Quantitative Structure–Activity Relationships in Acaricidal 4*H*-1,3,4-Oxadiazin-5(6*H*)-ones

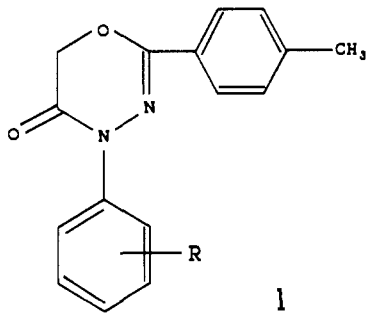
Mark A. Dekeyser,*,† David M. Borth,† Richard C. Moore,*,‡ and Anupama Mishra†

Research Laboratories, Uniroyal Chemical Ltd., P.O. Box 1120, Guelph, Ontario, Canada N1H 6N3, and New Product Research, Uniroyal Chemical Company, Inc., 74 Amity Road, Bethany, Connecticut 06525

A series of 37 2,4-diphenyl-1,3,4-oxadiazin-5-one acaricides has been synthesized. Their acaricidal activity has been related to certain of their physicochemical properties by using a Hansch-type regression equation. The initial equation developed was validated by predicting the activity of an additional nine compounds which were subsequently synthesized and tested. The QSAR study was carried out to optimize activity, resulting in a 6-fold increase in activity over the lead compound. Two novel aspects of the study were (i) the use of a new technique for selecting the compounds in the original set, so as to maximize the information obtained for a given amount of synthesis effort, and (ii) the use of a statistical technique called censored data regression to make use of information from compounds that were insufficiently acaricidal to allow determination of an ED_{50}.

INTRODUCTION

2,4-Diphenyl-1,3,4-oxadiazin-5-ones have good acaricidal activity (Dekeyser et al., 1987), especially against the two-spotted spider mite, *Tetranychus urticae*, which is a serious plant pest in crop protection. This paper is concerned with the development of quantitative structure–activity relationships (QSAR) required to obtain the most acaricidally active member in 2-(4-methylphenyl)-4-(substituted)phenyl-1,3,4-oxadiazin-5-ones **1**.



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An examination of the literature on 4*H*-1,3,4-oxadiazin-5(6*H*)-ones reveals that only a scant few of these are known (Van Alphen, 1924, 1928, 1929; Hoppenbrouwers, 1934). It was this realization that interested us in systematically exploring the 2,4-diphenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones. Acaricidal activity in this series was first discovered with compound **1** (**1**, R = H). In an earlier QSAR study, exploration of the effects of 20 different substituents in place of the methyl group resulted in greatly reduced acaricidal activity; thus, our attention was devoted to introducing various substituents, R, in **1**.

Structures and biological data for the new 1,3,4-oxadiazin-5-one compounds reported herein are collected in Table I.

Chemistry. The new 4*H*-1,3,4-oxadiazin-5(6*H*)-ones **1** were prepared from the substituted phenylhydrazide **3** by reaction with chloroacetyl chloride and potassium carbonate. Each hydrazide **3** was synthesized by treatment of the precursor substituted phenylhydrazine **2** with 4-methylbenzoyl chloride (Scheme I).

Compound **9** having a quaternary nitrogen was prepared from the nitro precursor, compound **11**, via reduction with stannous chloride, generating amino compound **23**, which was subsequently quaternized by reaction with methyl iodide. Compounds **8** and **22** were also prepared by reduction of their nitro precursors, compounds **12** and **10**, respectively. Compound **24** was prepared from compound **13** by cleavage of the methyl ether using boron tribromide. Compound **33** was prepared by esterification of compound **34**. Carbamate derivative **37** was prepared by treatment of hydroxy compound **24** with methyl isocyanate. Substituted phenylhydrazines used to prepare compounds **5–7**, **14**, **19–21**, and **29–32** were made from their corresponding anilines by diazotization with sodium nitrite and reduction with stannous chloride. Compound **36** had as its starting material *m*-nitrobiphenyl, which was reduced to the aniline derivative with stannous chloride and then treated as the other anilines to give the *m*-hydrazinobiphenyl. Compound **35** had as its starting material *m*-nitrobenzyl bromide, which on Friedel–Crafts treatment with benzene and aluminum chloride gave *m*-benzylnitrobenzene. Again, this nitro compound with stannous chloride gave *m*-benzylaniline, and then diazotization gave *m*-benzylphenylhydrazine.

