Synthesis and Quantitative Structure–Activity Relationships of Herbicidal *N*-(2-Fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimides

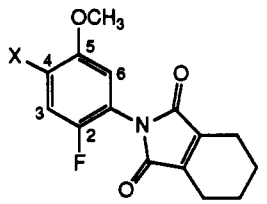
John W. Lyga,* Russell M. Patera, George Theodoridis, Blaik P. Halling, Frederick W. Hotzman, and Marjorie J. Plummer

Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, New Jersey 08543

The effect of substitution at position 4 of the phenyl ring of *N*-(2-fluoro-5-methoxyphenyl)tetrahydrophthalimide on herbicidal activity was investigated by using a factorial design strategy. The substituents were chosen by use of cluster analysis and confirmed as an orthogonal set by use of correlation and factor analysis. Multiple linear regression analysis was used to interpret the herbicide data. For optimal activity, we found that the 4-position should be submitted by a small, hydrophobic, electronegative group. An optimal molecular molar refractivity and lipophilicity are also important for good postemergence activity. The synthesis and quantitative structure–activity relationships (QSAR) are presented.

INTRODUCTION

N-Phenyl-3,4,5,6-tetrahydrophthalimide (I) is one of a class of light-activated membrane-disrupting herbicides which are also reported to be chlorophyll biosynthesis inhibitors (Wakabayashi et al., 1986; Sandmann et al., 1984a,b). The more active compounds have halogens at positions 2 and 4 of the phenyl ring and a variety of substitutents at the 5-position. These include oxygen (Nagano et al., 1983), sulfur (Nagano et al., 1985), nitrogen (Jukihara et al., 1982), phosphorus (Okado et al., 1984), or carbon (Yamada et al., 1982; Wheeler et al., 1987). Quantitative structure–activity relationships (QSAR) have been reported (Wakabayashi, 1988; Ohta et al., 1980), but they have been limited, for the most part, to simple mono- and disubstituted analogues. Here we report on our efforts, using a QSAR approach, to understand the effects of substitution at the 4-position of (2-fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (1) on herbicidal activity.



I

QSAR

Substituent Selection. The successful application of QSAR requires a carefully conceived experimental design strategy. A key step is the critical selection of substituents that represent the factors believed to be important for optimal biological activity. Using a 2^n factorial design strategy (Austel, 1982), we needed to prepare 16 compounds to explore the physiochemical parameter space represented by π (hydrophobic), F (inductive electronic), R (resonance electronic), and MR (molar refractivity steric) (Table I). The compounds were selected by using cluster analysis (Hansch and Unger, 1973) and confirmed as a representative set by using correlation and factor analysis (Tables II and III) (Martin and Panas, 1979). Statistical analyses were performed with BMDP (Dixon, 1983) software on a VAX 8530 computer.

Table I. Factorial Design Set, Physicochemical Data

compd	X	π	F_p	R_p	MR
1	H	0.00	0.00	0.00	1.03
2	SCH_3	0.61	0.20	−0.18	13.82
3	NO_2	−0.28	0.67	0.16	7.36
4	NH_2	−1.23	0.02	−0.68	5.42
5	NHAc	−0.97	0.28	−0.26	14.93
6	$NHSO_2CH_3$	−1.18	0.25	−0.20	18.17
7	I	1.12	0.40	−0.19	13.94
8	OH	−0.67	0.29	−0.64	2.85
9	OAc	−0.64	0.41	−0.07	12.47
10	OCH_3	−0.02	0.26	−0.51	7.87
11	O-*i*-C_3H_7	1.05	0.30	−0.72	17.06
12	O-*n*-C_5H_{11}	2.04	0.25	−0.57	26.26
13	$OSO_2C_6H_5$	0.93	0.36	0.00	36.70
14	Br	0.86	0.44	−0.17	8.88
15	CH_3	0.56	−0.04	−0.13	5.65
16	Cl	0.71	0.41	−0.15	6.03
	high	2.04	0.67	0.16	36.70
	low	−1.23	−0.04	−0.72	1.03

Table II. Correlation Matrix

	π	F_p	R_p	MR
π	1.00			
F_p	0.13	1.00		
R_p	−0.01	0.32	1.00	
MR	0.41	0.21	0.03	1.00

Table III. Factor Analysis

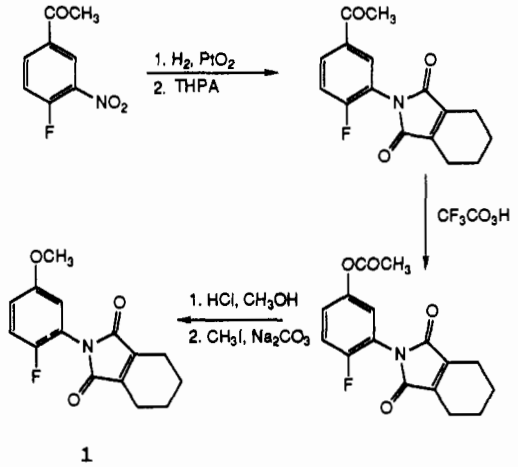
	factor			
	1	2	3	4
π	0.977	0.000	0.000	0.000
R_p	0.000	0.987	0.000	0.000
F_p	0.000	0.000	0.980	0.000
MR	0.000	0.000	0.000	0.972
VP	1.001	1.001	0.999	0.998

METHODOLOGY

Synthesis. The unsubstituted "parent" compound 1 was prepared as outlined in Scheme I by using the Baeyer–Villiger reaction as the key step. The 4-fluoro-3-nitroacetophenone, prepared according to a modification of a reported procedure (Oelschlager, 1957), was catalytically reduced and then converted to the 3,4,5,6-tetrahydrophthalimide (THP) with 3,4,5,6-tetrahydrophthalic anhydride (THPA). Subsequent treatment with tri-

