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Structure–Activity Correlations of the Insecticide Prolan and Its Analogs

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Structure–activity correlations for 45 insecticidal diaryl nitropropanes (Prolan analogs) were analyzed by multiple regression analysis. Molecular bulk constants including van der Waal's radii, molar attraction constants, parachor, steric constants such as Taft's E_s and Verloop's dimensional steric constants, hydrophobic constants such as Π, and electronic parameters such as σ, F, and R were evaluated. It was concluded that the diaryl nitropropanes like the diaryl trichloroethanes fit into a receptor site which has an optimum volume for maximum interaction. The interaction between the insecticide and the receptor shows high correlation with steric constants for the aryl substituents and with intermolecular attractive forces. Highly asymmetrical compounds such as 1-(*p*-fluorophenyl)-1-(*p*-hexoxyphenyl)-2-nitropropane were surprisingly effective insecticides.

Prolan or 1,1-bis(*p*-chlorophenyl)-2-nitropropane was shown by Haas *et al.* (1) to be an effective DDT-like insecticide. Twenty-nine diaryl nitroalkanes were prepared but no quantitative insecticidal evaluation was given, although it was stated that none of the other analogs was as effective as 1,1-bis(*p*-chlorophenyl)-2-nitropropane and the corresponding 2-nitrobutane which were about five times as effective as DDT to thrips and aphids. Metcalf and Fukuto (2) found the topical LD_{50}[7] of Prolan to the house fly *Musca domestica* (S_{NAIDM}) to be 0.17 μg per female, and this was decreased to 0.066 μg by deuteration at the α-hydrogen and to 0.125 μg by deuteration at the β-hydrogen. Holan (3) showed that 1,1-bis(*p*-ethoxyphenyl)-2-nitropropane (topical LD_{50} of 0.48 μg to the S_{WHO} house fly) was much more effective than the *p,p'*-dimethoxy derivative (LD_{50} of 20 μg) and that activity in the diaryl 2-nitropropane series was still further increased in the asymmetrical analogs *p*-C_2H_5O

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[7] Abbreviations used: MA, Molar attraction; MR, molar refraction; V_r, Van der Waal's radii; V_v, Van der Waal's volume; P_c, parachor; R_{sp}, DDT-resistant super pollard house fly; S_{WHO}, susceptible strain supplied by World Health Organization; S_{NAIDM}, susceptible house fly strain supplied by National Association Insecticide and Disinfectant Manufacturers; LC_{50}, median lethal concentrations; LD_{50}, median lethal dose; PB, piperonyl butoxide.

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p-C_2H_5S (LD_{50} of 0.16 μg), and p-C_2H_5O, 3,4-OCH_2O (LD_{50} of 0.14 μg). Clearly insecticidal activity of the diaryl nitropropanes like that of the diaryl trichloroethanes is substantially affected by the size, shape, and polarity of the p,p'-substitutents, and asymmetrical as well as symmetrical analogs have an interesting range of insecticidal activity (4). Therefore, in continuing studies of the spatial nature of the DDT–receptor (5), we have investigated the effects of various combinations of p,p'-substituents in the diaryl 2-nitropropane upon quantitative insecticidal activity in the susceptible and DDT-resistant house fly *Musca domestica* Linnaeus, to the black blowfly *Phormia regina* Meigen, and to larvae of *Culex pipiens quinquefasciatus* Say and *Anopheles albimanus* Wiedemann. The toxicity data for Prolan and 44 analogs have been analyzed by multiple regression analysis to seek correlations with various physical–chemical parameters including the steric substituent constant E_s (5).

MATERIALS AND METHODS

Synthetic Procedures

The 45 diaryl 2-nitropropanes listed in Table 1 were prepared by the general procedure of Jacob *et al.* (6), first reacting an appropriate aromatic aldehyde with the nitropropane to form the aryl nitroalcohol which is then condensed with the appropriate aryl moiety to give the desired compound. The following procedures were typical:

1-(p-Fluorophenyl)-1-(p-n-propoxyphenyl)-2-nitropropane. 1-(*p*-Fluorophenyl)-2-nitropropane-1-ol was prepared as described by Holan (7), and 1.9 g or 9.5 mmol was combined with *n*-propyl phenyl ether (1.4 g or 10.5 mmol). The mixture was added dropwise to 20 ml of concentrated H_2SO_4 at −30°C using a dry ice acetone bath and continuous stirring. After the addition was complete, the reaction mixture was stirred for an additional 1.5–2 hr at −30°C, poured onto ice, and extracted with diethyl ether. After washing and drying the ether extract, the ether was evaporated, and the crude product was purified by column chromatography on silica gel with ether–pentane [1:9, (v/v)] to give a colorless oil (1.34 g or 45%).