Biology. Data on the acaricidal activities of the oxadiazinones are presented in Table I. The efficacy data (ED_{50}, ppm) are for foliage spray against two-spotted spider mite adults. The efficacy data were obtained by running six rates (500, 250, 125, 63, 21, and 15 ppm), two replicates per rate, for each selected compound. A mean average of percent alive mites in the two replicates was calculated 6 days following treatment. Each compound was compared to a commercial standard, propargite, and two untreated checks. Compounds exhibiting less than 50% control at 500 ppm were retested at higher rates in an attempt to determine their ED_{50} values. However, some compounds failed to exhibit 50% control at biologically meaningful rates.

EXPERIMENTAL PROCEDURES

All hydrazines **2**, hydrazides **3**, and oxadiazinones **1** were characterized by NMR and IR spectra and elemental analyses. The melting points are uncorrected. NMR spectra were obtained

† Uniroyal, Ontario.
‡ Uniroyal, Connecticut.

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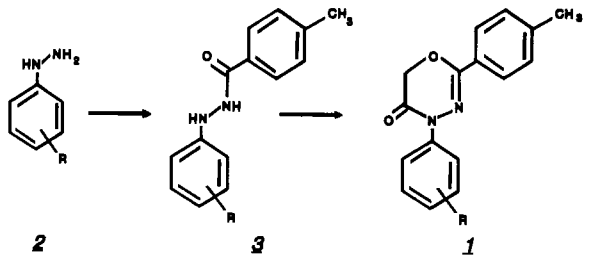
Scheme I



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on a Varian EM 360L spectrometer at 60 MHz with Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Elemental analyses were obtained from a Perkin-Elmer 240C elemental analyzer.

2-(Phenylmethyl)phenylhydrazine Hydrochloride (2, R = *o*-$CH_2C_6H_5$). 2-(Phenylmethyl)benzenamine (37.0 g) was added to 500 mL of concentrated HCl at 0 °C and mechanically stirred for 20 min. A solution of 15.0 g of sodium nitrite in 60 mL of water was added dropwise over 30 min. The temperature was maintained at 0 °C for 30 min further, at which time a −20 °C solution of 89.0 g of stannous chloride in 200 mL of concentrated HCl was added in one portion. The resulting slurry was stirred at 0 °C for 1 h, at which time the mixture was filtered. Recrystallization from water afforded 25.3 g (53.5%) of hydrazine 2 (R = *o*-$CH_2C_6H_5$) as its hydrochloride. Structure was confirmed by spectral analyses.

2-[2-(Phenylmethyl)phenyl]hydrazide of 4-Methylbenzoic Acid (3, R = *o*-$CH_2C_6H_5$). 4-Methylbenzoyl chloride (20.0 g) was added dropwise to a stirred mixture of 2-(phenylmethyl)phenylhydrazine hydrochloride (20.0 g) and 80 mL of pyridine, which was cooled to maintain a temperature of 0–10 °C in an ice bath. After the addition, the mixture was stirred overnight and poured into 1 L of ice water. Filtration and recrystallization from ethanol gave 18.5 g (68.5%) of hydrazide 3 (R = *o*-$CH_2C_6H_5$): mp 136–138 °C. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 25.9; H, 4.7; N, 7.8. Found: C, 26.2; H, 5.0; N, 8.1.

2-(4-Methylphenyl)-4-[2-(phenylmethyl)phenyl]-4*H*-1,3,4-oxadiazin-5(6*H*)-one (1, R = *o*-$CH_2C_6H_5$). A 10.0-g sample of hydrazide 3 (R = *o*-$CH_2C_6H_5$) was dissolved in 80 mL of 2-butanone. Chloroacetyl chloride (8.0 g) was added dropwise, and the resulting solution was heated to reflux for 4 h, cooled to room temperature, and treated with 25.0 g of potassium carbonate powder. The mixture was then refluxed again for 4 h. After filtration and evaporation of the solvent, 10.0 g of crude oxadiazinone was obtained. Recrystallization from ethanol afforded oxadiazinone 1 (R = *o*-$CH_2C_6H_5$): 7.0 g (61.9%); mp 125–127 °C. Anal. Calcd for $C_{23}H_{20}N_2O_2$; C, 28.3; H, 5.5; N, 10.2. Found: C, 28.6; H, 5.2; N, 9.9.

3-(Phenylmethyl)phenylhydrazine Hydrochloride (2, R = *m*-$CH_2C_6H_5$). 1-Nitro-3-(phenylmethyl)benzene was synthesized by Friedel–Crafts alkylation of 1-(chloromethyl)-3-nitrobenzene on benzene in the presence of aluminum chloride as described in the literature (Mease et al., 1968). The nitro compound (11.0 g) was reduced with stannous chloride (40.0 g) by refluxing in 150 mL of ethanol, cooling the mixture to room temperature, and pouring slowly into 300 mL of 10% aqueous sodium hydroxide. Extraction with methylene chloride provided 9 g of 3-(phenylmethyl)benzenamine as an oil, 94.7% yield. Structure was confirmed by spectral analysis. The amine was converted into the hydrazine as its hydrochloride in 80.5% yield by the method described in example 1. Structure was confirmed by spectral analysis.

