chlorobiphenyl, 38380-04-0; 2,4,5,3',4'-pentachlorobiphenyl, 31508-00-6; 2,4,5,2',4',5'-hexachlorobiphenyl, 35065-27-1; 2,3,4,5,2',5'-hexachlorobiphenyl, 52712-04-6; 2,3,4,2',4',5'-hexachlorobiphenyl, 35065-28-2; 2,3,5,6,2',4',5'-heptachlorobiphenyl, 52663-68-0; 2,3,4,2',3',4'-hexachlorobiphenyl, 38380-07-3; 2,3,4,5,2',4',5'-heptachlorobiphenyl, 35065-29-3; 2,3,4,5,2',3',4'-heptachlorobiphenyl, 35065-30-6; Aroclor 1254, 11097-69-1.

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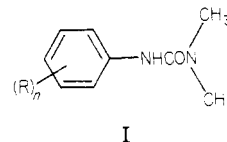Yoshimura, H.; Yoshihara, S.; Oazwa, N.; Miki, M. *Ann. N.Y. Acad. Sci.* **1979**, *320*, 179.

The Design of Postemergence Phenylurea Herbicides Using Physicochemical Parameters and Structure–Activity Analyses

Barrington Cross,* Peggy P. Hoffman, George T. Santora, David M. Spatz,[1] and Andrew R. Templeton

A series of herbicidal 3-[*p*-(benzyloxy)phenyl]-1,1-dimethylureas was prepared from an assessment of a published Hill inhibition correlation equation on 1,1-dimethyl-3-phenylureas. By use of herbicidal data for our compounds, the correlation equation obtained was $\log(1/C) = 1.3 + 0.42\pi - 5.4E_R$, where $r^2 = 0.89$ and $s = 0.30$. In this expression C is a molar concentration obtained from ED_{85} herbicidal data, where ED_{85} is the effective dose of compound to cause 85% kill of wild mustard, π refers to the hydrophobic substituent parameter, and E_R is a free radical parameter. Critical analysis of this equation led to the discovery of new herbicidal compounds of which a series of 1,1-dimethyl-3-[*m*- (or *p*-) (phenylalkoxy)phenyl]ureas were particularly effective postemergence herbicides.

Over 300 patents have been issued on herbicidal phenylureas since the discovery of monuron [1,1-dimethyl-3-(*p*-chlorophenyl)urea]. In spite of this seemingly insurmountable patent domination of this structural class, we questioned whether the most potent phenylurea herbicides have already been made, and if not, how they might be identified.

It is known that phenylureas exert their effect by blocking an electron-transfer step in the oxygen-evolving photochemical reaction of plants, and this light-catalyzed activity of isolated chloroplasts is known as the Hill reaction (1937). In 1956, Wessels and Van der Veen (1956) reported on the 50% inhibition of the Hill reaction (pI_{50}) for twelve 3- and 4-substituted 1,1-dimethyl-3-phenylureas (I).

Agricultural Research Division, American Cyanamid Company, Princeton, New Jersey 08540.
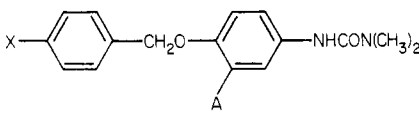
[1]Present address: Chevron Chemical Co., Richmond, CA 94804.

I

Where R is H, 3-Cl, 4-Cl, 4-Cl, 3,4-Cl$_2$, 3-NO$_2$, 4-NO$_2$, 3-CF$_3$, 4-CF$_3$, 4-CH$_3$, 4-N(CH$_3$)$_2$, 4-OCH$_3$, and 4-NHCOCH$_3$. Ten years later Hansch and Deutsch analyzed these data by regression and correlation analyses using the physicochemical parameters σ, the Hammett electronic parameter, and π, the free energy related lipophilicity substituent constant. The best-fit eq 1 suggested that the lipophilic nature of the substituent plays a major role and its degree of electron withdrawal a lesser role in the inhibition of the Hill reaction.
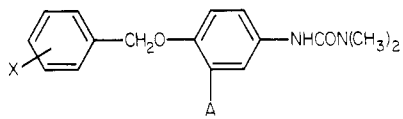
$$pI_{50} = 0.54\sigma + 1.29\pi + 4.18 \qquad (1)$$