1,1-Bis(p-n-butoxyphenyl)-2-nitropropane. This was prepared from a mixture of 1-(*p*-*n*-butoxyphenyl)-2-nitropropanol (7) (3.3 g or 12.1 mmol) and *n*-butylphenyl ether cooled to −10°C in a methanol ice bath. A 60/40 mixture of sulfuric and acetic acids (30 ml) was added dropwise with stirring at 0°C. After the addition was complete, the reaction mixture was stirred for an additional 2 hr at −10°C and worked up as above to give a pale yellow oil (2.48 g or 53%).

Physical Constants

All of the compounds listed in Table 1 were purified by recrystallization and/or column chromatography to constant melting point, or by vacuum distillation and were analyzed by 60-mHz nmr. The melting points of the compounds were (compound no., mp given): 1, 73–5°C; 12, 90°C; 13, 80°C; 14, 80°C; 17, 106–8°C; 20 70°C; 23, 115°C; 24, 110°C; 26, 35°C; 27, 140°C; 28, 98–9°C. Other compounds listed in Table 1 were oils. All the 45 diaryl 2-nitropropanes showed α-H, δ4.1–4.48; β-H, δ4.78–5.60; and CH_3, δ1.31–1.56.

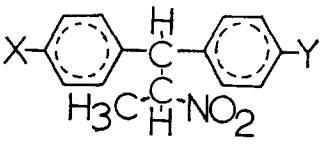
Methoxyphenyl alkoxyphenyl 2-nitro propanes (seven compounds) showed in addition: CH_3O, δ3.61–3.73; CH_3, δ0.8–1.4; CH_2O, δ3.58–3.98; and CH_2, δ1.15–1.78.

Symmetrical and unsymmetrical dialkoxyphenyl 2-nitropropanes (nine compounds) showed in addition: CH_2O, δ3.63–4.06; and CH_2, δ1.58–1.98.

F- and Cl-phenyl alkoxyphenyl 2-nitropropanes (12 compounds) showed in addition: CH_2O, δ3.67–4.07.

TABLE 1

Biological Activity of the Prolan Analogs



Number	X	Y	LD_{50} (μg/g)						LC_{50} (ppm)	
			Snaidm		R_{sp}		*Phormia*		*Culex* larvae	*Anopheles* larvae
			Alone	With PB	Alone	With PB	Alone	With PB		
1	F	H	>2500.0	145.0	>500.0	>500.0	>250.0	>250.0	0.950	3.000
2	F	F	185.0	55.0	300.0	115.0	157.5	145.0	0.190	0.460
3	F	OCH_3	200.0	15.5	>500.0	13.0	23.75	9.0	0.120	0.340
4	F	OC_2H_5	36.0	1.75	75.0	4.8	7.0	5.0	0.088	0.140
5	F	OC_3H_7	52.5	8.0	180.0	11.0	37.5	9.75	0.120	0.145
6	F	OC_4H_9	55.0	7.5	100.5	14.5	>250.0	80.0	0.078	0.200
7	F	OC_5H_{11}	44.0	14.0	105.0	19.0	>250.0	112.5	0.098	0.400
8	F	OC_6H_{13}	65.0	15.0	120.0	18.0	105.0	92.5	0.140	0.170
9	F	OC_8H_{17}	240.0	22.0	>500.0	26.5	210.0	95.0	>1.000	>1.000
10	F	$OC_{10}H_{21}$	>2500.0	>2500.0	>500.0	>500.0	>250.0	>250.0	>1.000	>1.000
11	Cl	H	>500.0	115.0	>500.0	232.0	>250.0	>250.0	0.200	0.800
12	Cl	Cl	22.5	5.5	34.0	13.0	11.0	11.0	0.064	0.066
13	Cl	Br	15.5	4.9	44.0	7.0	11.75	9.75	0.021	0.045
14	Cl	CH_3	72.5	2.25	160.0	5.5	21.5	5.25	0.032	0.100
15	Cl	C_2H_5	47.0	2.05	75.0	3.1	16.0	5.0	0.018	0.100
16	Cl	OCH_3	110.0	8.25	>500.0	13.5	140.0	21.0	0.032	0.175
17	Cl	OC_2H_5	21.0	3.0	43.0	7.25	22.75	7.0	0.024	0.048
18	Cl	OC_3H_7	13.5	2.1	20.5	9.0	77.5	25.0	0.100	0.094
19	Cl	OC_4H_9	18.5	9.0	50.0	10.5	47.5	10.7	0.029	0.048
20	CH_3	CH_3	145.0	1.9	250.0	4.5	13.0	6.0	0.032	0.100
21	CH_3	C_2H_5	47.0	1.8	49.0	3.05	8.75	8.50	0.022	0.120
22	CH_3	C_3H_7	15.0	2.0	35.0	3.1	5.75	2.0	0.031	0.087
23	CH_3	OCH_3	>500.0	1.95	>500.0	4.2	17.5	4.5	0.062	0.100
24	CH_3	OC_2H_5	38.0	1.5	125.0	2.5	4.25	1.7	0.021	0.068
25	CH_3	OC_3H_7	14.0	4.6	57.5	4.9	15.5	7.0	0.044	0.150
26	CH_3	OC_4H_9	17.5	3.5	33.0	12.0	>250.0	15.5	0.048	0.165
27	CH_3O	OCH_2O	>500.0	14.0	>500.0	22.5	>250.0	>250.0	0.092	0.240
28	CH_3O	OCH_3	>500.0	2.75	>500.0	3.5	12.5	7.75	0.098	0.330
29	CH_3O	OC_2H_5	28.0	1.6	105.0	1.75	7.0	7.0	0.115	0.140
30	CH_3O	OC_3H_7	42.0	6.5	70.0	6.5	35.0	9.0	0.098	0.105
31	CH_3O	OC_4H_9	21.0	5.5	37.0	11.0	>250.0	9.0	0.062	0.160
32	CH_3O	OC_5H_{11}	21.0	1.9	55.0	19.5	>250.0	35.0	0.175	0.190
33	CH_3O	OC_6H_{13}	37.0	10.5	50.0	21.0	92.5	37.5	0.190	0.140
34	CH_3O	OC_8H_{17}	75.0	15.0	310.0	22.5	>250.0	8.5	>1.000	1.000
35	C_2H_5O	OCH_2O	60.0	1.8	>500.0	6.0	20.0	10.8	0.058	0.086
36	C_2H_5O	OC_2H_5	5.0	1.25	33.5	—	32.5	1.35	0.045	0.048
37	C_2H_5O	OC_3H_7	5.5	1.7	14.0	2.35	37.5	3.5	0.045	0.040
38	C_2H_5O	OC_4H_9	6.25	1.9	8.5	1.9	8.5	6.5	0.027	0.036
39	C_3H_7O	OCH_2O	19.5	1.7	55.0	3.2	125.0	25.0	0.097	0.086
40	C_3H_7O	OC_3H_7	15.0	2.3	20.5	11.0	14.5	10.0	0.028	0.043
41	C_3H_7O	OC_4H_9	20.5	2.05	30.0	4.2	15.2	16.2	0.078	0.190
42	C_4H_9O	OCH_2O	41.0	10.0	145.0	21.0	>250.0	55.0	0.060	0.140
43	C_4H_9O	OC_4H_9	23.0	4.3	36.0	11.5	>250.0	72.5	0.300	0.230
44	C_4H_9O	OC_5H_{11}	80.0	15.5	170.0	25.0	>250.0	>250.0	>1.000	>1.000
45	C_4H_9O	OC_6H_{13}	>500.0	255.0	>500.0	>500.0	>250.0	>250.0	>1.000	>1.000