4-(3-Aminophenyl)-2-(4-methylphenyl)-4*H*-1,3,4-oxadiazin-5(6*H*)-one (1, R = *m*-NH_2). Nitrooxadiazinone (1, R = *m*-NO_2) (6.0 g) was reduced with stannous chloride as in previous example, resulting in 1.7 g (31.5%) of aminooxadiazinone (1, R = *m*-NH_2): mp 205–208 °C. Structure was confirmed by spectral analysis.

***N,N,N*-Trimethyl-3-[5,6-dihydro-2-(4-methylphenyl)-5-oxo-4*H*-1,3,4-oxadiazin-4-yl]benzenaminium Iodide (1, R = *m*-NMe_3^+ I^-).** Aminooxadiazinone (1, R = *m*-NH_2) (5.0 g) was dissolved in 15 mL of *N,N*-dimethylformamide at room temperature and treated with 6.0 g of *N,N*-diethylbenzenamine followed by 14.0 g of iodomethane. The mixture was stirred overnight and then filtered, giving 5.2 g (92.8%) of aminium oxadiazinone (1, R = *m*-NMe_3^+ I^-). Structure was confirmed by spectral analysis.

SUBSTITUENT SELECTION

A list of 433 substituents of known physiochemical parameter values was rated according to difficulty of synthesis. Of the 433 potential analogues, 78 were judged to be impractical to synthesize. The remaining 355 compounds were rated for difficulty on a scale from 1 to 8 with a 1 rating indicating a relatively easy analogue to synthesize. (A rating of 8 indicates that a compound is expected to take about 8 times as long to synthesize as a compound with a rating of 1.)

The primary sources for the physicochemical parameters were Hansch and Leo (1979) and Exner (1978). For some substituents, values not previously reported were obtained by interpolation and extrapolation from values for closely related substituents (Relyea, 1989).

From this list a set of 20 compounds was chosen for synthesis by using a method of selection developed by Borth et al. (1985). The selection method took into account (i) the estimated difficulty of synthesis for each potential analogue and (ii) the amount of information (defined as expected change in statistical entropy) that each potential analogue provides for making predictions of activity over the whole set of 355 practical monosubstituted analogues. Essentially, the selection method is based on balancing statistical efficiency against synthesis difficulty. That is, some selections are better statistically in that they will provide better coverage of the parameter space and will allow more accurate predictions of activity for the 355 − 20 = 335 analogues not actually synthesized. However, a selection based on statistical efficiency alone may result in a heavy weighting toward compounds that are difficult to synthesize.

The set of analogues chosen for synthesis consists of the first twenty in Table I. This table also gives the relative synthesis difficulties for each compound as well as the QSAR parameters and the ED_{50} values. (Of course, the ED_{50} values were not known at the time the substituents were selected.) The average difficulty rating is 1.5, and the maximum is 4. The average difficulty rating over the entire set of feasible compounds was 6.32. Also, for the sake of comparison, a selection was made by assuming equal synthesis difficulty for all analogues. This selection is given in Table II. The average difficulty rating for the compounds chosen in this way is 6.25, which is more than 4 times the average for Table I. The statistical efficiency of the two selections can be evaluated in various ways. One criterion is the relative average standard error of prediction over the set of 355 feasible compounds. For the selection in Table I this is 0.76, vs 0.51 for the selection in Table II. Another criterion is the maximum relative standard error of prediction over the set of 355 feasible compounds. For the selection in Table I this is 1.45, vs 0.700 for the selection in Table II. Thus, if the selection in Table II were used, the average synthesis difficulty would increase by a factor of 4, while the average standard error of prediction would decrease by 33% and the maximum standard error of prediction would decrease by 52%. Hence, the loss in statistical efficiency is much less than the gain in ease of synthesis. Note, also, that as shown in Borth et al. (1985) the same statistical efficiency with less total synthesis effort could have been achieved by adding more easy to synthesize compounds. This was not done because the statistical efficiency of the 20 compounds selected was deemed to be adequate.