$$n = 12 \qquad r^2 = 0.94 \qquad s = 0.37$$

$pI_{50} = -\log I_{50}$, where I_{50} is the molar concentration of

Design of Postemergence Phenylurea Herbicides

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Table I. 3-[4-(Benzyloxy)phenyl]-1,1-dimethylureas[a] Used for Models: Properties and Activities

compd	X	A	mp, °C	π(A + X)	E_R	predicted Hill Inhibition, pI_{50} (eq 1)	observed phytotoxicity, log (1/C)	predicted phytotoxicity, log (1/C) (eq 4)
1	H	H	159.5–160	0	0	6.2	1.09	1.30
2	H	Cl	116–117.5	0.76	0	7.4	1.65	1.62
3	4-Cl	H	149.5–150	0.71	0.1	7.1	1.35	1.06
4	4-CH₃	H	149.5–150.5	0.56	0.03	6.9	1.79	1.37
5	4-Br	H	161.5–163	0.86	0.12	7.3	0.59	1.01
6	4-OCH₃	H	133–134	−0.02	0.11	6.2	0.43	0.70
7	3-CF₃	H	113–114.5	0.88	0.1	7.3	1.18	1.13
8	4-SCH₃	H	147–147.5	0.61	0.24	7.0	−0.14	0.26
9	4-SO₂CH₃	H	187–188	−1.63	0.12	4.1	0.014	−0.03
10	4-NO₂	H	172–173	−0.28	0.41	5.8	−0.75	−1.04
11	4-Cl	Cl	184–185	1.47	0.1	8.3	1.38	1.37
12	4-CH₃	Cl	144–145.5	1.32	0.03	8.1	1.85	1.69

[a] Cross (1974).

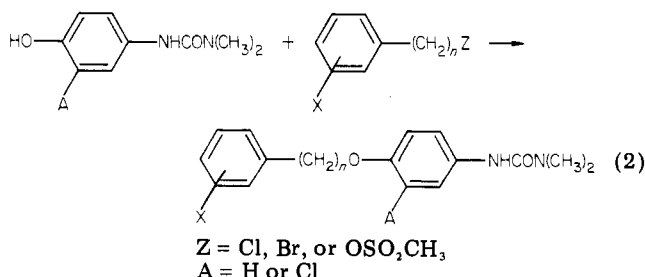Table II. 3-[4-(Benzyloxy)phenyl]-1,1-dimethylureas: Properties and Activities

compd	X	A	mp, °C	π(A + X)	E_R	observed phytotoxicity, log (1/C)	predicted phytotoxicity, log (1/C) (eq 4)
13	C(CH₃)₃	H	168–169	1.98	0.03	1.56	1.19
14	C₂H₅	Cl	122–123	1.78	0.03	1.17	1.21
15	CH(CH₃)₂	Cl	122–126	2.28	0.03	1.18	1.16
16	C₄H₉	Cl	92–93	2.81	0.03	1.09	1.08
17	C(CH₃)₃	Cl	128–131	2.76	0.03	0.6	1.09
18	C₈H₁₇	Cl	100–101	4.78	0.03	−0.21	0.58
19	C₁₀H₂₁	Cl	102–103	5.78	0.03	−0.24	0.21
20	C₁₈H₃₇	Cl	104–105	8.78	0.03	−0.94	−1.38
21	F	Cl	145–147.5	0.90	−0.07	1.68	1.82

compound giving 50% inhibition of the Hill reaction rate.
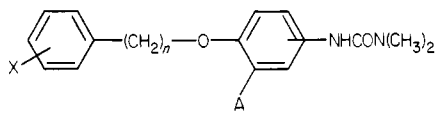
This paper will describe our approach to the design of a phenylurea herbicide using eq 1 as the starting point for our investigations.