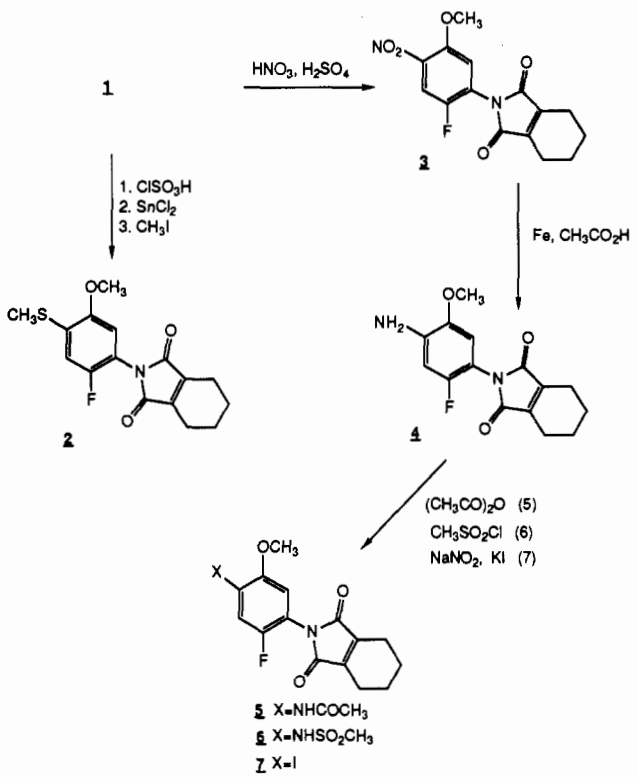
0021-8561/91/1439-1667$02.50/0

Scheme I

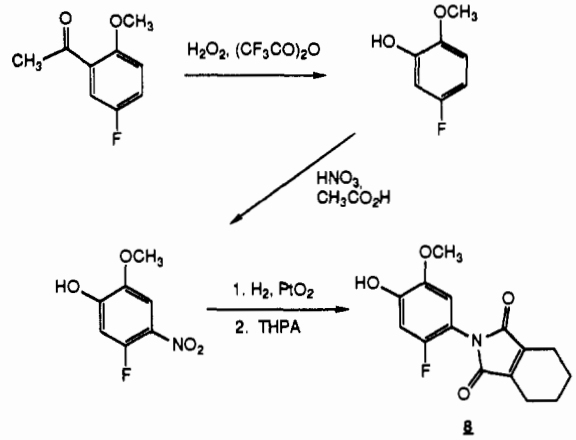


1

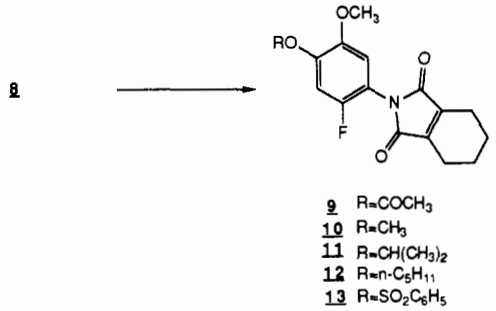
Scheme II



Scheme III

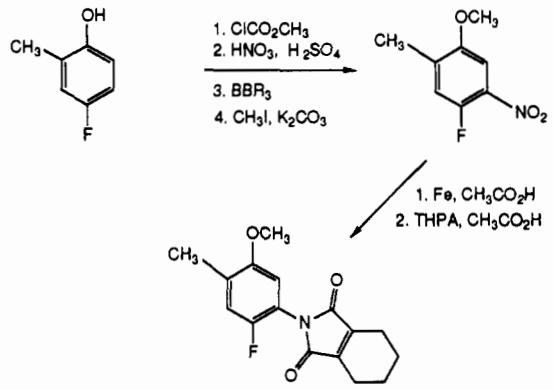


Scheme IV



9 R=COCH3
10 R=CH3
11 R=CH(CH3)2
12 R=n-C5H11
13 R=SO2C6H5

Scheme V



fluoroperacetic acid, prepared in situ from the anhydride and either 30% or 70% H_2O_2, afforded the acetate, which was hydrolyzed to the phenol and then methylated.

The methylthio (2), nitro (3), amino (4), acetamido (5), methylsulfonamino (6), and iodo (7) analogues were all prepared as outlined in Scheme II. Sulfonation of 1 with chlorosulfonic acid followed by reduction with tin(II) chloride gave the thiol, which was methylated to give 2. Nitration of 1 with a mixture of nitric and sulfuric acid cleanly gave the nitro compound (3) which was reduced to the aniline (4) with iron powder and acetic acid. Treatment of 4 with acetic anhydride gave 5 and with methanesulfonyl chloride gave 6. The iodo compound (7) was prepared by reacting the diazotized aniline (4) with KI.

The key intermediate 8, for the synthesis of the oxygen-substituted compounds, was prepared as outlined in Scheme III. The 5-fluoro-2-methoxyphenol was prepared according to a modification of a reported procedure (Course and Ingraham, 1951). We found it more satisfactory to oxidize the substituted acetophenone using the previously mentioned Baeyer–Villiger conditions (CF_3CO_3H). Nitration of the methoxyphenol with a mixture of nitric and acetic acid gave the desired isomer in moderate yield which was catalytically reduced to the aniline and converted to the THP (8).

Compounds 9–13 were prepared from the phenol (8) by treatment with acetic anhydride (9), alkyl iodide and K_2CO_3 (10–12), or benzenesulfonyl chloride (13) as shown in Scheme IV. The methyl analogue, 15 (Scheme V), was prepared from 5-fluoro-2-hydroxytoluene (Finger et al., 1959; Scheme V). Deactivation of the phenol through carbonate formation allowed selective nitration to give the desired 4-nitro isomer in good yield. Deprotection with BBr_3 gave the phenol, which was methylated, reduced to the aniline, and then converted to the THP.

Experimental Chemistry. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Proton NMR spectra were recorded on Varian T60-A (60 MHz) or EM 360-L (60 MHz) or General Electric QE300 (300 MHz) spectrometers. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Elemental analyses were performed at FMC Corp., Analytical Services Department (see Table IV for NMR and CHN data). Compounds 14 and 16 were prepared according to literature methods (Nagano et al., 1984).

***N*-(5-Acetyl-2-fluorophenyl)-3,4,5,6-tetrahydrophthalimide.** A solution of 5.55 g (0.03 mol) of 4-fluoro-3-nitroacetophenone (Oelschlager, 1957) in 50 mL of acetic acid was hydrogenated over 0.1 g of PtO_2 at 3 atm of H_2. The catalyst was