Table I. Physical Data, Synthesis Difficulty Rating, and Efficacy Data for Compounds 1

no.	substituent	difficulty rating	π	F	R	MR	H_d	ED_{50}
1	H	1	0.00	0.00	0.00	0.0	0	152
2	o-CH_3	1	0.84	−0.05	−0.11	4.7	0	>10000
3	m-CH_3	1	0.52	−0.04	−0.04	4.7	0	33
4	p-CH_3	1	0.60	−0.04	−0.13	4.7	0	123
5	o-$CH_2C_6H_5$	2	2.01	−0.07	0.00	29.0	0	66
6	o-C_6H_5	2	2.39	0.10	−0.07	24.3	0	25
7	p-cyclo-C_6H_{11}	2	2.51	−0.17	0.04	25.7	0	905
8	p-NH_2	2	−1.30	0.02	−0.68	4.2	1	453
9	m-$N(CH_3)_3^+$	4	−5.96	0.87	−0.02	20.2	0	>1000
10	o-NO_2	1	0.11	0.84	0.09	6.0	0	>10000
11	m-NO_2	1	0.11	0.66	0.04	6.0	0	>10000
12	p-NO_2	1	0.22	0.67	0.11	6.0	0	>823
13	p-OCH_3	1	−0.03	0.26	−0.53	6.5	0	29
14	o-$SO_2C_6H_5$	2	0.27	0.71	0.12	32.2	0	655
15	o-F	1	0.00	0.54	−0.32	−0.4	0	917
16	p-F	1	0.15	0.43	−0.37	−0.4	0	425
17	o-Br	1	0.84	0.55	−0.18	7.6	0	>1000
18	p-Br	1	1.19	0.44	−0.21	7.6	0	171
19	m-$OCH_2C_6H_5$	2	1.66	0.21	−0.15	30.7	0	31
20	p-$OCH_2C_6H_5$	2	1.66	0.21	−0.43	30.7	0	826
21	p-C_2H_5	2	1.10	−0.05	−0.10	9.4	0	151
22	o-NH_2	2	−1.40	0.02	−0.59	4.2	1	>1000
23	m-NH_2	2	−1.29	0.02	−0.24	4.2	1	>1000
24	p-OH	8	−0.61	0.29	−0.66	1.5	1	>1000
25	m-OCH_3	1	0.12	0.25	−0.18	6.5	0	728
26	p-SO_2CH_3	4	−1.20	0.54	0.18	12.5	0	714
27	m-F	1	0.22	0.43	−0.13	−0.4	0	1000
28	o-Cl	1	0.76	0.51	−0.16	4.8	0	>1000
29	o-C_2H_5	2	1.39	−0.06	−0.09	9.4	0	120
30	m-C_2H_5	2	0.99	−0.05	−0.04	9.4	0	116
31	m-SCH_3	2	0.64	0.19	−0.07	13.0	0	117
32	p-C_6H_5	2	1.74	0.08	−0.09	24.3	0	902
33	p-$COOC_2H_5$	8	0.46	0.33	0.12	16.2	0	>2251
34	p-COOH	8	−0.32	0.33	0.12	5.9	1	>4000
35	m-$CH_2C_6H_5$	8	2.01	−0.05	0.00	29.0	0	30
36	m-C_6H_5	8	1.92	0.08	−0.03	24.3	0	34
37	p-$OCONHCH_3$	8	−0.42	0.41	−0.15	15.3	1	>1000
	propargite							50

Table II. Selection and Actual Difficulty Ratings That Result from Basing Selection on Statistical Efficiency Alone

substituent	difficulty rating
m-$N(CH_3)_3^+$	4
p-$N(CH_3)_3^+$	4
o-$N(CH_3)_3^+$	4
o-COO−	8
p-OH	8
p-N=CHC_6H_5	4
o-N=CHC_6H_5	4
o-NO_2	1
p-$SO_2C_6H_5$	8
o-SO_2CF_3	8
p-CH=$CHCOOC_2H_5$	8
m-CH=$CHCOC_6H_5$	8
o-CH=$CHCOC_6H_5$	8
p-$N(C_2H_5)_2$	4
o-cyclo-C_6H_{11}	8
p-CH=CHC_6H_5	8
m-CH=CHC_6H_5	8
o-CH=CHC_6H_5	8
p-COO−	8
m-$NHSO_2C_6H_5$	4

The following is a brief description of the mathematical method used for substituent selection. Let x_i be the row vector (corresponding to the ith substituent) such that the proposed mathematical model relating structure to activity is $\log (1/ED_{50_i}) = x_i\beta'$, where β is the vector of unknown coefficients to be estimated. (For a more specific definition of x_i, see eq 3 and the following discussion in the next section.) The selection process is iterative, as shown in Figure 1, and is based on the following criterion for adding a substituent to the selection