Methylphenyl alkoxyphenyl 2-nitropropanes (four compounds) showed: CH_3, δ2.26–2.28; and CH_2O, δ3.71–4.15.

Dialkylaryl 2-nitropropanes (two compounds) showed in addition: CH_2, δ2.26–2.73.

3,4-Methylenedioxyphenyl alkoxyphenyl 2-nitropropanes (four compounds) showed: —OCH_2O—, δ5.85–5.93; and CH_2O, δ3.73–4.11.

Biological Methods

The quantitative data on LD_{50} and LC_{50} values presented in Table 1 were obtained by standard methods used in Stage 1 of the WHO Insecticide Evaluation Programs (2). Female house flies, *Musca domestica*, under CO_2 anesthesia were treated by the topical application of 1-μl droplets of standard (w/v) acetone solutions. Three replicates of 20 flies 2–4 days old were treated on the pronotum at each dosage. Mortalities were determined by holding the flies at 22°C with 40% sucrose solution as food for 24 hr. Topical applications were also made to laboratory-reared black blowflies, *Phormia regina*, in exactly the same manner. The results are reported in Table 1 as LD_{50} values in micrograms per gram body weight determined from inspection of log dosage–probit mortality lines, using the average weight of the house fly as 20 mg and of the blowfly as 40 mg.

To determine the amount of detoxication of the insecticides in the fly body, the synergist piperonyl butoxide was applied topically to the ventral portion of the abdomen of the flies 1 hr before treatment with the insecticide, at a dosage of 1 μl of 5% solution (w/v) in acetone (50 μg/insect).

The toxicity data to larvae of *Culex pipiens quinquefasciatus* and *Anopheles albimanus* were evaluated by the standard WHO method (2). Twenty fourth instar larvae were placed in 100 ml of water, and an appropriate volume of (w/v) acetone solution was added. Replicates were carried out as described above, and mortality was determined after 24 hr. LC_{50} values were determined from inspection of the log dosage–probit mortality lines.

