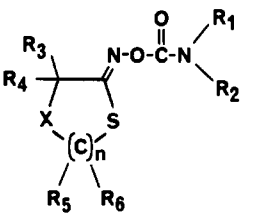
Chart I



	X	n
Ia	O	1
Ib	O	2
Ic	S	1
Id	S	2

ESTIMATION/DETERMINATION OF PHYSICOCHEMICAL PARAMETERS

1. Octanol/Water log P. log P, a measure of the overall lipophilicity/hydrophilicity in molecules, was determined experimentally according to the procedure of Fujita et al. (1964). The data are given in Table I where experimental determinations are noted by asterisks. The other log P values given in the table were estimated as detailed in the footnotes of Table I.

The lipophilic character of an entire molecule is important to its transport through and between cells and membranes. Of equal importance is the relative lipophilicity/hydrophilicity of specific groups within a molecule—i.e., side chains. For instance, a lipophilic side chain may promote binding in a lipophilic "pocket" in the active site of a target enzyme. However, the role of localized side-chain lipophilicity could not be independently studied in this work since $\sum\pi$ parameters at the α and γ ring positions (defined below) are highly correlated with the corresponding Taft $\sum E_s$ steric parameters for the group of compounds under study here (correlation coefficients 0.79 and 0.80, respectively). Thus, the $\sum E_s$ parameters may, in this case, express not only the role of substituent bulk in the biological activity of these compounds but also the role of regional lipophilicity.

2. Taft Steric Parameters ($\sum E_s^{\alpha}$, $\sum E_s^{\gamma}$). To quantitate the role of the size of substituents in the biological potency of these compounds, the Taft steric parameter, E_s (Craig, 1971), of substituents in the position α (adjacent to) the oximino carbon were summed to yield $\sum E_s^{\alpha}$ while E_s for the substituents at the position adjacent to the distal heteroatom (β to the oximino group) were summed to give

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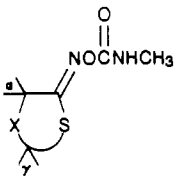
Table I. Physicochemical Parameters and Biological Data for 15 Oxathia and 13 Dithia Heterocyclic Oxime Methylcarbamates



no.	X	ring size	α subst	γ subst	$\sum E_s^{\alpha}$ [a]	$\sum E_s^{\gamma}$ [b]	log P [c]	LC_{50}, [d] ppm aphid	mite	SAW	MBB	HF	$I_{50} \times 10^6$ [e]	LD_{50} (rat), [f] mg/kg	MW
1	O	5			2.48	2.48	0.06*	25.0	150.0	150.0	180.0	3.0	2.50	49.2	176
2	O	5	CH_3, H		1.24	2.48	0.46*	6.0	340.0	14.0	14.0	5.0	0.80	11.7	190
3	O	5		CH_3, H	2.48	1.24	0.56	33.0	200.0	500.0	70.0	3.0	1.00	12.3	190
4	O	5		C_2H_5, H	2.48	1.17	1.06	45.0	200.0	500.0	500.0	18.0	0.40	59.5	204
5	O	5	C_2H_5, H		1.17	2.48	0.96	25.0	180.0	110.0	25.0	3.0		23.6	204
6	O	5	n-C_3H_7, H		0.88	2.48	1.52*	500.0	500.0	500.0	500.0	4.0	0.50	83.0	218
7	O	5	CH_3, H	CH_3, H	1.24	1.24	0.96*	15.0	85.0	25.0	17.0	11.0	0.05	4.5	204
8	O	5	i-C_3H_7, H		0.77	2.48	1.48*	40.0	500.0	500.0	60.0	9.0	0.80	16.2	218
9	O	5	$CH_3OCH_2CH_2$, H		1.10	2.48	0.51*	inact	500.0	500.0	170.0	5.0			234
10	O	5	CH_3OCH_2, H		1.05	2.48	0.01	44.0	200.0	inact	10.0	50.0			220
11	O	5	CH_3, H	C_2H_5, H	1.24	1.17	1.46	10.0	10.0	140.0	70.0	60.0		8.0	218
12	O	5	C_2H_5, H	CH_3, H	1.17	1.24	1.46	13.0	85.0	140.0	60.0	35.0		15.0	218
13	O	5	CH_3, H	n-C_3H_7, H	1.24	0.88	1.96	65.0	500.0	500.0	160.0	50.0			232
14	O	5	CH_3, CH_3		0.00	2.48	0.82*	4.0	40.0	11.0	14.0	16.0		1.6	204
15	O	6			2.48	2.48	0.00*	500.0	500.0	100.0	38.0	2.0	1.50	37.0	190
S16	S	6			2.48	2.48	0.49*	5.0	6.0	40.0	52.0	0.8	1.00	15.4	206
S17	S	6	CH_3, H		1.24	2.48	0.89	4.0	6.0	60.0	11.0	4.0	0.07	2.2	220
S18	S	6	CH_3, CH_3		0.00	2.48	1.51*	0.8	4.0	140.0	80.0	12.0	0.10	0.27	234
S19	S	6		CH_3, H	2.48	1.24	0.99	8.0	12.0	100.0	35.0	10.0	4.00	5.10	220
S20	S	6	CH_3, H	CH_3, H	1.24	1.24	1.39	3.0	30.0	110.0	65.0	13.0	0.15		234
S21	S	6	CH_3, CH_3	CH_3, H	0.00	1.24	2.01	1.5	7.0	1000.0	50.0	45.0	0.05		248
S22	S	6	n-C_3H_7, H		0.88	2.48	1.89	75.0	500.0	500.0	150.0	60.0	0.20		248
S23	S	6	i-C_3H_7, H		0.77	2.48	1.89	40.0	250.0	500.0	150.0	27.0	3.50		248
S24	S	5			2.48	2.48	0.51*	6.0	55.0	100.0	28.0	0.8	3.00	13.0	192
S25	S	5	CH_3, H		1.24	2.48	0.91*	5.0	15.0	22.0	10.0	1.5	2.00	1.0	206
S26	S	5	CH_3, CH_3		0.00	2.48	1.31*	6.0	2.0	16.0	23.0	4.0	0.25	0.7	220
S27	S	5		CH_3, CH_3	2.48	0.00	1.33*	2.0	13.0	250.0	35.0	6.0	0.20	2.0	220
S28	S	5	CH_3, H	CH_3, CH_3	1.24	0.00	1.73	3.0	7.0	75.0	21.0	6.0		1.0	234