Table IV. Compound Data

compd	mp, °C	analysis, % (calc, found) C	H	N	^{1}H NMR (deureiochloroform), ppm
1	oil	65.46, 65.73	5.13, 4.85	5.09, 5.02	1.78 (m, 4 H), 2.40 (m, 4 H), 3.73 (s, 3 H), 6.68–7.20 (m, 3 H)
2	158.5–160.5	59.81, 60.30	5.02, 4.72	4.36, 4.26	1.80 (m, 4 H), 2.40 (m, 4 H), 2.42 (s, 3 H), 3.83 (s, 3 H), 6.66 (d, 1 H, J_{HF} = 6 Hz), 6.98 (d, 1 H, J_{HF} = 10 Hz)
3	125–127	56.26, 56.11	4.06, 3.94	8.74, 8.64	1.80 (m, 4 H), 2.43 (m, 4 H), 3.90 (s, 3 H), 7.0 (d, 1 H, J_{HF} = 5 Hz), 7.73 (d, 1 H, J_{HF} = 9 Hz)
4	58–60	62.07, 62.32	5.21, 5.44	9.64, 9.90	1.82 (m, 4 H), 2.42 (m, 4 H), 3.80 (s, 3 H), 4.02 (s, 2 H), 6.50 (d, 1 H, J_{HF} = 11 Hz), 6.54 (d, 1 H, J_{HF} = 8 Hz)
5	177–179	61.44, 61.21	5.16, 5.43	8.43, 8.51	1.81 (m, 4 H), 2.19 (s, 3 H), 2.41 (m, 4 H), 3.85 (s, 3 H), 6.67 (d, 1 H, J_{HF} = 7 Hz), 7.81 (b s, 1 H), 8.40 (d, 1 H, J_{HF} = 11 Hz)
6	181–182	52.17, 52.40	4.65, 4.69	7.60, 7.51	1.83 (m, 4 H), 2.44 (m, 4 H), 3.04 (s, 3 H), 3.84 (s, 3 H), 6.75 (d, 1 H, J_{HF} = 6 Hz), 6.99 (b s, 1 H), 7.48 (d, 1 H, J_{HF} = 11 Hz)
7	139–141	44.89, 45.45	3.51, 3.30	3.49, 3.82	1.75 (m, 4 H), 2.38 (m, 4 H), 3.78 (s, 3 H), 6.58 (d, 1 H, J_{HF} = 6 Hz), 7.57 (d, 1 H, J_{HF} = 9 Hz)
8	142–144	61.85, 62.01	4.84, 4.59	4.81, 4.83	1.79 (m, 4 H), 2.40 (m, 4 H), 3.80 (s, 3 H), 6.65 (d, 1 H, J_{HF} = 7 Hz), 6.75 (d, 1 H, J_{HF} = 10 Hz)
9	173–174	61.56, 61.70	4.84, 5.11	4.20, 4.50	1.83 (m, 4 H), 2.30 (s, 3 H), 2.45 (m, 4 H), 3.81 (s, 3 H), 6.78 (d, 1 H, J_{HF} = 7 Hz), 6.97 (d, 1 H, J_{HF} = 10 Hz)
10	170–171	62.94, 63.06	5.28, 4.98	4.59, 4.48	1.83 (m, 4 H), 2.43 (m, 4 H), 3.83 (s, 3 H), 3.90 (s, 3 H), 6.70 (d, 1 H, J_{HF} = 7 Hz), 6.78 (d, 1 H, J_{HF} = 11 Hz)
11	glass	64.85, 64.65	6.05, 5.79	4.20, 4.19	1.38 (d, 6 H), 1.80 (m, 4 H), 2.42 (m, 4 H), 3.82 (s, 3 H), 4.50 (m, 1 H), 6.68 (d, 1 H, J_{HF} = 7 Hz), 6.75 (d, 1 H, J_{HF} = 11 Hz)
12	66–67	66.47, 66.60	6.69, 6.41	3.87, 3.69	0.91 (t, 3 H), 1.40 (m, 4 H), 1.80 (m, 6 H), 2.41 (m, 4 H), 3.80 (s, 3 H), 3.98 (t, 3 H), 6.65 (d, 1 H, J_{HF} = 7 Hz), 6.72 (d, 1 H, J_{HF} = 11 Hz)
13	186–188	59.46, 59.48	4.18, 4.29	3.25, 3.00	1.80 (m, 4 H), 2.40 (m, 4 H), 3.50 (s, 3 H), 6.69 (d, 1 H, J_{HF} = 7 Hz), 7.08 (d, 1 H, J_{HF} = 10 Hz), 7.48–7.97
15	115–116	66.42, 66.15	5.58, 5.51	4.84, 4.84	1.67 (m, 4 H), 2.14 (s, 3 H), 2.33 (m, 4 H), 3.73 (s, 3 H), 6.62 (d, 1 H, J_{HF} = 7 Hz), 6.97 (d, 1 H, J_{HF} = 10 Hz)

removed by filtration; then 4.65 g (0.03 mol) of 3,4,5,6-tetrahydrophthalic anhydride was added, and the solution was heated at reflux for 18 h. The reaction mixture was cooled, poured into water, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated at reduced pressure. The crude product was flash chromatographed (2:3 ethyl acetate/heptane) to afford 5.24 g (62%) of a light yellow solid: mp 119.5–121 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.83, 2.47 (m, 8 H), 2.57 (s, 3 H), 7.22 (t, 1 H, J_{HF} = 9 Hz), 7.77–8.13 (m, 2 H). Anal. Calcd for $C_{16}H_{14}FNO_3$: C, 66.89; H, 4.91; F, 6.61; N, 4.87. Found: C, 66.68; H, 5.20; F, 6.71; N, 4.95.

N-(2-Fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (1). A solution of 10.5 g (0.05 mol) of trifluoroacetic anhydride and 100 mL of CH_2Cl_2 was chilled to 0 °C, and then 2 g of 70% aqueous H_2O_2 was added slowly at 0 °C. After 30 min at 0 °C, a solution of 6.35 g (0.023 mol) of N-(5-acetyl-2-fluorophenyl)-3,4,5,6-tetrahydrophthalimide in 50 mL of CH_2Cl_2 was added dropwise at 0 °C and then allowed to warm slowly to room temperature. The reaction mixture was washed with water, saturated aqueous Na_2SO_3, and saturated aqueous $NaHCO_3$ and then dried over $MgSO_4$ followed by removal of the solvent at reduced pressure. The crude solid (5.62 g) was dissolved in 100 mL of methanol and cooled to 0 °C. Hydrogen chloride was then bubbled in at such a rate to keep the temperature below 40 °C. After the exotherm subsided, the reaction mixture was stirred for an additional 1 h and then partitioned between ether and water. After an acid–base workup, the crude phenol was flash chromatographed (3:7 ethyl acetate/heptane) to afford 2.64 g (57%).

The above phenol was dissolved in 75 mL of acetone, and then 2.8 g (0.02 mol) of K_2CO_3 was added followed by 2.84 g (0.02 mol) of CH_3I. The mixture was heated at reflux temperature for 24 h and then partitioned between water and ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated at reduced pressure, and then flash chromatographed (3:7 ethyl acetate/heptane) to afford 1.95 g (71%) of an oil.