MATERIALS AND METHODS

Chemical Methods. (A) *Synthesis.* All of the 1,1-dimethylureas in Tables I, II and III were prepared by reaction of the appropriate 3-[m- (or p-) hydroxyphenyl]-1,1-dimethylurea with either a benzyl halide or an aralkyl methanesulfonate in the presence of potassium *tert*-butoxide in DMF or 2-propanol at 80 °C. Intermediate aralkylmethanesulfonates were prepared by the method of Crossland and Servis (1970).

Z = Cl, Br, or OSO₂CH₃
A = H or Cl

(1) 3-[4-[(p-Bromobenzyl)oxy]phenyl]-1,1-dimethylurea (5). To a solution of 3-(p-hydroxyphenyl)-1,1-dimethylurea (3.6 g, 0.02 mol) in 2-propanol (100 mL) was added potassium *tert*-butoxide (2.24 g, 0.02 mol) at 80 °C. After

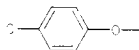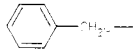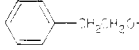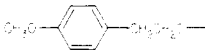Table III. 3-[m- (or p-) (Phenylalkoxy)phenyl]-1,1-dimethylureas:[a] Chemical Properties

compd	X	A	NHCON(CH₃)₂	n	mp, °C
22	H	Cl	p	2	113–114
23	H	Cl	p	3	102–103
24	H	Cl	p	4	79–81
25	H	Cl	p	5	83–84
26	H	H	m	2	99–100
27	4-OCH₃	H	m	2	116–119
28	4-CH₃	H	m	2	130–131
29	4-F	H	m	1	135–137

[a] Spatz and Cross (1981).

15 min, p-bromobenzyl bromide (5 g, 0.02 mol) was added and the mixture heated at reflux for 17 h, cooled, and poured into 1% aqueous NaOH. A fluffy white solid crystallized out and was recrystallized from benzene to give colorless plates: mp 161.5–163 °C, 4.5 g (64%). Anal. Calcd for C₁₆H₁₇N₂O₂Br: C, 55.03; H, 4.98; N, 8.02; Br 22.89. Found: C, 55.25; H, 4.96; N, 7.77; Br 22.88.

(2) *1,1-Dimethyl-3-[m-[(p-methoxyphenethyl)oxy]-phenyl]urea* **(27)**. Potassium *tert*-butoxide (1.68 g, 0.015 mol) was added to a well-stirred solution of 3-(m-hydroxyphenyl)-1,1-dimethylurea (2.70 g, 0.015 mol) in DMF (75 mL). After 30 min, freshly prepared (p-meth-

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Table IV. Values for Hill Inhibition of Plant Chloroplasts

compd	X_3	X_4	pI_{50} found[c]	calcd[d] (eq 1)
diuron[a]	Cl	Cl	6.98	6.4
chloroxuron[b]	H	(p-chlorophenoxy)phenyl	7.01	7.8
2	Cl	benzyl	7.35	7.4
22	Cl	phenethyloxy	7.54	8.0
27	(methoxyphenyl)methyl	H	7.33	7.0

[a] Diuron is 3-(3,4-dichlorophenyl)-1,1-dimethylurea. [b] Chloroxuron is 3-[(p-chlorophenoxy)phenyl]-1,1-dimethylurea. [c] pI_{50} on S. oleracea. [d] Calculated pI_{50} on Brassica spp.

oxyphenethyl)methanesulfonate (3.45 g, 0.015 mol) in DMF (5 mL) was added dropwise and the reaction mixture warmed to 80 °C for 5 h. DMF was removed in vacuo, and the residue was dissolved in $H_2O-CH_2Cl_2$. The separated CH_2Cl_2 layer was washed successively with dilute NaOH, H_2O, and saturated NaCl and dried over anhydrous Na_2SO_4. Evaporation afforded an oil, 4.6 g (96%), which solidified rapidly. Crystallization from toluene (35 mL)–hexane (5 mL) gave off-white crystals, 2.6 g (57%): mp 116–119 °C. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.76; H, 7.06; N, 8.91. Found: C, 68.69; H, 7.01; N, 8.90.