[a] $\sum$ of Taft steric parameters (Craig, 1971) for substituents at the α-position. The E_s of methoxyethyl was taken as −0.14, twice that of ethyl (−0.07); the E_s of methoxymethyl, −0.19, was taken as half that of ethoxymethyl (−0.37; Talvik, 1971). [b] $\sum$ of Taft steric parameters for substituents at the γ-position. [c] log of octanol/water partition coefficient determined spectrophotometrically according to the method of Fujita et al. (1964) or calculated from log P of nearest analogue and π values derived from experiment or the literature (Craig, 1971). Values marked with an asterisk were determined experimentally; others were calculated from data for the nearest analogue as follows (compound, calculation): **3**, log P (**1**) + 0.50; **4**, log P (**3**) + 0.50; **5**, log P (**2**) + 0.50; **10**, log P (**9**) − 0.50; **11**, log P (**2**) + 1.00; **12**, log P (**2**) + 1.00; **13**, log P (**11**) + 0.50; **S17**, log P (**S16**) + 0.40 (Δ between **1** and **2**); **S19**, log P (**S16**) + 0.50; **S20**, log P (**S16**) + 0.50 + 0.40; **S21**, log P (**S18**) + 0.50; **S22**, log P (**S17**) + 1.00; **S23**, log P (**S17**) + 1.00; **S28**, log P (**S27**) + 0.40. 0.50 and 1.00 are the literature π values for, respectively, CH_3 and CH_3CH_2 increments. [d] Bean plants sprayed to runoff infested with buckthorn aphid, two-spotted spider mite, southern armyworm larvae, or Mexican bean beetle larvae. Housefly test: cotton fibers impregnated with solution of appropriate concentration (Payne et al., 1966). [e] Determined with Warburg apparatus (Moorefield and Tefft, 1958). [f] Intubation in corn oil; acute oral LD_{50} determinations were carried out by C. S. Carpenter and colleagues at the Carnegie-Mellon Institute of Research, Carnegie Hygiene Fellowship, Pittsburgh, PA.

$\sum E_s^{\gamma}$. Data and estimation details are given in the footnotes to Table I.

3. Indicator Variable for X = S. A major difference between the dithia and oxathia compounds in this series is the presence or absence of an oxidizable sulfur atom. An indicator variable, $I_{\beta\text{-S}}$ was created to account for this difference in correlation studies. For oxathia compounds, $I_{\beta\text{-S}}$ was set equal to 0; for dithia compounds, 1.0.

4. Ring Size. Table I contains compounds having either five- or six-membered rings. Preliminary regression work indicated no significance to an indicator variable designed to examine the role of ring size on activity.

BIOLOGICAL DATA

The methods of synthesis and biological evaluation of compounds reviewed in this study are described in companion papers (D'Silva et al., 1985; Kurtz et al., 1987) and references cited therein.

Toxicity data (LC_{50}, ppm) from foliage spray tests against buckthorn aphid adults, two-spotted spider mite (all stages), southern armyworm larvae, and Mexican bean beetle larvae and from a bait test involving the adult housefly (Payne et al., 1966) are presented in Table I. Mammalian toxicity data from acute oral tests in the rat (LD_{50}, mg/kg, stomach intubation suspended in corn oil) and the molar I_{50} for fly head acetylcholinesterase inhibition (Moorefield and Tefft, 1958) are also given in Table I. All data are from a single series of dose/response experiments. In general, the 95% confidence interval for individual LC_{50}'s in these tests is $LC_{50}/2$ to $LC_{50} \times 2$ (e.g. the CI for an LC_{50} of 50 is 25–100.) In foliage spray tests the arthropods are exposed to the toxicant by both contact and feeding routes as the animals forage on treated leaves.