N-[2-Fluoro-4-(methylthio)-5-methoxyphenyl]-3,4,5,6-tetrahydrophthalimide (2). Chlorosulfonic acid (7 g) was cooled to 10 °C and stirred as 1.74 g (6.32 mmol) of 1 was added in three portions. The mixture was then warmed to 40 °C for 30 min and then poured into rapidly stirred ice water. The solid was filtered, dried, and then recrystallized from ethyl acetate to afford 1.12 g (48%) of a white solid: mp 188–189 °C.

A solution of 0.85 g (2.27 mmol) of the above solid in 10 mL of acetic acid was added to a warm (80 °C) solution of 1.56 g (6.9 mmol) of tin(II) chloride dihydrate in 15 mL of acetic acid previously saturated with HCl gas. The solution was warmed to 85 °C for 30 min, cooled, poured into concentrated HCl, and then extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated at reduced pressure. The crude mercaptan was dissolved in 15 mL of THF containing 2 mL of triethylamine and then treated with excess CH_3I (2 mL). After 30 min, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, concentrated at reduced pressure, and then flash chromatographed (3:7 ethyl acetate/heptane) to afford 0.34 g (46%) of a light yellow solid.

N-(2-Fluoro-5-methoxy-4-nitrophenyl)-3,4,5,6-tetrahydrophthalimide (3). Sulfuric acid (10 mL) was chilled to 0 °C, and then 0.75 g (2.87 mmol) of 1 was added portionwise. The solution was then treated with 0.27 g (3 mmol) of 70% HNO_3 at 0 °C, stirred for 30 min, and then poured into 100 mL of ice water. The solid was collected, dried, and flash chromatographed (1:1 ethyl acetate/heptane, to remove a small amount of the 3,5-dinitro isomer) to afford 0.55 g (62%) of a light yellow solid.

N-(4-Amino-2-fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (4). To 20 mL of acetic acid at 80 °C was added 0.92 g (large excess) of iron powder in portions while a solution of 0.55 g (1.63 mmol) of 3 in 20 mL of acetic acid was added dropwise. The mixture was stirred at 80–85 °C for 1 h, cooled, filtered through Celite to remove the unreacted iron, and

then concentrated at reduced pressure. The residue was partitioned between ether and water and then neutralized with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and then concentrated to afford 0.3 g (74%) of a light yellow solid.

***N*-(4-Acetamino-2-fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (5).** A solution of 0.43 g (1.7 mmol) of 4 in 20 mL of CH_2Cl_2 containing 0.2 g (2 mmol) of triethylamine was stirred at room temperature as 0.14 g (1.8 mmol) of acetyl chloride was added dropwise. After 2 h, the mixture was poured into dilute HCl and the organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to a solid which was triturated with ethyl ether to give 0.44 g (72%) of a white solid.

***N*-[4-(Methylsulfonamino)-2-fluoro-5-methoxyphenyl]-3,4,5,6-tetrahydrophthalimide (6).** A solution of 0.9 g (3.3 mmol) of 4 in 35 mL of CH_2Cl_2 was treated with 0.4 g (5 mmol) of pyridine and 0.38 g (3.5 mmol) of methanesulfonyl chloride and then heated at reflux temperature for 16 h. The concentrated reaction mixture was chromatographed (3:7 ethyl acetate/heptane) to afford 0.45 g (1.65 mmol) of recovered 4 and 0.5 g of a white solid (80% based on recovered 4).

***N*-(2-Fluoro-4-iodo-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (7).** A suspension of 0.38 g (1.31 mmol) of 4 in 20 mL of water, 20 mL of acetic acid, and 0.5 mL of H_2SO_4 was cooled to 0 °C and stirred while a solution of 90 mg (1.32 mmol) of $NaNO_2$ in 5 mL of water was added dropwise beneath the surface. After 1 h at 0 °C, the diazonium salt mixture was poured slowly into a vigorously stirred solution of 0.33 g (2 mmol) of KI in 25 mL of water at room temperature. The dark mixture was stirred for 1 h and then extracted with ethyl acetate. The organic layer was washed with aqueous $Na_2S_2O_5$, water, and saturated $NaHCO_3$, dried over $MgSO_4$, concentrated at reduced pressure, and then flash chromatographed (1:1 ethyl acetate/heptane) to afford 0.32 g (61%) of a white solid.

5-Fluoro-2-methoxyphenol. Trifluoroacetic anhydride (365 mL) was cooled to 0 °C, and then 37 g (0.327 mol) of 30% H_2O_2 was added dropwise. The solution was stirred at 0 °C as a solution of 18.3 g (0.108 mol) of 5-fluoro-2-methoxyacetophenone in 50 mL of trifluoroacetic anhydride was added cautiously. After 2 h, the mixture was poured into 1 L of ice water and then extracted several times with ethyl ether. The combined organic layers were washed with water, aqueous Na_2CO_3, and saturated aqueous NaCl, dried over $MgSO_4$, and then concentrated at reduced pressure to afford 18.2 g (91%) of a white solid: mp 32–34 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 3.73 (s, 3 H), 6.70–6.87 (m, 3 H).

To a solution of 4 g (100 mmol) of NaOH in 60 mL of water was added 120 mL of THF and 15.5 g (84.2 mmol) of the above solid. The mixture was stirred for 24 h and then poured into water and washed with ethyl ether. The basic layer was acidified and then extracted with ethyl acetate, which was then washed with saturated aqueous NaCl, dried over $MgSO_4$, concentrated at reduced pressure, and then flash chromatographed (7:3 heptane/ethyl acetate) to afford 10.9 g (91%) of a yellow oil: ^1H NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 6.80–7.25 (m, 3 H).

***N*-(2-Fluoro-4-hydroxy-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (8).** A solution of 3 g (21.1 mmol) of 5-fluoro-2-methoxyphenyl in 60 mL of acetic acid was cooled to 15 °C, and then a solution of 1.5 mL (23.3 mmol) of 70% HNO_3 in 15 mL of acetic acid was added dropwise. After 30 min, the mixture was poured into ice water and then extracted with ethyl ether. After a base–acid workup, the ether layer was dried over $MgSO_4$ and concentrated at reduced pressure to afford 2.0 g (51%) of a yellow solid: mp 171–173 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 6.75 (d, 1 H, J_{HF} = 12 Hz), 7.53 (d, 1 H, J_{HF} = 7 Hz).