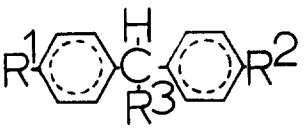
RESULTS AND DISCUSSION

Examination of the data in Table 1 for Prolan and 44 analogs leads to several generalities. Symmetrical ring substitution is not a prerequisite for biological activity; e.g., the appreciable insect toxicity of 1-(*p*-fluorophenyl)-1-(*p*-octoxyphenyl)-2-nitropropane (compound 9), 1-(*p*-chlorophenyl)-1-(*p*-butoxyphenyl)-2-nitropropane (compound 19), 1-(*p*-methylphenyl)-1-(*p*-butoxyphenyl)-2-nitropropane (compound 26), and 1-(*p*-methoxyphenyl)-1-(*p*-octoxyphenyl)-2-nitropropane (compound 34). Very large or very small ring substituents, e.g., H (compounds 1 and 11) or $OC_{10}H_{21}$ (compound 10), generally produced inactive compounds, while ring substituents of intermediate size generally produced the most toxic compounds. There is an obvious correlation between the size and shape of the compound and its toxicity to four species of insects. These facts support the earlier model of Fahmy *et al.* (5) for toxicity of the DDT-type compound and suggest that both the diaryl 2-nitropropanes and diaryl trichloroethanes interact with an identical receptor site in the nerve axon.

In this regard it is noteworthy that the Prolan series with $HC(NO_2)CH_3$ as the aliphatic moiety allows a greater range of aryl substituents for biological activity than does the DDT series with $HCCl_3$. This is shown clearly by the data in Table 2. Especially interesting examples include 1,1-bis(*p*-butoxyphenyl)-2-nitropropane (highly toxic) vs 2,2-bis(*p*-butoxyphenyl)-1,1,1-trichloroethane (nontoxic), and 1-(*p*-methoxyphenyl)-1-(*p*-hexoxyphenyl)-2-nitropropane (highly toxic) vs 2-(*p*-methoxyphenyl)-2-(*p*-hexoxyphenyl)-1,1,1-trichloroethane (nontoxic). It is evident that the total molecular volume of the molecule is involved in receptor site interaction, and it appears that the greater flexibility in the aliphatic moiety of the 2-nitropropanes, resulting from the presence of the small H atom, allows for larger substituents on the aryl rings.

TABLE 2

Comparison of Insecticidal Activity of Diaryl trichloroethanes and Diarylnitropropanes to Musca, Phormia, and mosquito larvae



R^1	R^2	R^3	*Musca*		*Phormia*		*Culex* larvae	*Anopheles* larvae
			Alone	PB	Alone	PB		
CH_3O	CH_3O	CCl_3	45	3.5	10.0	4.6	0.067	0.18
CH_3O	CH_3O	$CHCH_3NO_2$	>500	2.75	12.5	7.75	0.098	0.33
C_2H_5O	C_2H_5O	CCl_3	7.0	1.75	6.9	7.4	0.04	0.086
C_2H_5O	C_2H_5O	$CHCH_3NO_2$	5.0	1.25	32.5	1.35	0.045	0.048
C_3H_7O	C_3H_7O	CCl_3	125	18.5	250	61.2	0.6	0.777
C_3H_7O	C_3H_7O	$CHCH_3NO_2$	15.0	2.3	14.5	10.0	0.025	0.03
C_4H_9O	C_4H_9O	CCl_3	>500	>500	>250	>250	>1.0	>1.0
C_4H_9O	C_4H_9O	$CHCH_3NO_2$	23.0	4.3	>250	72.5	0.030	0.23
CH_3O	C_2H_5O	CCl_3	16	3.7	10	10	0.039	0.061
CH_3O	C_2H_5O	$CHCH_3NO_2$	28	1.6	7.0	7.0	0.11	0.14
CH_3O	C_3H_7O	CCl_3	24	8.5	30	27.5	0.18	0.052
CH_3O	C_3H_7O	$CHCH_3NO_2$	42	6.5	35	9.0	0.105	1.11
CH_3O	C_4H_9O	CCl_3	21	20.5	107	75	0.18	0.01
CH_3O	C_4H_9O	$CHCH_3NO_2$	21	5.5	>250	9.0	0.062	0.16
CH_3O	$C_5H_{11}O$	CCl_3	160	26	185	130	>1.0	0.053
CH_3O	$C_5H_{11}O$	$CHCH_3NO_2$	21	1.9	>250	35	0.17	0.19
CH_3O	$C_6H_{13}O$	CCl_3	500	72.5	>250	>250	>1	>1
CH_3O	$C_6H_{13}O$	$CHCH_3NO_2$	37	10.5	92.5	37.5	0.19	0.14
CH_3O	$C_8H_{17}O$	CCl_3	>500	>500	>250	>250	>1	>1
CH_3O	$C_8H_{17}O$	$CHCH_3NO_2$	75	15.0	>250	8.5	>10	10

Thus the concept of Fahmy *et al.* (5) of the DDT–receptor as a flexible pouch of fixed dimensions seems an appropriate one, and this is in accord with conclusions of Verloop *et al.* (8) who reanalyzed much of our data using new five-dimensional steric constants to obtain improved correlations between toxicity and size and shape of the aryl substitutents. Holan and Spurling (9) used molecular orbital calculations to estimate the charge distribution on the DDT-type molecule and found a high correlation of synergized LD_{50} with electron density at the apex of the molecule.