(B) *Physicochemical Parameters.* Compilations of Hansch et al. (1973) and Hansch and Leo (1979) were used as sources for π values in Tables I and II. The estimation of π by additivity principles (Hansch and Leo, 1979) was employed in some cases, assuming an increment of $0.5/CH_2$ for π. The free radical parameter, E_R, was obtained from the compilations of Yamamoto and Otsu (1967) and for the CF_3 group using the Hansch and Kerley (1970) equation:

$$\sigma^+ = -1.32E_R + 1.6\sigma - 0.02 \qquad (3)$$

$$n = 16 \qquad r^2 = 0.99 \qquad s = 0.10$$

Biological Methods. (A) *Hill Reaction Assay.* The following procedures, based upon those of Moreland (1977), were used to isolate and assay chloroplasts from spinach (*Spinacia oleracea* L) leaves. The homogenization medium consisted of 0.4 M sucrose, 1 mM $MgCl_2$, and 50 mM Mes buffer (pH 6.7) and the resuspension medium of 50 mM Hepes buffer (pH 7.8), 1 mM $MgCl_2$, and 0.4 M sucrose. The reaction mixture (5 mL) contained in test tubes (18 × 150 mm) consisted of 50 mM Hepes buffer (pH 7.8), 1 mM $MgCl_2$, and 0.4 mM potassium ferricyanide as the electron acceptor and 50 μg of chlorophyll which was determined by the method of Arnon (1949). The test compounds were dissolved in methanol, which was 1% in the assay mixture. Test tubes were illuminated with saturating white light for 4 min. The reaction was stopped by the addition of 1 mL of 10% trichloroacetic acid. Precipitated chloroplast protein was removed by centrifugation at top speed for 10 min in an IEC clinical centrifuge. The rate of ferricyanide reduction was determined by its absorption at 420 nm. Control rates averaged 300 μmol of ferricyanide reduced per mg of chlorophyll per h. Hill reaction inhibition is expressed as pI_{50} which is $-\log I_{50}$, where I_{50} is the molar concentration required to decrease the amount of ferricyanide reduction by 50% from the control values.

Table V. Postemergence Response of Five Plant Species[a]

test species	compd chloroxuron	2	22	28
ragweed (*Ambrosia artemisiifolia* L)	5	9	8	9
mustard [*Brassica kaber* (DC.) L.C. Wheeler]	8	9	9	8
cocklebur (*Xanthium pennsylvanicum* Wallr)	9	9	9	9
soybean [*Glycine max* (L) Merr]	1	4	6	0
rice (*Oryza sativa* L)	3	3	0	0

[a] Values represent plant response to the chemical treatment on a scale of 0–9 where 0 equals no effect and a 9 equals complete kill.

Experimentally determined pI_{50} values are reported in Table IV.

(B) *Herbicidal Data.* The postemergence herbicidal activity of the compounds in Tables I and II was detected by spraying the test compounds on the foilage of a variety of 2-week-old monocotyledonous and dicotyledonous plants. The test compounds were dispersed in 50:50 acetone–water mixtures containing 0.5% Tween 20 (polyoxyethylene sorbitan monolaurate surfactant; Atlas Chemical Industries) in sufficient quantity to provide the equivalent of 0.063–10 kg/ha. Two weeks after treatment, the seedling plants were examined visually by using a rating scale of 0–9, with 0 indicating no herbicidal control and a 9 indicating complete control. This rating system is employed in Table V. In order to run regression analyses we selected wild mustard [*Brassica kaber* (DC.) L.C. Wheeler] as the test species. From the visual herbicidal responses (0–9) obtained over a range of application rates, we converted the activity of each compound on wild mustard to an ED_{85} (an estimated dose to cause 85% kill). All ED_{85} data were transposed to molar concentrations, C, and expressed as $\log (1/C)$ in Tables I and II.