A solution of 1.87 g (10 mmol) of the above solid in 50 mL of acetic acid was hydrogenated over 50 mg of PtO_2 at 3 atm of H_2. The catalyst was filtered, and the filtrate was combined with 1.45 g (9.5 mmol) of 3,4,5,6-tetrahydrophthalic anhydride and heated to reflux temperature. After 16 h, the mixture was concentrated at reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was neutralized with aqueous $NaHCO_3$, washed with water, dried over $MgSO_4$, concentrated, and then flash chromatographed (7:3 ethyl acetate/heptane) to afford 1.78 g (64%) of a yellow solid.

***N*-(4-Acetoxy-2-fluoro-5-methoxyphenyl)-3,4,5,6-tetrahydrophthalimide (9).** A solution of 0.58 g (2.0 mmol) of 8 in 10 mL of THF was treated with 0.03 g of 4-pyrrolidinopyridine followed by the addition of 0.22 g (2.1 mmol) of acetic anhydride. After 1 h, the mixture was poured into water and extracted with ethyl ether. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, concentrated at reduced pressure, and then recrystallized from petroleum ether to afford 0.51 g (75%) of a light yellow solid.

***N*-(2-Fluoro-4,5-dimethoxyphenyl)-3,4,5,6-tetrahydrophthalimide (10).** A mixture of 0.58 g (2 mmol) of 8, 0.54 g (4 mmol) of K_2CO_3, excess CH_3I (16 mmol), and 15 mL of acetone was heated at reflux temperature for 2 h and then poured into water and extracted with ethyl ether. The organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and then concentrated at reduced pressure to afford 0.51 g (79%) of a light yellow solid.

***N*-[2-Fluoro-5-methoxy-4-(2-propoxy)phenyl]-3,4,5,6-tetrahydrophthalimide (11)** was prepared as for 10 from 0.59 g (2.05 mmol) of 8 and excess 2-iodopropane: yield 0.58 g (84%) of a yellow oil.

***N*-[2-Fluoro-5-methoxy-4-(1-pentoxy)phenyl]-3,4,5,6-tetrahydrophthalimide (12)** was prepared as for 10 from 0.58 g (2 mmol) 8 and excess 1-bromopentane: yield, 0.38 g (53%) of a light yellow solid.

***N*-[4-(Phenylsulfonyl)-2-fluoro-5-methoxyphenyl]-3,4,5,6-tetrahydrophthalimide (13).** A solution of 0.58 g (2 mmol) of 8, 10 mL of CH_2Cl_2, and 0.18 g (2.2 mmol) of pyridine was treated with 0.36 g (2.1 mmol) of benzenesulfonyl chloride, stirred at room temperature for 72 h, and then concentrated at reduced pressure. The residue was dissolved in ethyl acetate, washed with 5% HCl, dried over $MgSO_4$, and concentrated at reduced pressure to afford 0.75 g (86%) of a white solid.

4-Fluoro-2-methyl-5-nitrophenol. A solution of 18.4 g (0.1 mol) of methyl 4-fluoro-2-methylphenyl carbonate [prepared from 5-fluoro-2-hydroxytoluene (Finger et al., 1959) and methyl chloroformate] in 60 mL of H_2SO_4 was treated dropwise at 10 °C with 9 g (0.11 mol) of 70% HNO_3. After 1 h, the mixture was poured into ice/water and then extracted with ethyl ether, dried over $MgSO_4$, and filtered through a plug of silica gel to afford 17.9 g (74%) of a solid: mp 50–53 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 3.93 (s, 3 H), 7.15 (d, 1 H, J_{HF} = 11 Hz), 7.90 (d, 1 H, J_{HF} = 7 Hz).

A solution of 15 g (0.065 mol) of the carbonate in 60 mL of CH_2Cl_2 was slowly added to a solution of 13 mL (0.013 mol) of BBr_3 at −40 °C. After warming to room temperature, the mixture was stirred for 6 h and then poured into ice/water. The CH_2Cl_2 layer was separated, dried over $MgSO_4$, and then concentrated to give 7.0 g (63%) of the phenol: mp 134–135 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 6.97 (d, 1 H, J_{HF} = 12 Hz), 7.53 (d, 1 H, J_{HF} = 6 Hz), 9.49 (b s, 1 H).

***N*-(2-Fluoro-5-methoxy-4-methylphenyl)-3,4,5,6-tetrahydrophthalimide (15).** A solution of 4 g (0.023 mol) of 4-fluoro-2-methyl-5-nitrophenol in 20 mL of acetone was combined with 4.7 g (0.035 mol) of K_2CO_3 and 6.5 g (0.046 mol) of CH_3I and heated at reflux temperature for 16 h. The solvent was evaporated and the residue filtered through a plug of silica gel with CH_2Cl_2 to yield 3.7 g (87%) of a solid: mp 110–112 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.93 (s, 3 H), 7.10 (d, 1 H, J_{HF} = 11 Hz), 7.50 (d, 1 H, J_{HF} = 6 Hz).

The above solid was dissolved in 50 mL of 20% aqueous acetic acid and stirred as 3 g of powdered Fe was added portionwise. After stirring at 35 °C for 2 h, the mixture was filtered through Celite and washed with ethyl ether. The ether layer was washed with water and 10% $NaHCO_3$, concentrated, and then chromatographed on silica gel with CH_2Cl_2 to afford 2.0 g (67%) of an oil: ^1H NMR (60 MHz, $CDCl_3$) δ 2.10 (s, 3 H), 3.75 (s, 3 H), 6.30 (d, 1 H, J_{HF} = 8 Hz), 6.77 (d, 1 H, J_{HF} = 11 Hz).

A mixture of 1.7 g (11 mmol) of the above oil, 1.53 g (10 mmol) of 3,4,5,6-tetrahydrophthalic anhydride, and 15 mL of acetic acid was heated at reflux temperature for 1 h and then poured into ice/water and extracted with ethyl ether. The ether layer was washed with water, dried over $MgSO_4$, concentrated at reduced pressure, and recrystallized from methylene chloride/heptane to afford 1.40 g (48%) of a solid.