For the regression trials, biological activity is expressed on a log scale in which larger numbers indicate greater activity as follows (MW = molecular weight):

aphid, mite, SAW, MBB, HF, rat	$\log (1/C) = -\log (LC_{50}/MW)$
I_{50}, M	$\log (1/C) = -\log I_{50}$

MULTIPLE REGRESSION ANALYSIS

The data presented in Table I were analyzed by standard multiple linear regression and other statistics routines

Table II. Range of Data for the Mixed Data Set of 28 Compounds

variable	mean	S	min	max	range
$\sum E_s^{\alpha}$	1.28	0.90	0.0	2.48	2.48
$\sum E_s^{\gamma}$	1.89	0.80	0.0	2.48	2.48
log P	1.11	0.56	0.0	2.01	2.01
$[(\log P - \overline{\log P})^2]$[a]	0.30	0.33	0.0009	1.188	1.187
MW	214.9	18.78	176.0	248.0	72.0
$I_{\beta\text{-S}}$	0.50	0.51	0.0	1.0	1.0
aphid[b]	1.15	0.77	−0.42	2.47	2.89
mite[b]	0.68	0.84	−0.42	2.04	2.89
SAW[b]	0.26	0.53	−0.61	1.27	1.88
MBB[b]	0.68	0.48	−0.39	1.44	1.83
HF[b]	1.44	0.51	0.56	2.41	1.85
I_{50}[c]	0.30	0.63	−0.60	1.30	1.90
rat[d]	1.48	0.70	0.42	2.89	1.47

[a] The $\overline{\log P}$ used in the regression analysis was 1.09 for the mixed and oxathia sets; $\overline{\log P}$ = 1.31 was used for the dithia set. [b] Variable: −log (LC$_{50}$/MW). [c] Variable: −log I_{50}. Range of data given for I_{50} is for the set of 20 mixed compounds. See Table IV for a listing of the exclusions. [d] Range of data given for the rat is for the set of 21 mixed compounds. See Table IV for a listing of the exclusions.

on an IBM-370 MVS batch system. The means and ranges covered by the physicochemical parameters that serve as independent variables in these regression studies are presented in Table II. A percent covariance matrix (r^2) reviewing one-on-one intercorrelation between all variables is given in Table III. For the "mixed" data set of 28 compounds, the range in log P (Table II) is limited (range 2.01); in this situation, log P is highly correlated with its square (r = 0.96), making specious the examination of (log P)^2 terms in regression trials. To break this internal correlation, the mean log P ($\overline{\log P}$ = 1.09) for the oxathia data set was subtracted from each log P prior to squaring for regression studies of the oxathia and mixed data sets; the mean log P ($\overline{\log P}$ = 1.31) for the dithia data set was subtracted prior to squaring for studies on the dithia series. Raw regressions in the form [log $(1/C) = a + b(\log P) + c(\log P - \overline{\log P})^2 + d(\sum E_s^{\alpha}) + e(\sum E_s^{\gamma}) + f(I_{\beta\text{-S}})$] were algebraically expanded to the form [log $(1/C) = a + b(\log P) + c(\log P)^2 + d(\sum_s{}^{\alpha}) + e(\sum E_s^{\gamma}) + f(I_{\beta\text{-S}})$] before extracting the coefficient data recorded for each equation in Table IV.

In Table IV are presented data for equations correlating activity with physicochemical effects for the four insects, the mite, the rat, and fly head AChE for the oxathia set (maximum of 15 compounds), the dithia set (maximum of 13 compounds), and the mixed set (maximum of 28 compounds). Where n in Table IV is less than 28 for the mixed data set, less than 15 for the oxathia data set, or less than 13 for the dithia data set, specific compounds are missing from the regression trial either because data were missing or compounds proved to be serious outliers in preliminary regression runs. Details on outlier exclusions are clearly noted in Table IV. In no case were more than two compounds removed from regression data sets because of lack of fit (see Table IV); where required, such exclusions were made to assure that equations used to predict activity for new structures had coefficients as reliable as possible. The sense and size of equation coefficients were not significantly affected in any case by the noted removals of outliers.

RESULTS AND DISCUSSION

Intervariable Correlations. The correlations presented in Table III provide insights into which parameters exert discernible effects on biological activity when examined one-on-one and also provide an opportunity to examine the structural and physicochemical parameters for covariance, a property to be avoided where possible in the independent variables in multiple-regression work.