RESULTS AND DISCUSSION

The 50% inhibition of the Hill reaction (pI_{50}) for all permutations of 3- and 4-substituted and 3,4-disubstituted phenyl-1,1-dimethylureas was predicted by entering the values of σ and π from our 40-substituent physicochemical data bank into eq 1. Many of the predictions of the more potent Hill inhibitors were already known herbicides, but

Design of Postemergence Phenylurea Herbicides

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Table VI. Correlation Equations[a]

| properties	eq no.	eq	compd	n	r^2	s
herbicidal activity [log (1/C) with Hill inhibition pI_{50}]	4	$\log (1/C) = -2.36 + 0.48 pI_{50} \ (\pm 0.4)$[b]	1–12	12	0.41	0.67
herbicidal activity	5	$\log (1/C) = 0.83 - 0.44\sigma \ (\pm 1.47) + 0.59\pi \ (\pm 0.59)$	1–12	12	0.41	0.70
herbicidal activity	6	$\log (1/C) = 1.3 + 0.42\pi \ (\pm 0.26) - 5.4E_R \ (\pm 1.88)$	1–12	12	0.89	0.30
herbicidal activity of alkyl homologues	7	$\log (1/C) = 1.14 + 0.42\pi$				
herbicidal activity of all benzyloxy analogues	8	$\log (1/C) = 1.4 + 0.05\pi \ (\pm 0.23) - 0.04\pi^2 \ (\pm 0.03) - 5.5E_R \ (\pm 2.3)$	1–21	21	0.77	0.44
herbicidal activity of all benzyloxy analogues	9	$\log (1/C) = 1.34 + 0.48\pi \ (\pm 0.3) - 0.86 \log (10^\pi \beta + 1) \ (\pm 0.3) - 5.1E_R \ (\pm 1.8)$	1–21	21	0.88	0.34
herbicidal activity of all benzyloxy analogues	10	$\log (1/C) = 1.46 + 0.27\pi \ (\pm 0.2) - 0.17\pi^2 \ (\pm 0.08) + 0.013\pi^3 \ (\pm 0.007) - 5.4E_R \ (\pm 1.7)$	1–21	21	0.88	0.33

[a] n represents the number of congeners upon which the equation is based. r is the correlation coefficient. s is the standard standard deviation. [b] The number in parentheses represents the 95% confidence limit.

compounds 1 and 2 attracted our attention because of their novelty and high predicted pI_{50} values of 6.2 and 7.4, respectively (Table I). Moreland and Hill (1963) had previously noted that for several classes of Hill reaction inhibitors, a close agreement exists between Hill inhibition and phytotoxicity. Therefore, the synthesis of compounds 1 and 2 was undertaken and resulted in the preparation of highly active nonselective postemergence herbicides with good control of most weed species at 0.5 kg/ha, especially for 2. Encouraged by this result, a series of analogues, compounds 3–12, were prepared and evaluated as herbicides. The herbicidal activity of compounds 1–12, as measured by ED_{85} on mustard and converted to log (1/C) values, was found to correlate only weakly, eq 4, Table VI, with the predicted Hill inhibitory values (pI_{50}) calculated from eq 1. In an attempt to gain more understanding of this apparently anomolous result we ran regression and correlation analyses on compounds 1–12 using the raw herbicidal data [log (1/C) from ED_{85} mustard] as the dependent variable. Little success was encountered with the traditional electronic, steric, and hydrophobic parameters. Using π and σ as employed by Hansch and Deutsch (1966) on the Hill inhibition gave only a poor correlation, eq 5. However, with the introduction of the free radical parameter, E_R, of Yamamoto and Otsu, eq 6 with a remarkably high correlation was obtained.