Table V. Biological Data

		lab pI_{50}		greenhouse		
					log $1/ED_{50}$	
compd	substituent	obs[a]	calc[b]	ED_{50}[c]	obs	calc[e]
1	H	4.9	5.2	0.45	0.34	0.48
2	SCH_3	4.5	5.1	0.37	0.43	0.21
3	NO_2	6.7	6.3	0.05	1.30	1.71
4	NH_2	2.7	2.6	13.8	−1.14	−1.01
5	NHAc	4.1	3.4	d	<−1.6	−0.06
6	$NHSO_2CH_3$	3.5	3.0	d	<−1.5	−0.47
7	I	6.3	6.1	0.05	1.30	1.43
8	OH	3.7	4.1	d	<−1.7	−0.33
9	OAc	3.2	4.6	d	<−1.6	−0.67
10	OCH_3	4.8	4.6	0.41	0.39	0.41
11	O-*i*-C_3H_7	4.7	4.9	d	<−1.6	0.35
12	O-*n*-C_5H_{11}	5.5	5.4	d	<−1.5	0.89
13	$OSO_2C_6H_5$	4.3	4.5	d	<−1.4	0.07
14	Br	6.7	6.4	0.017	1.77	1.71
15	CH_3	5.6	5.2	0.11	0.97	0.96
16	Cl	6.4	6.4	0.013	1.88	1.50

[a] pI_{50} = negative log of the concentration (M/l) to provide 50% fresh weight reduction of hydroponically grown cucumber. [b] Calculated by using eq 1. [c] Rate (M/ha) to provide 50% postemergence control of velvetleaf. [d] <50% control at 4 kg/ha (highest rate tested). [e] Calculated by using eq 3.

Biological Evaluation. This assay was adapted from a published procedure (Ross, 1974). Two 55-mm explants from 5-day-old etiolated cucumbers (*Cucumis sativus* cv. Wisconsin), retaining the cotyledons, apical meristem, and upper portion of the stem, were placed into vials containing 20 mL of B5 medium without sucrose, hormones, or vitamins (Gambourg et al., 1968) which had been treated with replicated 3-fold serial dilutions of the text chemical at five rates. The explants were incubated under continuous light at 100 $\mu E\ m^{-2}\ s^{-1}$ at 25 °C for 10 days. A pI_{50} value for each test chemical was calculated from a plot of the logarithm of the rate vs the percent relative growth inhibition, measured as weight gain after treatment. RS/1 (available from BBN Software Products Corp.) was used to fit a regression line to the linear portion of the curve.

Postemergent Herbicidal Evaluation. Seeds of velvetleaf (*Abutilon theophrasti* Medik.) were planted in a loam soil in 10-cm plastic pots and grown in the greenhouse with supplemental lighting (minimum 14-h photoperiod). Plants were treated with the test chemical at varying rates when at the two- to three-leaf stage. The test chemical was diluted to 10 mL with acetone/water (1/1 v/v) containing 0.5% (v/v) Tween 20. The diluted chemical spray was applied to velvetleaf plants by use of a hand-held atomizer sprayer at five rates (2-fold serial dilutions bracketing the 50% control rate) with five replicates. Herbicidal activity was assessed visually on a 0–100% scale (0%, no effect; 100%, complete kill) 14 days after treatment and expressed as a ED_{50} (Table V). The ED_{50} values were obtained from a least-squares fit to the linear portion of the curve of percent control vs rate of application using BMDP software.

RESULTS AND DISCUSSION

The set of 16 compounds was subjected to a multiple linear regression analysis using the cucumber inhibition data from Table V. The correlation eq 1 was obtained,

$$pI_{50} = (1.08 \pm 0.18)\pi + (2.41 \pm 0.92)F_p + (1.40 \pm 0.60)R_p - (0.072 \pm 0.019)\mathrm{MR} + 5.25 \quad (1)$$

$$n = 16,\ r^2 = 0.84,\ s = 0.59,\ F_{4,11} = 14.3\ (p = 0.00)$$

where π is the Hansch hydrophobicity constant, F_p and R_p are the Swain and Lupton parainductive and resonance parameters, respectively, and MR is the molar refractivity, which also can be considered to be a "corrected" form of the molar volume (Hansch and Leo, 1979). All terms included are significant at the 95% level on the basis of Student's *t*-test. A stepwise regression analysis for the development of eq 1 (Table VI) indicated that the Hansch hydrophobicity term π singularly accounted for 41% of the variance of biological activity. The steric term MR was the next most important term, increasing the explained variance to 57%. Adding the inductive parameter term *F* improved the explained biological variance to 78%, and adding the resonance term *R* increased that to 84%.

Table VI. Stepwise Regression Analysis: Development of Equation 1

step 1	$pI_{50} = 8.4\pi + 4.70$ $n = 16,\ r^2 = 0.41,\ s = 1.01,\ F_{(1,14)} = 9.54$
step 2	$pI_{50} = 1.09\pi - 0.06\mathrm{MR} + 5.41$ $n = 16,\ r^2 = 0.57,\ s = 0.89,\ F_{(2,13)} = 8.60$
step 3	$pI_{50} = 1.06\pi + 3.11F_p - 0.07\mathrm{MR} + 4.69$ $n = 16,\ r^2 = 0.78,\ s = 0.69,\ F_{(3,12)} = 12.6$
step 4	$pI_{50} = 1.08\pi + 2.41F_p + 1.40R_p - 0.07\mathrm{MR} + 5.25$ $n = 16,\ r^2 = 0.84,\ s = 0.59,\ F_{(4,11)} = 14.3$

By use of eq 1, pI_{50} values were calculated and compared with the measured values (Table V). The predicted potency of all of the compounds except **2**, **5**, and **9** was within one standard deviation of the observed values. The deviation of two of the compounds, **2** and **9**, could be explained by metabolic detoxification. Oxidation of the methylthio group in **2** to the sulfoxide or sulfone would be expected to reduce activity due to the large decrease in hydrophobicity (the calculated pI_{50} values are 3.8 and 4.1, respectively). The lower than expected potency for compound **9** is most likely due to hydrolysis of the acetate to the hydroxyl, which is consistent with the data for compound **8**. The slightly higher potency than expected for acetamide, **5**, is not readily explained, although the error is only slightly more than the limits of eq 1. It is apparent from this study that the selection criteria for the original compound set should also take into consideration the metabolic stability under the conditions of biological testing.

Equation 1 is consistent with a previous study of 4-substituted phenyltetrahydrophthalimides (Ohta et al., 1980) in which electronic and steric parameters were found to correlate with root growth inhibition. Hydrophobic parameters were included in the study but were highly cross correlated with one of the steric terms.