The following generalizations can be made from the data in Table III:

1. There is little one-on-one correlation between I_{50} (a measure of intrinsic activity) and the activity of the compounds studied against the four insects, the mite, or the rat. This suggests that factors other than activity at the target enzyme are important, e.g., efficiency of transport in vivo or susceptibility to detoxifying metabolism.
2. Rat toxicity is highly correlated with activity against the aphid and the mite.
3. Mite and aphid activities are highly correlated as are bean beetle and armyworm toxicities.
4. Housefly activity is poorly correlated with activity against any of the other species.
5. $\sum E_s^{\alpha}$ may be important to both I_{50} and rat toxicity.
6. I_{50} correlates somewhat with log P. It is important to note, however, that the more detailed multivariate analyses presented in Table IV clearly show the $\sum E_s^{\alpha}$ and $\sum E_s^{\gamma}$ play an important role in activity against both the enzyme and in the activities in most of the whole-animal tests. The role of $\sum E_s^{\alpha}$ and $\sum E_s^{\gamma}$ in enzyme activity would not be apparent in the correlation matrix since that matrix only evaluates one-on-one correlations. A special regression run showed that log P is covariant with $(\sum E_s^{\alpha} + \sum E_s^{\gamma})$ for the I_{50} data set. For this data set, log P or $\sum E_s^{\alpha}$ and $\sum E_s^{\gamma}$ express in slightly different ways that ring substituents promote enzyme inhibition. More detailed analysis

Table III. Percent Covariance (r^2 × 100)

	aphid	mite	SAW	MBB	HF	I_{50}	rat	$\sum E_s^{\alpha}$[c]	$\sum E_s^{\gamma}$[c]	log P	$(\log P - \overline{\log P})^2$	$I_{\beta\text{-S}}$
aphid	+100.0	+55.1	+7.9	+17.5	−0.3	+14.6[b]	+65.4[b]	−6.2	−8.8	+7.3	−13.0	+31.8
mite	+55.1	+100.0	+15.5	+29.8	+2.7	+15.7[b]	+62.4[b]	−9.0	−1.9	+1.2	−15.4	+45.0
SAW	+7.9	+15.5	+100.0	+56.6	+12.8	+0.0[b]	+28.4[b]	−5.9	+7.0	−19.6	−12.2	+0.5
MBB	+17.5	+29.8	+56.6	+100.0	+12.0	+2.7[b]	+38.9[b]	−9.0	+1.1	−7.4	−10.0	+8.9
HF	−0.3	+2.7	+12.8	+12.0	+100.0	−19.5[b]	+0.8[b]	+13.2	+12.5	−44.2	−0.8	+4.0
I_{50}	+14.6[b]	+15.7[b]	0.0[b]	+2.7[b]	−19.5[b]	+100.0	+21.2[b]	−38.1	−23.3	+43.2[d]	+25.3	−11.6
rat	+65.4[b]	+62.4[b]	+28.4[b]	+38.9[b]	+0.8[b]	+21.2[b]	+100.0	−31.3	−2.56	+0.18	−16.3	+43.7
$\sum E_s^{\alpha}$[c]	−6.2	−9.0	−5.9	−9.0	+13.2	−38.1	−31.3	+100.0	−8.0	−20.6	+3.0	−0.9
$\sum E_s^{\gamma}$[c]	−8.8	−1.9	+7.0	+1.1	+12.5	−23.3	−2.5	−8.0	+100.0	−13.8	+1.3	−0.2
log P	+7.3	+1.2	−19.6	−7.4	−44.2	+43.2[d]	+0.18	−20.6	−13.8	+100.0	−1.1	+8.9
$(\log P - \overline{\log P})^2$	−13.0	−15.4	−12.2	−10.0	−0.8	+25.3	−16.3	+3.0	+1.3	−1.1	+100.0	−1.3
$I_{\beta\text{-S}}$	+31.8	+45.0	+0.5	+8.9	+4.0	−11.6	+43.7	−0.9	−0.2	+8.9	−1.3	+100.0

[a] Except where otherwise noted, the number of compounds involved in each correlation is as described in the notes to Table II; signs noted are for r, the correlation coefficient. [b] Number of compounds limited to those where *all* biological variables were available: n = 20 for I_{50}/insect intercorrelation; n = 16 for rat/I_{50} intercorrelation; rat/insect, n = 21. [c] (−) sign indicates biological potency increases with increasingly negative $\sum E_s$, i.e. greater steric bulk. [d] Possibly a function of overall molecular size. r^2 for log P vs. MW was 0.841.