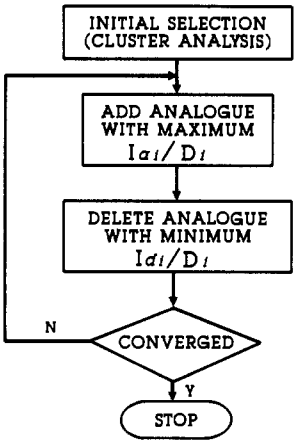

Figure 1. Flow diagram of substituent selection process.

$$I_{ai}/D_i = (1/2)\{\ln [1 + x_i(X_{i-1}'X_{i-1})^{-1}x_i']\}/D_i \quad (1)$$

and the following closely related criterion for deleting a compound from the selection

$$I_{di}/D_i = (1/2)\{\ln [1 + x_i(X_i'X_i)^{-1}x_i']\}/D_i \quad (2)$$

where D_i is the difficulty rating for the ith substituent and X_i is a matrix whose rows are the vectors x_1, x_2, ..., x_i, corresponding to the substituents currently selected. The numerators of the above expressions are equal to the statistical information (specifically the expected entropy change) due to adding or deleting the ith substituent to or from the group of substituents already selected.

Note that the quantity $x_i(X_{i-1}'X_{i-1})^{-1}x_i'$ is proportional to the standard error of prediction for the ith substituent

(Draper and Smith, 1981), assuming data are available for substituents 1, 2, ..., $i-1$. The constant of proportionality is σ, the residual standard deviation from the fitted model. Of course, this is unknown at the substituent selection stage but is assumed to apply equally to all substituents. Thus, the addition criterion, i.e., eq 1, has the intuitively appealing property that, in considering substituents of equal synthesis difficulty, the one for which the uncertainty of prediction is the greatest, given the substituents already in the selection, will be chosen. As discussed by Borth (1975), this is related to a principle of the statistical design of experiments which applies quite generally. Similar considerations apply to the deletion criterion, i.e., eq 2.

As shown in Figure 1, the selection process is an iterative one in which the selection is improved by alternately adding and deleting substituents, until convergence is achieved. The starting point for this process was generated by clustering the 355 feasible substituents into 20 (the number of substituents to be selected) on the basis of the elements of the vector x_i for each substituent. The initial selection was the substituent in each cluster with the lowest difficulty rating. In the case of a tie, the cluster closest to the cluster center was chosen. The SAS procedure FASTCLUS (SAS Institute, 1988) was used for this purpose. Full details of the statistical justification of the selection method are given by Borth et al. (1985).

STATISTICAL ANALYSIS

Statistical analyses were carried out to relate log $(1/ED_{50})$ to the following physicochemical parameters: π (lipophilicity), F (inductive effect), R (resonance effect), H_d (a zero-one indicator variable describing hydrogen-donating effect), and MR (molar refractivity). The initial data analyzed consisted of the first 28 compounds in Table I. These compounds are the 20 selected as described in the previous section plus 8 compounds that were made prior to the selection. However, the *o*-CH_3 analogue was found to be extremely inactive and did not fit the regression model and was deleted from the analysis (see Results and Discussion). The remaining compounds in Table I were not used in developing the initial regression model but were used to validate the model. Subsequently, the model was refitted by using all of the data (with the exception of the *o*-CH_3 analogue).

Some of the data in Table I consist of a lower bound for the ED_{50} rather than a specific value. This is because less than 50% control was exhibited at all rates tested. Statistically, this is referred to as censored data. Rather than attempting to obtain ED_{50} values for these very inactive compounds, the data were analyzed by using a special technique for regression analysis that allows for censored observations (Aitkin, 1981; Wolynetz, 1979). The computations were carried out by using a SAS procedure called LIFEREG (SAS Institute Inc., 1988) on a Compaq 386/20 computer. This technique recovers a substantial amount of the information that would be lost if the censored observations were merely deleted from the analysis. However, the reporting of the statistical analysis results is different from that of standard regression packages.

Initially, the mathematical model considered for the data was

$$\log(1/ED_{50}) = \beta_0 + \beta_1\pi' + \beta_2\pi'^2 + \beta_3F' + \beta_4R' + \beta_5(\mathrm{OMR})' + \beta_6(\mathrm{MMR})' + \beta_7(\mathrm{PMR})' \quad (3)$$

where the prime indicates that the variable has been standardized by subtracting the mean and dividing by the standard deviation calculated over the compounds included in the analysis. The variables OMR, MMR, and PMR take on the MR value for the substituent when the substituent is in the corresponding position and take on the value 0 otherwise. [Equation 3 was used at the substituent selection stage. Specifically, $x_i = (1, \pi_i, \pi_i^2, F_i, R_i, \mathrm{OMR}_i, \mathrm{MMR}_i, \mathrm{PMR}_i)$ was used in eqs 1 and 2. Standardization of the variables was not required at the selection stage, although it is desirable at the analysis stage.]