We chose next to examine how well the parameters identified in eq 1 described the observed greenhouse postemergence herbicidal activity. Regression analysis using the data from Table V provided eq 2. Compounds that

$$\log 1/ED_{50} = (1.1 \pm 0.1)\pi + (2.27 \pm 0.3)F_p - (0.10 \pm 0.02)\mathrm{MR} + 0.69 \quad (2)$$

$$n = 9,\ r^2 = 0.97,\ s = 0.21,\ F_{2,6} = 51.7\ (p = 0.00)$$

provided less than 50% control of velvetleaf at 4 kg/ha were not included in the analysis since we did not have ED_{50} values. The stepwise regression analysis for the development of eq 2 is shown in Table VII. As in eq 1, the π term accounted for a significant portion of the biological variance followed by the *F* and MR terms. Although the MR term was included, there was a significant cross correlation between π and MR in the reduced set. Due to the similarity of eqs 1 and 2, the analysis was repeated to include the pI_{50} term from eq 1 as a descriptor of intrinsic potency (eq 3).

Equation 3 indicated that there was an excellent correlation between the hydroponic assay and greenhouse activity with the pI_{50} term alone explaining 93% of the

Table VII. Stepwise Regression Analysis: Development of Equation 2

step 1	$\log 1/ED_{50} = 1.0\pi + 0.55$ $n = 9, r^2 = 0.65, s = 0.59, F_{(1,7)} = 12.8$
step 2	$\log 1/ED_{50} = 0.86\pi + 1.8F_p + 0.12$ $n = 9, r^2 = 0.85, s = 0.42, F_{(2,6)} = 16.4$
step 3	$\log 1/ED_{50} = 1.1\pi + 2.3F_p - 0.10MR + 0.69$ $n = 9, r^2 = 0.97, s = 0.21, F_{(3,5)} = 51.67$

Table VIII. Molecular Parameters

compd	substituent	CMR	CLOGP	greenhouse activity[a]
1	H	6.86	2.67	m
2	SCH_3	8.13	3.30	m
3	NO_2	8.36	2.37	a
4	NH_2	7.23	1.77	i
5	NHAc	8.19	1.46	i
6	$NHSO_2CH_3$	8.56	1.03	i
7	I	8.16	3.59	a
8	OH	7.01	2.04	i
9	OAc	7.97	1.70	i
10	OCH_3	7.47	2.19	m
11	O-*i*-C_3H_7	8.40	3.03	i
12	O-*n*-C_5H_{11}	9.33	4.30	i
13	$OSO_2C_6H_5$	10.39	3.21	i
14	Br	7.63	3.33	a
15	CH_3	7.32	3.32	a
16	Cl	7.35	3.18	a

[a] i, inactive, $\log 1/ED_{50} < 0$; m, moderately active, $0.9 > \log 1/ED_{50} > 0$; a, active, $\log 1/ED_{50} > 0.9$.

biological variance. The addition of any of the other terms did not statistically improve the regression equation. By

$$\log 1/ED_{50} = (0.68 \pm 0.07)pI_{50} - 2.85 \quad (3)$$

$$n = 9, r^2 = 0.93, s = 0.26, F_{1,7} = 98.4 \ (p = 0.00)$$

use of eq 3, the $\log 1/ED_{50}$ values were calculated and compared with the observed (Table V). Only compounds **3** and **16** had calculated values that differed by slightly more than one standard deviation. The nitro compound **3** was slightly less active and the chloro compound **16** was slightly more active than predicted. Equation 3 was not as effective, however, at predicting the inactive compounds, especially the lipophilic alkoxy-substituted compounds **11** and **12**. Both compounds were predicted to be much more active than observed in the greenhouse postemergence test. In this case, there was no obvious reasoning for the discrepancy in activity.

A major difference between the hydroponic assay and the postemergence greenhouse test is the barrier that each test system imposes on the uptake of the test chemical. In the hydroponic assay, uptake of the test chemical occurs readily through the cut stem of the cucumber explant. A postemergence application, however, is presented with the multiple barriers of foliar absorption. Penetration of the herbicide through the leaf cuticle is influenced by the molecular properties of the herbicide (Stevens, 1988) such as hydrophobicity and molecular size (Price, 1985). We chose to use the calculated molar refractivity (CMR) as a measure of molecular size and calculated log *P* (CLOGP) for hydrophobicity. MR is an additive property that has been shown to be highly linear in van der Waals values (Charton, 1983). Both CLOGP and CMR are readily accessible by use of MedChem software (version 3.33 from A. Leo and D. Weiniger, Pomona College).

A plot of CLOGP vs CMR values (from Table VIII) is shown in Figure 1. Each compound was classified as being active ($\log 1/ED_{50} > 0.9$), moderately active ($0.9 > \log 1/ED_{50} > 0$), and inactive ($\log 1/ED_{50} < 0$) on the basis of the greenhouse data. The resulting graph indicated that the greenhouse active compounds were clustered into a distinct region of CMR and CLOGP. These compounds all have CMR values within the range 7.3–8.4 and CLOGP values within the range 2.3–3.6. Two of the compounds, **2** (methylthio) and **11** (isopropoxy), which were not classified as highly active, appeared within the high active cluster. Both of these, however, were on average an order of magnitude less active in the hydroponic assay than the rest of the cluster set. Since the hydroponic assay is used as a measure of intrinsic potency, high pI_{50} values are essential for high greenhouse activity. The compounds that were inactive in the postemergence test either have low hydroponic activity or fall outside the range of CMR and CLOGP for optimum foliar penetration.

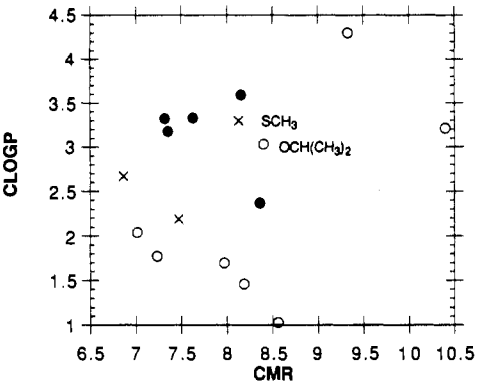


Figure 1. Plot of CMRE vs CLOGP: (●) $\log 1/ED_{50} > 0.9$; (×) $0.9 > \log 1/ED_{50} > 0$; (○) $\log 1/ED_{50} < 0$.

It was not possible to test the significance of CMR and CLOGP at improving the predictive power of eq 3 since we did not have ED_{50} values for the inactive compounds. It would be expected from Figure 1, however, that a regression equation with the inclusion of CMR and CLOGP would be more able to explain the observed postemergence activity of the inactive compounds.

LITERATURE CITED

Austel, V. A. Manual Method for Systematic Drug Design. *Eur. J. Med. Chem. Chim. Ther.* **1982**, *17*, 9–16.