Table IV.[a] $-\log (LC_{50}/MW) = a + b(\log P) + c(\log P)^2 + d\sum E_s^{\alpha} + e\sum E_s^{\gamma} + fI_{\beta\text{-}S}$ **Equation Constants (*a*), Coefficients (*b*–*f*), and Statistical Parameters (Standard Error of Each Coefficient Given in Parentheses)**

eq			a	$b(\log P)$	$c(\log P)^2$	$d(\sum E_s^{\alpha})$	$e(\sum E_s^{\gamma})$	$f(I_{\beta\text{-}S})^b$	n	s	r^2	excl compds: poor fit	excl compds: no data
1		mix	1.96			−0.46 (0.12)	−0.43 (0.15)		20	0.46	0.52		**5, 9, 10, 11, 12, 13, 14, S28**
2	[I_{50}]	oxathia	2.29			−0.47 (0.15)	−0.63 (0.17)		8	0.29	0.78		**5, 9, 10, 11, 12, 13, 14**
3		dithia	1.67			−0.48 (0.18)	−0.35 (0.22)		12	0.58	0.45		**S28**
4		mix	2.93	+0.34 (0.22)[c]	−0.52 (0.22)[c]	−0.57 (0.13)	−0.51 (0.13)	0.90 (0.16)	27	0.40	0.74		**9**
5	[aphid]	oxathia	1.47	+1.17 (0.29)[c]	−0.66 (0.29)[c]	−0.37 (0.14)			13	0.37	0.60	**6**	**9**
6		dithia	5.11	−1.22 (0.31)		−0.66 (0.16)	−0.57 (0.13)		13	0.32	0.72		
7	[two-	mix	1.98	0.35 (0.22)[c]	−0.56 (0.22)[c]	−0.53 (0.13)	−0.47 (0.13)	1.40 (0.17)	26	0.40	0.82	**11, 20**	
8	spotted	oxathia		low levels of activity precluded meaningful equation					15				
9	mite]	dithia	6.39	−2.04 (0.36)		−1.03 (0.19)	−0.69 (0.15)		13	0.37	0.80		
10	[southern	mix	2.02	−0.10 (0.20)[c]	−0.45 (0.20)[c]	−0.53 (0.12)	−0.20 (0.11)	0.30 (0.14)	26	0.34	0.69	**9**	**10**
11	army-	oxathia	3.64	−1.23 (0.20)		−0.93 (0.14)	−0.47 (0.15)		13	0.26	0.86	**9**	**10**
12	worm]	dithia	0.56	1.40 (0.40)[c]	−0.92 (0.40)[c]	−0.25 (0.11)			13	0.30	0.72		
13	[Mexican	mix	2.63	−0.89 (0.17)		−0.48 (0.11)	−0.30 (0.10)	0.45 (0.14)	27	0.33	0.61	**9**	
14	bean	oxathia	1.92			−0.52 (0.14)	−0.58 (0.11)		13	0.28	0.76	**6, 9**	
15	beetle]	dithia	2.88	−0.94 (0.25)		−0.33 (0.13)	−0.26 (0.10)		13	0.26	0.61		
16		mix	2.07	−0.81 (0.10)				0.497 (0.12)	26	0.28	0.73	**6, 10**	
17	[housefly]	oxathia	1.92	−0.56 (0.17)					13	0.35	0.51	**4, 10**	
18		dithia	2.81	−1.00 (0.15)					13	0.27	0.80		
19		mix	4.08	−0.79 (0.16)		−0.84 (0.09)	−0.53 (0.08)	1.00 (0.09)	21	0.20	0.94		**9, 10, 13, S20, S23**
20	[rat]	oxathia	4.36	−0.84 (0.13)		−0.85 (0.09)	−0.64 (0.09)		12	0.16	0.93		**9, 10, 13**
21		dithia	3.29	–[d]		−0.58 (0.08)	−0.23 (0.08)		9	0.22	0.90		**S20, S23**

[a] $-\log I_{50}$ for I_{50} equation. [b] $I_{\beta\text{-}S}$ is 0.0 for oxathia compounds and 1.0 for dithia compounds. The term is relevant only in the regressions for the mixed set. [c] $\log P$ optima: aphid mix, 0.33; aphid oxathia, 0.56; mite mix, 0.31; southern armyworm mix, −0.11; southern armyworm dithia, +0.76. [d] $\log P = 2.203 - 0.35\sum E_s^{\alpha}$ (0.027) − $0.33\sum E_s^{\gamma}$ (0.025); $s = 0.033$, $r^2 = 0.98$. The internal correlation prohibits appearance of both $\log P$ and $\sum E_s$ terms in the same equation for this limited data set.

detailed below indicates that higher levels of lipophilicity actually *detract* from activity in the whole-animal tests.

7. Housefly activity is *inversely* correlated with log P. The negative role of log P in activity in essentially all the whole-animal tests developed below is most significant in the housefly. It appears substantial in the correlation matrix only for housefly because only with housefly does log P alone explain a high percentage of variation in the biological variable.

8. Much of the variation in biological activity for the aphid, mite, and the rat in the mixed data sets is accounted for by the presence or absence of a β-sulfur atom, i.e. an oxidizable sulfur.

9. Notwithstanding the log $[P/(\sum E_s^{\alpha} + \sum E_s^{\gamma})]$ functional relationship noted above, there are no serious one-on-one intercorrelations of the physicochemical independent variables.