Table III. Summary of Statistical Analysis of Compounds 1 and 3–28, of Table I, on the Basis of Equation 4

variable	mean	SD	i	β_i	SE	χ^2	P
constant	–	–	0	−2.52	0.10	637.7	0.0001
F	0.304	0.305	1	−0.59	0.09	45.7	0.0001
R	−0.171	0.240	2	−0.48	0.11	18.3	0.0001
OMR	3.989	9.143	3	0.33	0.08	15.6	0.0001
MMR	2.663	7.009	4	0.25	0.08	9.3	0.0023
PMR	4.014	7.821	5	0.55	0.19	8.3	0.0039
PMR^2	–	–	6	−0.28	0.07	16.2	0.0001
H_d	0.148	0.362	7	−0.70	0.14	26.3	0.0001

Table IV. Results of Validating Equation 4 on Nine Additional Compounds

substituent	log $(1/ED_{50})$	predicted log $(1/ED_{50})$	ED_{50}	predicted ED_{50}
o-C_2H_5	−2.08	−1.95	120	89
m-C_2H_5	−2.06	−2.07	116	117
m-$CH_2C_6H_5$	−1.48	−1.45	30	28
m-C_6H_5	−1.53	−1.81	34	64
p-C_6H_5	−2.96	−2.64	902	439
p-COOH	<−3.60	−4.94	>4000	86151
p-$COOC_2H_5$	<−3.35	−2.92	>2250	839
m-SCH_3	−2.07	−2.34	117	220
p-$OCONHCH_3$	<−3.00	−4.45	>1000	28069

After preliminary data analysis, it was discovered that π and π^2 were not significant but that the inclusion of the H_d parameter as well as a term involving $(\mathrm{PMR})'^2$ significantly improved the fit. Thus, the final model is

$$\log(1/ED_{50}) = \beta_0 + \beta_1F' + \beta_2R' + \beta_3(\mathrm{OMR})' + \beta_4(\mathrm{MMR})' + \beta_5(\mathrm{PMR})' + \beta_6(\mathrm{PMR})'^2 + \beta_7H_d \quad (4)$$

Table III summarizes the statistical analysis of compounds 1 and 3–28 of Table I, as fitted to eq 4. The mean and standard deviation are provided for converting from actual to coded values, e.g., $F' = (F - 0.304)/0.305$ and $(\mathrm{PMR})'^2 = [(\mathrm{PMR} - 4.014)/7.821)]^2$. Note that $n = 27$ and $s = 0.34$ (maximum likelihood estimate). Although r^2 is undefined for censored data regression, it is possible to estimate the value that would have been obtained without censoring. This may be done by calculating 1 minus the residual variance from eq 4 divided by the residual variance from the model log $(1/ED_{50})$ = constant, i.e., $1 - (0.34^2/0.91^2) = 0.86$. Therefore, we estimate $r = 0.93$.

Equation 4, with the parameter estimates given in Table III, was validated by predicting the ED_{50} of nine additional compounds which were subsequently synthesized and tested. A comparison, indicating good agreement between predicted and actual values for these compounds, is shown in Table IV. Subsequently, the equation was refitted to take all of the available data (with the exception of the *o*-CH_3 analogue) into account. These results are shown in Table V. The final equation has $n = 36$, $s = 0.32$ (maximum likelihood estimate), and an estimated $r = 0.94$. A plot of actual vs predicted values for these 36 compounds is shown in Figure 2. Note that points plotted as + represent censored data [upper bounds on actual log $(1/ED_{50})$]. When these censored data points fall above the line, they do not indicate lack of correlation with the

Table V. Summary of Statistical Analysis of Compounds 1 and 3–37, of Table I, on the Basis of Equation 4

variable	mean	SD	i	β_i	SE	χ^2	P
constant	–	–	0	−2.54	0.09	718.4	0.0001
F	0.263	0.286	1	−0.55	0.07	64.3	0.0001
R	−0.134	0.221	2	−0.48	0.09	25.8	0.0001
OMR	3.253	8.125	3	0.28	0.07	18.0	0.0001
MMR	4.100	8.540	4	0.33	0.07	21.8	0.0001
PMR	4.725	8.183	5	0.39	0.15	8.3	0.0108
PMR^2	–	–	6	−0.27	0.07	15.9	0.0001
H_d	0.167	0.377	7	−0.75	0.13	32.0	0.0001