Charton, M. Applications of Various Steric Constants to Quantitative Analysis of Structure-Activity Relationships. *Top. Curr. Chem.* **1983**, *114*, 107–118.

Corse, J.; Ingraham, L. The Monofluorocatechols. *J. Org. Chem.* **1951**, *16*, 1345–1348.

Dixon, W. J., Ed. *BMDP Statistical Software*; University of California, Berkeley, 1983.

Finger, G. C.; Gortatowski, M. J.; Shiley, R. H.; White, R. H. Aromatic Fluorine Compounds. VII. Plant Growth Regulators and Intermediates. *J. Am. Chem. Soc.* **1959**, *81*, 94–101.

Gambourg, O. L.; Miller, R. A.; Ojima, K. Nutrient Requirements of Suspension Cultures of Soybean Root Cultures. *Exp. Cell. Res.* **1968**, *50*, 151–161.

Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, 1978.

Hansch, C.; Unger, U. Strategy in Drug Design. Cluster Analysis as an Aid in the Selection of Substituents. *J. Med. Chem.* **1973**, *16*, 1217–1222.

Jukihara, T.; Ushinohama, K.; Natsume, B.; Watanabe, H.; Suzuki, S. N-(3-Substituted aminophenyl)tetrahydrophthalimides and Herbicidal Composition. Eur. Patent Appl. 77938, 1982. Mitsubishi Chemical Industries. *Chem. Abstr.* **1983**, *99*, 122298.

Martin, Y. C.; Panas, H. N. Mathematical Considerations in Series Design. *J. Med. Chem.* **1979**, *22*, 784–791.

Nagano, E.; Hashimoto, S.; Yoshida, R.; Matsumoto, H.; Oshio, H.; Kamoshita, K. Tetrahydrophthalimides, and Their Use. Eur. Patent Appl. 61 741, 1982. Sumitomo Chemical Co., Ltd. *Chem. Abstr.* **1983**, *98*, 71924.

Nagano, E.; Yoshida, R.; Matsumoto, H.; Hashimoto, S.; Kamoshita, K. 2-Substituted phenyl-5,6,7,8-tetrahydro-2H-isoindol-1,3-diones and Their Use. Eur. Patent Appl. 126419, 1983. Sumitomo Chemical Co., Ltd. *Chem. Abstr.* **1985**, *102*, 149106.

Nagano, E.; Hashimoto, S.; Yoshida, R.; Matsumoto, H.; Kamoshita, K. Tetrahydrophthalimides, and Their Use as Herbicide. U.S. Patent 4484940, 1984. Sumitomo Chemical Co.

Oelschlager, H. Synthesis of New Local Anesthetics. I. α-Amino-3-alkylacetanilides as Local Anesthetics. *Arch. Pharm.* **1957**, *290*, 587–596.

Ohta, H.; Jikihara, T.; Wakabayashi, K.; Fujita, T. Quantitative Structure-Activity Study of Herbicidal N-Aryl-3,4,5,6-tetrahydrophthalimides and Related Cyclic Imides. *Pestic. Biochem. Physiol.* **1980**, *14*, 153–160.

Okada, I.; Suzuki, S. (Phosphonophenyl)tetrahydrophthalimides as Herbicides. Jpn. Kokai Tokkyo Koho J.P. 60228494, 1984; *Chem. Abstr.* **1986**, *104*, 149168.

Price, C.E.; Anderson, N. H. Uptake of Chemicals from Foliar Deposits: Effects of Plant Species and Molecular Structure. *Pestic. Sci.* **1985**, *16*, 369–377.

Ross, C. W. *Plant Physiology Laboratory Manual*; Wadsworth Publishing: Belmont, CA, 1974; Chapter 6.

Sandmann, G.; Clarke, I. E.; Bramley, P. M.; Boger, P. Inhibition of Phytoene Desaturase—Mode of Action of Certain Bleaching Herbicides. *Z. Naturforsch. C* **1984a**, *39*, 443–449.

Sandmann, G.; Reck, H.; Boger, P. Herbicidal Mode of Action on Chlorophyll Formation. *J. Agric. Food Chem.* **1984b**, *32*, 868–872.

Stevens, P. J. G.; Baker, E. A.; Anderson, N. H. Factors Affecting the Foliar Absorption and Redistribution of Pesticides 2. Physiochemical Properties of the Active Ingredient and Role of Surfactant. *Pestic. Sci.* **1988**, *24*, 31–53.

Wakabayashi, K. Molecular Design of Cyclic Imide Herbicides Using Biorational Approaches. *J. Pestic. Sci.* **1988**, *13*, 337–361.

Wakabayashi, K.; Matsuya, K.; Teraoka, T.; Sandmann, G.; Boger, P. Effect of Cyclic Imine Herbicides on Chlorophyll Formation in Higher Plants. *J. Pestic. Sci.* **1986**, *11*, 635–640.

Wheeler, T. N.; Craig, T. A.; Morland, R. B.; Ray, J. A. Novel N-[4-Chloro-2-fluoro-5-(substituted methyl)phenyl]imides. *Synthesis* **1987**, 883–887.

Yamada, O.; Yanagi, M.; Futatsuya, F.; Kobayashi, K. Herbicidal N-Substituted tetrahydrophthalimide Derivatives. Br. Patent Appl. GB 2071100, 1982, Nippon Kayaku Co., Ltd.; *Chem. Abstr.* **1982**, *96*, 199517.

Received for review February 7, 1991. Accepted June 3, 1991.

Registry No. **1**, 134882-48-7; **2**, 134882-49-8; **3**, 134882-50-1; **4**, 134882-51-2; **5**, 134882-52-3; **6**, 134882-53-4; **7**, 134882-54-5; **8**, 134882-55-6; **9**, 134882-56-7; **10**, 134882-57-8; **11**, 134882-58-9; **12**, 134882-59-0; **13**, 134882-60-3; **14**, 84478-57-9; **15**, 134882-61-4; **16**, 84478-44-4; *N*-(5-acetyl-2-fluorophenyl)-3,4,5,6-tetrahydrophthalimide, 110322-62-8; 4-fluoro-3-nitroacetophenone, 400-93-1; 3,4,5,6-tetrahydrophthalic anhydride, 2426-02-0; 5-fluoro-2-methoxyphenol, 72955-97-6; 5-fluoro-2-methoxyacetophenone, 445-82-9; 5-fluoro-2-methoxy-4-nitrophenol, 134882-62-5; 4-fluoro-2-methyl-5-nitrophenol, 122455-84-9; 1-fluoro-4-methoxy-5-methyl-2-nitrobenzene, 134882-63-6.