Several tenable reasons may explain why our herbicidal activity correlated only poorly with predicted Hill inhibition, eq 4. Comparative examination of eq 1, 5, and 6 shows that Hill inhibition in Hansch's series depended primarily on π and σ, while herbicidal activity of our compounds depends more heavily upon the E_R parameter. It could be that the benzyloxy group introduced in our studies is acting quite uniquely. Indeed, free radical mechanisms of action have been postulated for the benzyl group in pharmacological processes (Hansch and Kerley, 1970; Hansch et al. 1969). Furthermore, Hill inhibition eq 1 was derived from substituents over a π range of −0.79 to 1.46, whereas the predicted Hill inhibition data for compounds of Table I were obtained over a π range of 0.03 to 3.13. The π value for the benzyloxy group is 1.66. Most of the predicted Hill inhibitions of Table I were, therefore, made beyond π data space used by Hansch to determine eq 1, and this unknown region cannot be forecast with any degree of certainty. Recently, Brown et al. (1981) showed in a study on 3-alkoxyuracils that the degree of Hill inhibition increased with increasing lipophilicity of the 3-alkoxy side chain, until a pI_{50} limiting value of 8.0 beyond which the pI_{50} value essentially plateaus. This plateau region is related to the total number of sites in the chloroplast occupied by the inhibitor molecules when the Hill reaction rate is reduced by 50%. For herbidical phenyl-

ureas and uracils respectively, one site per 200–400 and one site per 350 chlorophyll molecules was deduced by Izawa and Good (1965) to be occupied for 100% inhibition of the Hill reaction. It is perhaps not surprising that compounds in Table I with calculated $pI_{50} > 8.0$ show little increase in herbicidal activity, and our higher predicted pI_{50} values are probably incorrect. Nonetheless, our initial discovery of compounds 1 and 2 was not fortuitous, since both predicted pI_{50} values of 6.2 and 7.4 are just below the limiting plateau region. A pI_{50} value of 7.4 was determined for 2, confirming its anticipated potent Hill inhibition (Table IV). Equation 6 appears to represent a qualitatively acceptable model for describing the herbicidal activity for 3-[p-(benzyloxy)phenyl]-1,1-dimethylureas of Table I in terms of leaf penetration and transport (π) and free radical processes (E_R) which occur during photosynthesis. Interestingly, Giacobbe and Blau (1974) reported in vivo herbicidal activity of phenylureas on grasses to be correlated with π and σ^2. Yamamoto and Otsu (1967) have noted that aromatic radical intermediates are known to display curvature in their dependance on σ (σ^2 or $\sigma + \sigma^2$), and Craig (1971) showed the E_R parameter is well correlated with σ^2.

In our first attempt at exploitation of eq 6 we noted that E_R is the dominant parameter. The negative sign on the E_R term suggested that the most radical destabilizing benzyl ring substituents, such as fluorine and hydrogen, should provide the most herbicidally active compounds. A p-fluoro analogue, 21 was therefore prepared and found to be as active as predicted and as active as 2. Meta orientation of the (p-fluorobenzyl)oxy group afforded 29, a compound with greatly enhanced preemergence activity on broadleaf species. In 1979 the Sumitomo Chemical Co. (Takemoto et al., 1978a), reported on the very closely related 3-[[(p-fluorobenzyl)oxy]phenyl]-1-methoxy-1-methylureas as herbicides.