Regression Equations (Table IV). *Role of Ring Substitution in Acetylcholinesterase Inhibition.* One of the more fundamental aspects of the toxicology of oxime methylcarbamates is their activity as inhibitors of acetylcholinesterase, the target enzyme. Molar fly head acetylcholinesterase I_{50} data (molar concentrations giving 50% inhibition of the enzyme) are a measure of relative activity in this regard (Moorefield and Tefft, 1958).

Data were available for 8 oxathia and 12 dithia compounds. Despite the relatively low r^2 values that were achieved, eq 2 and 3 for the oxathia and dithia sets demonstrate the importance to enzyme inhibition of steric bulk or branching in both the α- and γ-positions of these compounds. Since groups with greater steric requirements have increasingly negative E_s values, the coefficients of these E_s terms suggest that potency should increase with increasing bulk.

The similarity of coefficients for eq 2 and 3 prompted examination of a combined data set; eq 1 was the result. The equation could not be improved by forcing in log P terms or the $I_{\beta\text{-S}}$ parameter.

Compounds **S17**, **S19**, and **S23** are major outliers in eq 1. A rationale for their lack of fit is not readily apparent. It is worth noting that their removal from the data set gave an equation [$-\log I_{50} = 1.96 - 0.4\sum E_s^{\alpha}$ ($\pm$0.08) $- 0.48\sum E_s^{\gamma}$ ($\pm$0.15); $n = 17$, $s = 0.28$, $r^2 = 0.78$] essentially identical with eq 1 in which nearly 80% of the variation in data for 17 compounds is explained by the two steric terms.

The critical role of the E_s terms to I_{50} found in all of eq 1–3 extends into the equations for the insects, mite, and rat as described below.

Because of the high correlation between log P and $(\sum E_s^{\alpha} + \sum E_s^{\gamma})$ noted earlier, the present equations do not permit a distinction between lipophilicity and steric bulk as operative factors in the enzyme inhibition effectiveness of these materials. The insensitivity of the I_{50}'s to $I_{\beta\text{-S}}$ is not surprising since sulfoxidation, which occurs in vivo, should not occur during the in vitro test.

The advantageous role of branching and the size of groups at the α- or γ-positions in these compounds is reminiscent of the branched quaternary group in the natural substrate acetylcholine (Payne et al., 1966). Indeed, Cohen et al. (1985) have assembled good evidence that the "anionic site" in acetylcholinesterase might better be considered a "branched alkyl" site: acetylcholine mimics having branching but no quaternary center bind only 1.5 kcal/mol more weakly than quaternary analogues.

Role of the Size of Substituents, Lipophilicity, and the Presence of an Oxidizable Sulfur in Insecticidal, Acaricidal, and Mammalian Toxicity. Regression Equations (Table IV). Increased steric requirement (branching) at the α- and/or γ-positions promotes activity in all three series in every case except the housefly equations where variation in potency is too limited to support both E_s and log P terms: the log P terms in the housefly equations probably "include" a favorable steric component that is masked by an unfavorable role of the lipophilicity of substituents as discussed below.

Two new factors, however, show up in the QSAR for the insects, the mite, and the rat, all in vivo tests, which were not present in the I_{50} equations: 1. As log P increases above about 0.25, potency decreases. 2. Potency increases with replacement of the oxygen in the oxathia series with a readily oxidizable sulfur atom.

The coefficients for the log P and $(\log P)^2$ terms given in Table IV yield three basic patterns:

1. In eight equations (6, 11, 13, 15, 16, 18–20) activity decreases linearly over the range of log P studied (0.0–2.01) according to a function having a slope averaging –0.97 (range of slopes –0.79 to –1.23). A steeper linear function (slope –2.04) was noted for the dithia mite eq 9 on the basis of the remarkable inactivity of compounds **S22** and **S23**; a much more gradual slope (–0.56) was observed in the oxathia housefly equation (17).

2. The Mexican bean beetle oxathia equation (14) and the rat dithia equation (21) show no dependence on log P. In the case of Mexican bean beetle, there is insufficient variation in biological data to support a strong regression analysis. The dithia rat equation shows no overt role of log P because any possible real effect of log P is hidden in the $\sum E_s$ terms (log P is a linear function of the $\sum E_s$ terms as noted at the bottom of Table IV).

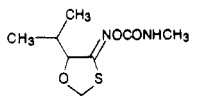
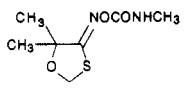
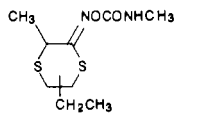
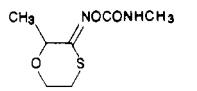
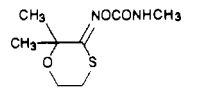
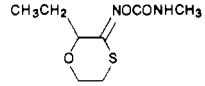
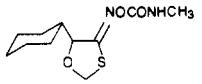
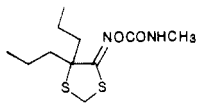
3. For all other cases (eq 4, 5, 7, 10, and 12), log P and $(\log P)^2$ terms described parabolas over the range of data in log P present in these data sets. The shapes of these parabolas are fairly uniform, with log P optima occurring between –0.11 and +0.76. Data sets having a point at which a dramatic loss in activity occurred at high log P values generally resulted in a parabolic log P function.