Correlation of Biological Activity and Structure

Multiple regression analysis with diaryl trichloroethanes related to DDT demonstrated that Taft's steric substituent constant E_s (10) for the *p,p'*-substituents, is the most important linear free energy parameter for the quantitative correlation of structure with insecticidal activity of DDT analogs (5). Approximately 50% of the variations in toxicity were explained by ΣE_s and its square term. The explained variations were increased to approximately 85% when new steric constants that describe the dimensions of the substituents in five directions were used with hydrophobic parameters such as Π and electronic parameters such as F and R (8).

In order to make meaningful comparisons of structure vs activity for the diaryl 2-nitropropanes described in Table 1 of this paper, we have carried out similar multiple regression analyses. Unfortunately E_s values are not available for many of the aryl substituents evaluated. Therefore we have considered other constants for representing the "bulk" of the substituents: (1) van der Waal's radii and volume, V_r and V_v (11); (2) molar attraction (MA) (12),

TABLE 3

Substituent Constants

R	V_v[a]	Π[b]	MA[c]	V_m[d]	MR[b]	P_c[e]	F[b]	R[b]	σ[b]	(E^c_s)[f]
H	3.45	0.00	80	14.90	1.03	16.8	0.00	0.00	0.00	0.00
F	5.80	0.14	66[g]	15.11	0.92	26.5	0.43	−0.34	0.06	−0.38
Cl	12.00	0.71	270	22.96	6.03	56.0	0.41	−0.15	0.23	−1.03
Br	15.12	0.86	340	26.19	8.88	69.0	0.44	−0.17	0.23	−1.29
CH_3	13.67	0.56	214	31.48	5.65	56.5	−0.04	−0.13	−0.17	−0.84
C_2H_5	23.90	1.02	347	48.06	10.30	96.2	−0.05	−0.10	−0.15	−1.22
n-C_3H_7	34.13	1.55	480	64.64	14.96	135.9	−0.06	−0.08	−0.13	−1.40
OCH_3	17.12	−0.02	284	38.22	7.87	76.2	0.26	−0.51	−0.27	−0.99
OC_2H_5	27.35	0.38	417	54.80	12.47	115.9	0.22	−0.44	−0.24	−1.15
OC_3H_7	37.58	1.05	550	71.38	17.06	155.6	0.22	−0.45	−0.25	−1.36
OC_4H_9	47.81	1.57[h]	683	87.96	21.66	195.3	0.25	−0.55	−0.32	−1.42
OC_5H_{11}	58.04	2.09[h]	816	104.54	26.26	235.0	0.25	−0.57	−0.34	−1.40
OC_6H_{13}	68.27	2.61[h]	949	121.12	30.86[i]	274.7	—	—	—	−1.33
OC_8H_{17}	88.73	3.65[h]	1215	154.28	40.06[i]	354.1	—	—	—	−0.92
$OC_{10}H_{21}$	109.19	4.69[h]	1481	187.44	49.26[i]	433.5	—	—	—	—
OCH_2O	20.63	−0.05	273	29.11	8.96	76.3	−0.17	0.00	−0.16	—

[a] From Bondi (11).
[b] From Hansch *et al.* (17).
[c] From Small (18).
[d] From Exner (20).
[e] From Exner (21).
[f] Calculated from Eq. 23 and then normalized by adding 0.18 to all E^c_s values.
[g] Calculated from Freon 21 (dichlorofluoromethane, MW = 102.93, d^g = 1.405, V_m = 74, δ = 8.3) of Burrell (19).
[h] Calculated allowing 0.52 for each methylene group added to the value for OC_3H_7.
[i] Calculated allowing 4.60 for each methylene group added to the value for OC_5H_{11}.

a molar volume and molar cohesive energy-related constant that measures the intermolecular attractive forces of a chemical species relative to a second entity; (3) molar refraction (MR) (13), a constant related to molar volume and refractive index; and (4) parachor (P_c) (14), a constant related to molar volume and surface tension.

Multiple regression analyses were carried out on the 45 analogs of Prolan shown in Table 1, using the quantitative parameters: V_v, Π, MA, V_m, MR, P_c, F, R, σ, and E_s as presented in Table 3, together with the dimensional steric constants L, B_1, B_2, B_3, and B_4 provided by Dr. A. Verloop (8). The partial F test value (15) was calculated for every variable, treated as though it were the last variable to enter the regression equation. The analysis was terminated when the lowest partial F test value for a variable was greater than the critical value of F on α-risk of 0.05. Because of the presence of intercorrelation among the substitutent constants, an effort was made to select equations which contain common substituent constants. Compounds in Table 1 for which toxicological values were listed as "greater than" or those for which substituent constants were unavailable were excluded from the multiple regression analysis. The use of intercorrelated parameters in the same equation is justified only when significant reduction in residual mean squares is obtained.