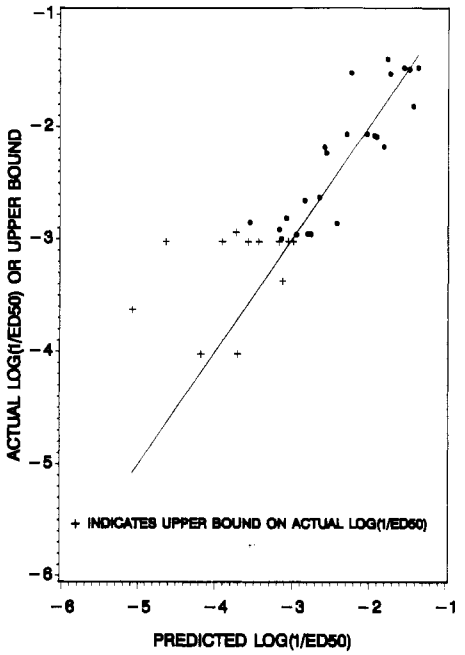

Figure 2. Actual vs predicted activity of compounds 1 and 3–37 on the basis of eq 4 with parameter estimates given in Table V. Note that points plotted as + which fall above the line do not indicate lack of fit, since they represent upper bounds on activity for the respective compounds.

predicted values, since the true value is known to fall below the plotted point.

The following is a brief description of the methodology of censored data regression. In the absence of censored data, multiple regression analysis involves determining the values of the vector of unknown constants, β, which minimize the sum of squares between the observed data and the values predicted from the equation. In censored data regression, the parameters β and σ are chosen to maximize the logarithm of the likelihood function. Let $y_i = \log (1/ED_{50i})$ with the data ordered so that the n_c censored observations come first, followed by $n - n_c$ non-censored observations. Also, let $\mu_i = x_i\beta'$. Then the natural logarithm of the likelihood function is, up to a constant independent of β and σ, given by

$$\ln L = -(n - n_c) \ln \sigma + \sum_{i=0}^{n_c} \ln \{\Phi[(y_i - \mu_i)/\sigma]\} - {}^1/_2 \sum_{i=n_c+1}^{n} (y_i - \mu_i)^2/\sigma^2 \quad (5)$$

(Wolynetz, 1979), where $\Phi(z)$ is the left tail area of the standardized normal distribution. The likelihood function is proportional to the probability of observing the data and is a function of β and σ. An important school of statistical inference is based on the idea of choosing parameter estimates that maximize the likelihood function and on the study of the properties of the resulting estimators. Examination of eq 5 indicates that when n_c equals zero, the log likelihood function is maximized with respect to β by minimizing the sum of squared differences between the observed and predicted values; i.e., censored data regression is equivalent to ordinary regression, as we would expect. When n_c is not zero, the censored observations do play a role in determining the parameter estimates. The actual amount of information contributed by particular censored observations will vary. In general, the censored data points will contribute most to the regression when they do not fall too far above the line depicting actual vs fitted points in Figure 2.

In ordinary regression analysis, the overall significance is evaluated via the F ratio which may be related to the level of statistical significance by reference to tables of the F distribution. In censored data regression the analogous statistic is computed from the logarithm of the likelihood function. [See, for example, Schneider (1986). Note, however, that his equation for the logarithm of the likelihood function relates to right-censored data, whereas we are dealing with left-censored data.] Specifically, to assess the overall significance of parameters β_1–β_7 in eq 4, we compute the difference between the log likelihood maximized for the full model and that for the restricted model $\log (1/ED_{50}) = \beta_0$. Twice this quantity is asymptotically distributed as χ^2 with seven degrees of freedom under the null hypothesis $\beta_1 = \beta_2 = \ldots \beta_7 = 0$. For the analysis of the 36 compounds referred to in Table V, the computed χ^2 value is 64.3. The probability of obtaining so large a value under the null hypothesis is less than 0.00001, so the null hypothesis is rejected. Similarly, for the analysis of the 27 compounds referred to in Table III, the computed χ^2 value is 43.8, for which the probability value is less than 0.00001, so the null hypothesis is also rejected on this smaller data set. Note that the p values are approximate (Schneider, 1986).

It is interesting to compare the χ^2 values with and without the censored data included, since this gives us some indication of the information provided by these observations. For the data analyzed in Table III the χ^2 value with the censored data omitted is 24.5, vs 43.8 with the censored observations included. For the full data set of 36 observations, including the 12 censored observations increases the χ^2 value from 37.5 to 64.3. The χ^2 statistic has an expected value of about 7 under the null hypothesis and the larger the χ^2 value, the stronger the evidence is against the null hypothesis.