Two curves are plotted in Figure 1: one is a line for the log P function of eq 19 having a slope of –0.79 representing the family of equations having linear log P functions; the second is a parabola for the log P function of eq 4 having optima at 0.33 and representing the family of equations having parabolic log P functions. It is important to note that, within the range of data studied, the parabolic function follows the linear function closely, certainly within the precision of the data and the standard errors of the regression equations. The general conclusion can be drawn that, for the biological activity parameters examined in this study, activity decreases monotonously with increase in log P above 0.5 with a slope approximating –1.0. Further definition within this generalization requires more data, particularly data for compounds having log P substantially below zero.

Finally, the $I_{\beta\text{-S}}$ terms in each mixed-set equation clearly express where and to what extent activity is promoted by the presence of an oxidizable sulfur atom. Aphid activity, mite activity, and acute toxicity to the rat are all increased about 1 log unit when the oxygen of the oxathia compounds is replaced with sulfur. Activity against the southern armyworm, Mexican bean beetle, and housefly is much less affected by the oxygen/sulfur change.

Predictions from the Regression Equations. In Table V are given predicted vs. observed data for eight compounds illustrating the predictive utility of the QSAR regression equations. Two examples (section a, Table V) are given illustrating predicted vs. observed data for compounds which were part of the data set underlying the

Table V. Regression Predictions (Mixed Equations)

	no.	$\sum E_s^{\alpha}$	$\sum E_s^{\gamma}$	$I_{\beta\text{-S}}$	log P^a	MW	predicted/observed LC_{50}, ppm: bean aphid	two-spotted mite	southern armyworm	Mexican bean beetle	housefly	LD_{50}, mg/kg acute oral, rat
a. Illustrative (Predicted/Observed) from Regression Set												
	8	0.77	2.48	0.0	1.48	218	57/40	437/500	227/500	137/60	30/9	25/16.2
	14	0.0	2.48	0.0	0.82	204	5/4	38/40	15/11	14/14	8/16	1.6/1.6
b. Test Cases (Predicted/Observed) — New Compounds												
	T-1	1.24	1.17	1.0	1.89[1]	248	15/60	35/45	580/1000	88/35	23/90	30/...
	T-2	1.24	2.48	0.0	0.45[2]	204	22/12	128/112	38/8	27/6	4/3	8.9/5.6
	T-3	0.0	2.48	0.0	0.76[3]	218	5/8	38/18	16/17	14/3	8/18	1.7/0.6
	T-4	1.17	2.48	0.0	0.95[4]	218	32/20	207/100	88/1000	73/1000	11/11	20.2/19.0
c. Other Predictions (Compounds Not Made)												
	P-1	0.45	2.48	0.0	2.12[5]	258	423	4080	3700	425	114	50
	P-2	−0.72	2.48	1.0	3.31[6]	276	10,000	66,000	313,000	507	359	5

[a] Key: 1, **S20** + 0.50; 2, **15** + 0.45; 3, **14** − **1** + **15**; 4, **T-2** + 0.50; 5, **1** + 2.51 (cyclohexyl; Tute, 1971) − 0.45 (ring–ring attachment); 6, **S26** + 2.00.

regression equations, compounds **8** and **14**. The validity of the models for compounds not present in the regression data sets is tested with compounds **T-1**–**T-4** (section b, Table V), compounds made *subsequent to* the development of the model. The data for **T-1**–**T-4** indicate how well the contributions of branching, log P, and $I_{\beta\text{-S}}$ calculated for the four test compounds correctly predict biological activity. Finally, section c of the table illustrates how activity levels predicted by QSAR equations can discourage the synthesis of disadvantageous analogues, **p-1** and **P-2** (P as a compound label prefix designates a compound proposed for synthesis but not made).

CONCLUSIONS

The potency of insecticidal oxathia and dithia heterocyclic oxime methylcarbamates is promoted by an increase in steric requirement at the α and γ sites on the molecule. This advantageous role of increased alkyl bulk is, however, modified by the negative contribution to activity in the insects, the mite, and the rat of increased lipophilicity. Changing the oxygen atom in the oxathia compounds to sulfur uniformly enhances activity.

It is interesting to speculate that the improvement in activity with α and γ branching is related to an improvement in how well the inhibitor mimics the natural target enzyme substrate acetylcholine. It is further interesting to attribute the negative role of increased lipophilicity to the role of increased lipophilicity in promoting metabolic detoxification. There is precedent (Gaudette and Brodie, 1959) for the premise that metabolism in vivo is promoted by increased lipophilicity.

Finally, the advantageous role of sulfur vs. oxygen may lie in the ease with which the former is oxidized in vivo; not only are sulfoxide-bearing oxime carbamates known to be excellent acetylcholinesterase inhibitors (Metcalf et al., 1965; Payne et al., 1966; Weiden, 1968), but sulfoxidation substantially lowers log P, a factor shown by the present work to be advantageous.