The use of MA together with σ or F and R constants is expressed in Table 4, Eqs. 1–4. Explained variations in LD_{50} ranged from 52% for the S_{NAIDM} house fly pretreated with the synergist piperonyl bu-

TABLE 4

The Relationship between the Physical Constants and Insect Toxicity of Prolan and Its Analogs

Equation	Insect toxicity data	LD_{50} (or LC_{50}) = Intercept $+ \beta_1X_1 + \beta_2X_2 + \cdots$		SE[a]	Partial F[b]	N[c]	r[d]	ANOVA F[e]
		Variables (X)	Regression coefficient (β)					
1	S_{NAIDM}	Intercept	2.9173×10^2	0.2549×10^2		34	0.8928	28.48
	House fly	ΣMA	−0.5854	0.0615	90.75			
		$(\Sigma MA)^2$	2.7944×10^{-4}	0.3522×10^{-4}	62.95			
		F_y	-1.3526×10^2	0.3870×10^2	12.21			
		R_y	-1.1277×10^2	0.3439×10^2	10.75			
2	S_{NAIDM}	Intercept	1.1473×10^2	0.1681×10^2		39	0.7228	19.69
	House fly	ΣMA	−0.2503	0.0437	32.77			
	(with PB)	$(\Sigma MA)^2$	1.3025×10^{-4}	0.2675×10^{-4}	23.71			
3	R_{sp}	Intercept	4.1403×10^2	0.5142×10^2		31	0.7882	14.77
	House fly	ΣMA	−0.7599	0.1239	37.64			
		$(\Sigma MA)^2$	3.5225×10^{-4}	0.6896×10^{-4}	26.09			
		$\Sigma\sigma_p$	-7.6578×10	0.3713×10	4.25			
4	R_{sp}	Intercept	2.2384×10^2	0.1655×10^2		37	0.9379	45.32
	House fly	ΣMA	−1.6419	0.1244	174.23			
	(with PB)	$(\Sigma MA)^2$	6.6341×10^{-4}	0.5154×10^{-4}	165.71			
		ΣMR	4.1243×10	0.3618×10	129.94			
		$(\Sigma MR)^2$	-4.9489×10^{-1}	0.4606×10^{-1}	115.47			
		$\Sigma\sigma_p$	9.2617×10	1.2041×10	59.17			
5	*Culex* larvae	Intercept	6.5057×10^{-1}	0.9814×10^{-1}		38	0.6961	16.46
		MA	-1.5426×10^{-3}	0.2733×10^{-3}	31.86			
		$(MA)^2$	9.4267×10^{-7}	1.8074×10^{-7}	27.20			
6	*Anopheles* larvae	Intercept	1.9043	0.3166		38	0.6760	14.73
		MA	-4.3431×10^{-3}	0.8817×10^{-3}	24.26			
		$(MA)^2$	2.4550×10^{-6}	0.5831×10^{-6}	17.73			
7	S_{NAIDM}	Intercept	6.7717×10^2	0.8751×10^2		31	0.8967	20.51
	House fly	F_y	-2.0295×10^2	0.5454×10^2	13.85			
		R_y	-2.2673×10^2	0.6128×10^2	13.69			
		ΣB_1	-5.5235×10	2.3091×10	5.72			
		ΣB_4	-1.4408×10^2	0.1755×10^2	67.42			
		$(\Sigma B_4)^2$	8.8789	1.2408	51.20			
8	S_{NAIDM}	Intercept	3.0830×10^2	0.3119×10^2		35	0.9149	29.79
	House fly	F_y	-5.6469×10	2.0341×10	7.71			
	(with PB)	ΣL	2.4838×10	0.7030×10	12.48			
		ΣB_1	-6.5908×10	1.0125×10	42.37			
		ΣB_4	-6.8312×10	0.7806×10	76.58			
		$(\Sigma B_4)^2$	2.2538	0.5908	14.56			
9	R_{sp}	Intercept	1.0719×10^3	0.1519×10^3		29	0.8609	13.17
	House fly	F_y	-2.7569×10^2	0.9688×10^2	8.09			
		R_y	-2.8204×10^2	1.2013×10^2	5.51			
		ΣB_1	-1.0460×10^2	0.4091×10^2	6.53			
		ΣB_4	-2.0435×10^2	0.3162×10^2	41.77			
		$(\Sigma B_4)^2$	1.2574×10	0.2160×10	33.88			