F—⟨benzene⟩—CH₂O—⟨benzene⟩

NHCON(CH₃)₂

29
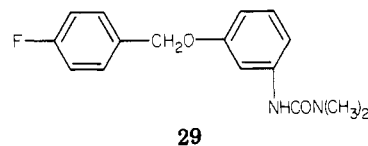
rate required for preemergence broadleaf control, kg/ha	tolerant crop species
0.25–0.5	corn (*Zea mays* L) cotton (*Gossypium hirsutum* L) soybeans [*Glycine max* (L) Merr]

In a further analysis of eq 6 we hypothesized that in a series of para substituted homologues, herbicidal activity [log (1/C)] should be a function of π, since the E_R contribution is essentially constant. At some higher π value the linear relationship would be expected to take on a

quadratic form with an increasingly dominant $-\pi^2$ term. This potential for increased activity with increments in π led us to synthesize a series of higher p-alkyl homologues containing from 1 to 18 carbon atoms (Table II). Since for alkyl groups $E_R \simeq 0.03$, the herbicidal activity should by predictable by a simplified eq 7. The results were disappointing. A substituent π_{max} value of only 0.61 was assessed from regression eq 8 which was obtained from the set of 21 compounds in Tables I and II. This result may again reflect attainment of the plateau region caused by near saturation of the active sites in the chloroplast by compounds with an X substituent possessing a $\pi_x > 0.61$. The herbicidal activity of compounds in Tables I and II diminished rapidly as the carbon content of the alkyl group was increased above four carbons. This diminishing activity, rather than reflecting saturation of the active site, more likely represents a decline in the ability of the more hydrophobic compounds to be transported to the active site. Interestingly, the data set is somewhat better explained by either a Kubinyi (1977) bilinear model, eq 9, or a cubic model, eq 10, suggesting that the symmetry of the quadratic eq 8 is slighly distorted.

Since the radical effect $(-E_R)$ in eq 6 is both dominant and detrimental to herbicidal control, we rationalized that its effect might be moderated or even diminishd by insulating the benzyl group from the ether oxygen atom. This should minimize carbon–oxygen cleavage to the herbicidally inactive 3-(p-hydroxyphenyl)-1,1-dimethylurea. This was accomplished by preparing a series of 3-[p-(phenylalkoxy)phenyl]-1,1-dimethylureas 22–25 with an insulating alkoxy bridge containing two to five methylene groups. The resulting nonselective postemergence herbicides were markeldy superior to the benzyloxy compound 2. Peak activity was observed for a methylene chain of two or three carbon atoms, with weed control below 0.25 kg/ha for monocotyledons and 0.25–0.5 kg/ha for dicotyledons. With the preparation of the meta-oriented series 26–28, we uncovered compounds with similar herbicidal activity, yet with significant selectivity in small grains and soybeans [$G. max$ (L) Merr]. These compounds (e.g., 22) are potent Hill inhibitors (pI_{50} = 7.5). Diuron (pI_{50} = 7.0) and chloroxuron (pI_{50} = 7.0) are compared in Table IV. The postemergence activity of these 3-[m- (or p-) (phenethyloxy)phenyl]-1,1-dimethylureas is at least comparable to that of the commerical urea herbicide, chloroxuron (Table V). Some of these compounds have also been described recently in a patent (Takemoto et al., 1978b).

SUMMARY AND CONCLUSIONS

A rational herbicide synthesis approach was generated first from analysis of a published Hill inhibition correlation, which led us to a series of [(benzyloxy)phenyl]-1,1-dimethylureas. Critical assessment of herbicidal activity, eq 6, developed for these compounds ultimately led us to a series of potent [(phenylalkoxy)phenyl]-1,1-dimethylurea herbicides, particularly 22, 27, and 28. Equation 6 has proven to be a satisfactory model for the design of a urea herbicide, and this equation is compatible with the early concept of Hansch and Deutsch (1966) that 3 or 4 substituents on the phenylurea ring are primarily involved in hydrophobic bonding. In addition, eq 6 suggests that our

phenylureas may interrupt the one-electron transfer process of photosynthesis. Our synthesized compounds have confirmed the prediction from eq 6 that herbicidal activity should be enhanced by eliminating or minimizing the radical stabilizing capability of the 3- or 4-phenylalkoxy substituent on the phenylurea ring.

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