The roles of substituent size at the α- and γ-positions and log P are essentially identical for the oxathia and dithia series; the individual QSAR for the oxathia series may be superimposed on the individual QSAR for the dithia series by the simple expedient of expressing the presence or absence of the oxidizable sulfur using the $I_{\beta\text{-S}}$ term.

Selective improvement in insect vs. mammalian toxicity is not likely to be achieved by further synthesis in this series. The compounds are toxic to the rat. Minimization of that toxicity by decreasing the size of groups at the α- or γ-positions or increasing log P is accompanied by parallel reduction in insecticidal activity. The single defined factor making possible reduced mammalian toxicity without equal loss of insect potency is the reduction in toxicity associated with removal of the sulfur. Unfortu-

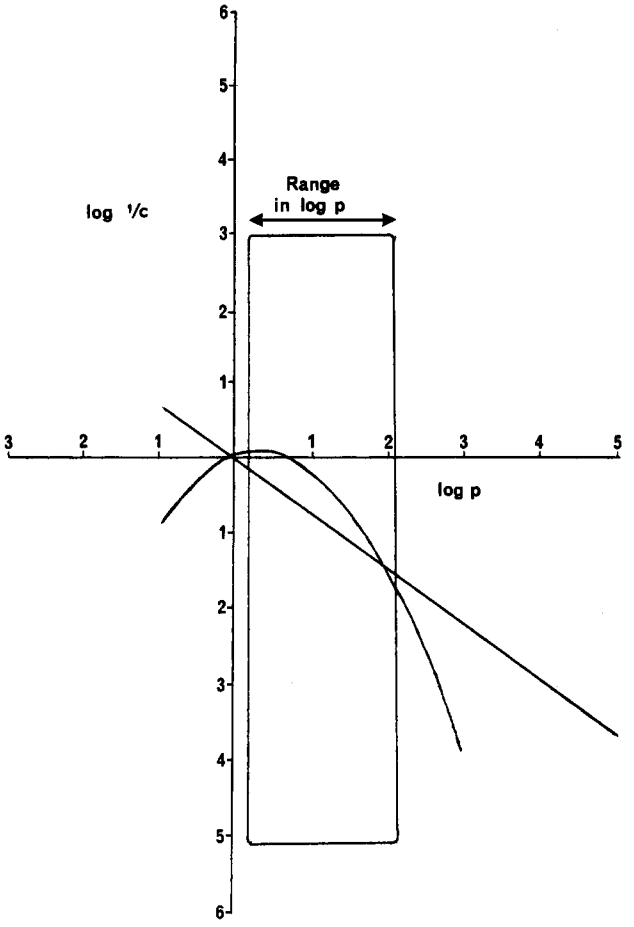


Figure 1. Biological potency vs. log *P*.

nately, reduction in bean aphid and two-spotted mite potency is realized concomitantly.

The optimum compounds in the series have probably been synthesized. They are analogues in which somewhat attenuated mammalian toxicity has been achieved at the expense of maximum insecticidal activity by some combination of limitation of branching α and γ to the oxime, avoidance of the oxidizable sulfur, or use of log *P* levels higher than those optimum for maximum insecticide performance.

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LITERATURE CITED

Cohen, S. G.; Chrishti, S. B.; Elkind, J. L.; Reese, H.; Cohen, J. B. *J. Med. Chem.* **1985**, *28*, 1309.
Craig, P. N. *J. Med. Chem.* **1971**, *14*, 680.
D'Silva, T. D. J.; Durden, J. A., Jr.; Sousa, A. A.; Weiden, M. H. J. *J. Agric. Food Chem.* **1985**, *33*, 110.
Fujita, T.; Isawa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175.
Gaudette, L. E.; Brodie, B. B. *Biochem. Pharmacol.* **1959**, *2*, 89.
Kurtz, A. P.; Durden, J. A., Jr.; Sousa, A. A.; Weiden, M. H. J. *J. Agric. Food Chem.* **1987**, preceding paper in this issue.
Metcalf, R. L.; Fukuto, T. R.; Frederickson, M.; Peak, L. *J. Agric. Food Chem.* **1965**, *13*, 473.
Moorefield, H. H.; Tefft, E. R. *Contrib. Boyce Thompson Inst.* **1958**, *19*, 295.
Payne, L. K., Jr.; Stansbury, H. A., Jr.; Weiden, M. H. J. *J. Agric. Food Chem.* **1966**, *14*, 356.
Talvik, I.; Palm, V. *Org. React. (USSR)* **1971**, *8*, 445.
Tute, M. S. *Advances in Drug Research*; Harper, N. J., Simmonds, A. B., Eds.; Academic: New York, 1971; Vol. 6, Chapter 1, pp 1–78.
Weiden, M. H. J. *J. Sci. Food Agric. Suppl.* **1968**, 19.

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