TABLE 4—*Continued*

Equation	Insect toxicity data	LD_{50} (or LC_{50}) = Intercept $+ \beta_1X_1 + \beta_2X_2 + \cdots$		SE[a]	Partial F^b	N^c	r^d	ANOVA F^e
		Variables (X)	Regression coefficient (β)					
10	R_{sp}	Intercept	4.9951×10^2	0.7751×10^2		33	0.8276	11.74
	House fly	F_y	-8.5188×10	4.1302×10	4.25			
	(with PB)	ΣL	4.0825×10	1.4074×10	8.41			
		ΣB_1	-1.0259×10^2	0.2278×10^2	20.29			
		ΣB_4	-1.1579×10^2	0.1762×10^2	43.18			
		$(\Sigma B_4)^2$	4.0032	1.2035	11.07			
11	*Phormia*	Intercept	3.2007×10^2	7.7220×10^2		26	0.8569	8.75
		$\Sigma\Pi$	-5.8636×10	1.4909×10	15.47			
		ΣB_1	1.6903×10^3	0.3789×10^3	19.89			
		$(\Sigma B_1)^2$	-2.4011×10^2	0.5681×10^2	17.86			
		ΣB_3	-1.7675×10^3	0.3976×10^3	19.76			
		$(\Sigma B_3)^2$	2.3345×10^2	0.5785×10^2	16.28			
		ΣB_4	4.1508×10	0.9854×10	17.74			
12	*Phormia*	Intercept	1.6883×10^3	0.4314×10^3		32	0.8874	19.27
	(with PB)	ΣB_1	2.0052×10^2	0.5891×10^2	11.58			
		ΣB_3	-1.1353×10^3	0.2574×10^3	19.48			
		$(\Sigma B_3)^2$	1.3261×10^2	0.3782×10^2	12.30			
		ΣB_4	1.1970×10	0.2866×10	17.45			
		$\Sigma\sigma_p$	-1.6875×10^2	0.6089×10^2	7.68			
13	*Culex* larvae	Intercept	7.5689	1.4580		34	0.8767	18.60
		F_y	−0.2985	0.1250	5.70			
		ΣB_1	−4.3369	1.0108	18.41			
		$(\Sigma B_1)^2$	0.6663	0.1651	16.29			
		ΣB_4	−0.1585	0.0546	8.41			
		(ΣB_4)	0.0115	0.0045	6.55			
14	*Anopheles* larvae	Intercept	3.1887×10	0.4458×10		34	0.9226	25.73
		F_y	−1.0034	0.3262	9.46			
		R_x	1.5529	0.4851	10.25			
		ΣB_1	-1.8663×10	0.2976×10	39.33			
		$(\Sigma B_1)^2$	2.8465	0.4762	35.73			
		ΣB_4	−0.3456	0.1405	60.47			
		$(\Sigma B_4)^2$	0.0254	0.0115	4.86			
15	S_{NAIDM}	Intercept	2.6318×10^2	0.2964×10^2		31	0.8338	20.53
	Housefly	$\Sigma\Pi$	-7.3958×10	2.3506×10	9.90			
		$(\Sigma\Pi)^2$	2.3105×10	0.5877×10	15.46			
		ΣE^c_s	7.9920×10	1.7233×10	21.51			
16	S_{NADIM}	Intercept	1.9897×10^2	0.1628×10^2		35	0.9099	77.04
	House fly	ΣE^c_s	1.7536×10^2	0.1866×10^2	88.30			
	(with PB)	$(\Sigma E^c_s)^2$	3.8640×10	0.5237×10	54.45			
17	R_{sp}	Intercept	4.2648×10^2	0.4604×10^2		29	0.8368	19.47
	House fly	$\Sigma\Pi$	-8.8713×10	3.7980×10	5.46			
		$(\Sigma\Pi)^2$	3.1611×10	0.9247×10	11.69			
		ΣE^c_s	1.3902×10^2	0.2488×10^2	31.23			
18	R_{sp}	Intercept	3.6742×10^2	0.5548×10^2		33	0.7837	23.87
	House fly	ΣE^c_s	3.2397×10^2	0.5849×10^2	30.68			
	(with PB)	$(\Sigma E^c_s)^2$	7.1481×10	1.5090×10	22.44			

TABLE 4—*Continued*

Equation	Insect toxicity data	LD_{50} (or LC_{50}) = Intercept + $\beta_1X_1 + \beta_2X_2 + \cdots$		SE[a]	Partial F[b]	N[c]	r[d]	ANOVA F[e]
		Variables (X)	Regression coefficient (β)					
19	*Phormia*	Intercept	4.7000×10^2	1.0017×10^2		26	0.7093	5.32
		$\Sigma\Pi$	-4.7172×10	1.9974×10	5.58			
		Rx	1.6959×10^2	0.6634×10^2	6.54			
		ΣE^c_s	4.2770×10^2	1.0299×10^2	17.25			
		$(\Sigma E^c_s)^2$	1.2272×10^2	0.3223×10^2	14.50			
20	*Phormia* (with PB)	Intercept	1.2124×10^2	0.2023×10^2		32	0.8095	17.75
		$\Sigma\Pi$	3.8941×10	0.6829×10	32.51			
		R_x	-9.6616×10	2.4790×10	15.19			
		ΣE^c_s	8.6507×10	1.2425×10	48.48			
21	*Culex* larvae	Intercept	1.1033	0.1013		34	0.8759	51.07
		ΣE^c_s	1.0531	0.1185	78.93			
		$(\Sigma E^c_s)^2$	0.2579	0.0339	57.95			
22	*Anopheles* larvae	Intercept	3.2962	0.3084		34	0.8836	55.22
		ΣE^c_s	3.0101	0.3610	69.53			
		$(\Sigma E^c_s)^2$	0.6949	0.1032	45.35			