RESULTS AND DISCUSSION

The acaricidal activity of 37 1,4-diphenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones was varied with the variation of the 4-phenyl ring substituents (Table I). The structure–activity correlation for the 4-substituted phenyl derivatives was represented by eq 4 and described in Table V. One substituent, *o*-CH_3, was omitted from the analysis because it showed unexpected poor activity (ED_{50} > 10 000 ppm) when compared to its predicted activity (ED_{50} = 121 ppm). The poor activity persisted on repeated testing. Also, the compound identification was carefully checked. Therefore, a rationale for its lack of fit is not readily apparent. However, in its UV spectrum a normally strong band at 250 cm^{-1} is not present, suggesting an unusual conformation or π-electron distribution in the oxadiazine ring. Although deleting observations when fitting a QSAR equation is not uncommon, it is undesirable statistically in that it indicates the existence of some phenomenon not explained. However, the credibility of the equation for

predicting the activity of new compounds is confirmed by the predictions in Table IV.

Lipophilicity does not seem to be a very important factor in the structure–activity relationship. Substituents that enhance acaricidal activity seem to be neutral, bulky ones such as phenyl and benzyl or electron-releasing ones such as methoxy and dialkylamino, which also have a hydrogen-accepting character.

CONCLUSIONS

The QSAR study was carried out to optimize acaricidal activity in 2,4-diphenyl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones. The stronger the electron-donating power, the larger the overall steric bulkiness, and the better the hydrogen-accepting ability of the 4-phenyl substituents, the more acaricidally active are the compounds. As a result, a 6-fold increase in activity over the lead compound was achieved with compound **6** (R = *o*-C_6H_5). The acaricidal activity of this compound (ED_{50} = 25 ppm) was superior to that of the commercial standard, propargite (ED_{50} = 50 ppm).

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Registry No. 1 R = H, 109462-78-4; 1 R = *o*-CH_3, 129786-74-9; 1 R = *m*-CH_3, 109463-23-2; 1 R = *p*-CH_3, 109463-19-6; 1 R = *o*-$CH_2C_6H_5$, 109463-24-3; 1 R = *o*-C_6H_5, 109491-87-4; 1 R = *p*-cyclo-C_6H_{11}, 129786-75-0; 1 R = *p*-NH_2, 109492-00-4; 1 R = *m*-$N(CH_3)^{3+}$, 129786-76-1; 1 R = *o*-NO_2, 129786-77-2; 1 R = *m*-NO_2, 129786-95-4; 1 R = *p*-NO_2, 109491-94-3; 1 R = *p*-OCH_3, 109491-77-2; 1 R = *o*-$SO_2C_6H_5$, 109491-86-3; 1 R = *o*-F, 109491-79-4; 1 R = *p*-F, 109525-24-8; 1 R = *o*-Br, 109491-78-3; 1 R = *p*-Br, 109491-81-8; 1 R = *m*-$OCH_2C_6H_5$, 109551-08-8; 1 R = *p*-$OCH_2C_6H_5$, 109491-97-6; 1 R = *p*-C_2H_5, 109491-89-6; 1 R = *o*-NH_2, 129786-78-3; 1 R = *m*-NH_2, 109491-99-8; 1 R = *p*-OH, 129786-79-4; 1 R = *m*-OCH_3, 109491-76-1; 1 R = *p*-SO_2CH_3, 109491-88-5; 1 R = *m*-F, 109491-80-7; 1 R = *o*-Cl, 129786-80-7; 1 R = *o*-C_2H_5, 129786-81-8; 1 R = *m*-C_2H_5, 129786-82-9; 1 R = *m*-SCH_3, 129786-83-0; 1 R = *p*-C_6H_5, 129786-84-1; 1 R = *p*-$COOC_2H_5$, 129786-85-2; 1 R = *p*-COOH, 129786-86-3; 1 R = *m*-$CH_2C_6H_5$, 129786-87-4; 1 R = *m*-C_6H_5, 129786-88-5; 1 R = *p*-$OCONHCH_3$, 129786-89-6; 1 R = *o*-CH_2Ph, 109463-24-3; 1 R = *m*-NH_2, 109491-99-8; 1 R = *m*-NMe_3^+ I^-, 129786-91-0; 1 R = *m*-NO_2, 129786-95-4; **3** R = *m*-CH_2-Ph, 129786-90-9; **3** R = *o*-CH_2-Ph·HCl, 129786-92-1; **3** R = *o*-CH_2-Ph, 129786-94-3; 4-methylbenzoyl chloride, 874-60-2; 1-nitro-3-(phenylmethyl)benzene, 5840-41-5; 1-(chloromethyl)-3-nitrobenzene, 619-23-8.