[a] SE = Standard error of the regression coefficient.
[b] Partial F = F value of the correct F test [Draper and Smith (15)].
[c] N = Number of data points used in regression analysis.
[d] r = Multiple correlation coefficient.
[e] ANOVA F = F value of the analysis of variance.

toxide (PB) to 88% for R_{sp} house fly pretreated with PB. The inclusion of electronic parameters did not significantly improve the correlation coefficients. Molar attraction forces were also correlated with toxicity to *Culex* and *Anopheles* mosquito larvae, and approximately 50% of the variations in LC_{50} are explained by Eqs. 5 and 6. Again the inclusion of electronic parameters did not improve the correlation coefficients. Since there is a high correlation between MA and MR, Eq. 4 should be accepted with caution. For the black blowfly, *Phormia*, no significant equation could be developed to show correlation of structure–activity relationships with MA.

Multiple regression analysis with the dimensional steric constants L, B_1, B_2, B_3, and B_4 is shown in Table 4, Eqs. 7–14. Comparisons of the correlation coefficients with those using MA values showed no change for the S_{NAIDM} house fly alone (Eqs. 1 and 7) but increased correlation with synergized LD_{50} (Eqs. 2 and 8); increased correlation for the R_{sp} house fly (Eqs. 3 and 9) but decreased correlation with synergized LD_{50} (Eqs. 4 and 10); and increased correlation for *Culex* (Eqs. 5 and 13) and *Anopheles* larvae (Eqs. 6 and 14). The use of the dimensional steric constants provided greatly increased correlation for *Phormia* alone (Eq. 11) and with synergized LD_{50} (Eq. 12).

Examination of Eqs. 7–14 indicates that B_1 and B_4 terms are common for the houseflies, *Phormia*, and mosquito larvae toxicity data. Furthermore regression analysis showed that Taft's steric substituent constant (E_s) correlates very well with the two width dimensions, B_1 and B_4, of the dimensional steric constants.

$$\log (1 - E^c_s) = -0.2978 + 0.2254B_1 + 0.1588B_4 - 0.0154(B^2_4) \quad [23]$$

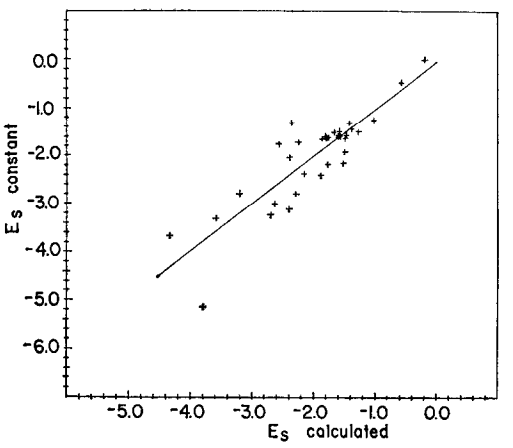


FIG. 1. Linear relationship between the Taft's steric constants (E_s) and the E_s values calculated from the Eq. (23).

(n = 36, r = 0.9023, s = 0.0616, $F_{3,32}$ = 46.76), where n = number of data points used in the regression analysis, r = correlation coefficient, and s = standard deviation from regression. For comparison, a series of E^c_s are calculated from Eq. 23 and plotted against Taft's E_s (Fig. 1). With the exception of the cyclobutyl and cyclopentyl groups, all calculated E^c_s values are closely comparable to the original Taft values (10). Calculated E_s values of Kutter and Hansch (16) and Hansch (13) are also comparable to E_s values calculated from Eq. 23.

The substitution of the dimensional steric constant by the calculated steric (E^c_s) in the multiple regression analysis produced a new set of highly significant equations (Eqs. 15–22) with correlation coefficients comparable to those found for MA (Eqs. 1–6) and the dimensional steric constants (Eqs. 7–14). However, the inclusion of Π terms seems to be important for most of the models using the calculated E^c_s values.

SUMMARY AND CONCLUSION

The diaryl 2-nitropropanes like the diaryl trichloroethanes fit into a critical receptor in the insect nerve axon. It seems highly probable that the same receptor site accommodates both the DDT-type and Prolan-type analogs. As suggested earlier by Fahmy *et al.* (5), this receptor has considerable flexibility and can accommodate up to a total of nine carbon atoms on the aryl ring with the production of biological activity. The receptor is slightly smaller in *Phormia* and accommodates only eight carbon atoms. The receptor evidently has an optimum volume for maximum interaction so that there is a parabolic relationship between insect toxicity and molecular volume of either the DDT- or Prolan-type compounds. This relationship is not perfect; for example, compounds 33 and 41 have the same molecular volume but exhibit different toxicities, and it is apparent that additional factors such as metabolism, partition, etc., are important in determining the overall biological response.

Multiple regression analysis has shown that E_s values are the simplest and most practical steric parameter to explain variations in toxicity caused by changes in molecular volume.

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