

## 2,6-Diphenylpyridines: A New Class of Herbicides

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A novel series of 4-substituted 2,6-diphenylpyridines was synthesized and found to possess potent bleaching herbicidal activity. These diphenylpyridines, which incorporate a pyridine nucleus substituted by two phenyl moieties, are new chemical families of bleaching herbicides. To clarify the structure-activity relationships, a variety of diphenylpyridines was prepared. The results indicated very specific structure requirement for herbicidal activity. In general, herbicidal activity was the highest in compounds that contain three substituents: a trifluoromethyl or methyl group at the 2- or 3-position of one phenyl ring, a trifluoromethyl group at the 4-position of the other, and a methoxy or methylthio group at the pyridine 4-position.

A variety of pyridines is known to possess herbicidal activities (Martin, 1966). However, only a few heterocycles with a pyridine nucleus have been reported as bleaching herbicides (Boger et al., 1989). Recently, a series of herbicidal pyridine derivatives was disclosed (Bartels et al., 1978; Cramp et al., 1987). In our continuing effort to find a new class of herbicides, we have determined the herbicidal activities of 3-(methylthio)-4-amino-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (Sanemitsu et al., 1985), 3-(dimethylamino)-4*H*-(1,2,4)triazino[5,6-*b*]indoles (Mizutani et al., 1987), and 3,6-dichloro-1,2,4-triazines (Sanemitsu et al., 1990). Further investigation in the search for herbicidal heterocycles led to the discovery of 2,6-diphenyl-4-(methylthio)pyridine (1) as a new lead compound, which showed bleaching symptoms at 8000 g/ha.

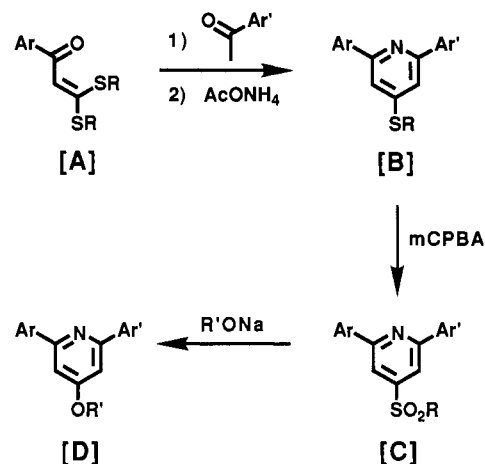
Our interest in the structure and herbicidal activity of this novel heterocyclic compound prompted us to examine a systematic screening study on diphenylpyridine herbicide. Here, we now report the syntheses and the herbicidal activities of diphenylpyridines.

### EXPERIMENTAL PROCEDURES

**Synthetic Methods.** The general syntheses and examples of diphenylpyridines (melting points) were reported in a U.S. patent (Kawamura et al., 1989).

2,6-Diphenyl-4-(alkylthio)pyridines (B) were synthesized in two steps (Scheme I) from 3,3-bis(alkylthio)-1-phenyl-2-propen-1-ones (A) which were prepared by the reaction of acetophenones with carbon disulfide followed by treatment with alkyl halides (Potts et al., 1982). Treatment of 3,3-bis(alkylthio)-1-phenyl-2-propen-1-ones (A) with acetophenones followed by treatment with ammonium acetate yielded the 2,6-diphenyl-4-(alkylthio)pyridines (B) (Potts et al., 1982). The conversion of alkylthio derivatives (B) to alkoxy derivatives (D) was achieved by a process through a nucleophilic displacement. Treatment of 4-alkylthio derivatives (B) with *m*-chloroperbenzoic acid gave the corresponding 4-(alkylsulfonyl)pyridines (C). The 4-(alkylsulfonyl)pyridines (C) were converted to the 4-(alkoxy)pyridines (D) by treatment with sodium alkoxides as exemplified in Scheme I.

### Scheme I



### BIOLOGICAL TESTING

The pre- and postemergent herbicide evaluations were conducted on all target compounds from the series mentioned above. The test species included in these evaluations were cleavers (*Galium aparine*), common chickweed (*Stellaria media*), field pansy (*Viola arvensis*), Persian speedwell (*Veronica persica*), rounded chamomile (*Matricaria matricarioides*), field pennycress (*Thlaspi arvense*), Japanese millet (*Echinochloa frumentacea*), oat (*Avena Sativa*), garden radish (*Raphanus sativus*), velvetleaf (*Abutilon theophrasti*), and morning glory (*Ipomoea purpurea*).

For the pre- and postemergent tests, an emulsifiable concentrate is prepared by mixing 10 parts of the compound, 14 parts of polyoxyethylene styrylphenyl ether, 6 parts of calcium dodecylbenzenesulfonate, and 70 parts of xylene.

**Postemergence Tests** (Table I). Upland field soil filled in a cylindrical plastic pot (10 cm in diameter and 10 cm deep) was sown with Japanese millet, oat, garden radish,

**Table I. Postemergence Herbicidal Activities of 2,6-Diphenyl-4-(methylthio)pyridines**

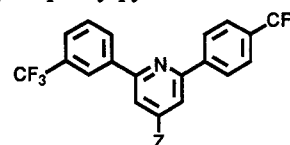
no.	X <sub>n</sub>	Y	dose giving 70% phototoxicity, g/ha			
			Japanese millet	oat	garden radish	velvetleaf
1	H	H	>8000	>8000	>8000	>8000
2	2-Me	H	1200	>8000	<500	<500
3	2-Cl	H	4400	>8000	2000	3800
4	2-Br	H	>8000	>8000	>8000	3600
5	2-CF <sub>3</sub>	H	1000	8000	500	<500
6	3-Me	H	500	8000	1100	500
7	3-F	H	700	8000	<500	<500
8	3-Cl	H	2000	8000	<500	<500
9	3-Br	H	>8000	>8000	<500	<500
10	3-CF <sub>3</sub>	H	1000	3800	<500	<500
11	3-Oi-Pr	H	>8000	>8000	800	<500
12	4-Me	H	>8000	>8000	8000	<500
13	4-F	H	2000	>8000	<500	<500
14	4-Cl	H	>8000	>8000	8000	3800
15	4-Br	H	>8000	>8000	<500	<500
16	4-CF <sub>3</sub>	H	>8000	>8000	900	900
17	4-OMe	H	>8000	>8000	>8000	>8000
18	2,4-Cl <sub>2</sub>	H	>8000	>8000	>8000	>8000
19	2,5-Cl <sub>2</sub>	H	>8000	>8000	>8000	>8000
20	3,4-Cl <sub>2</sub>	H	>8000	>8000	>8000	>8000
21	3,5-(CF <sub>3</sub> ) <sub>2</sub>	H	>8000	>8000	>8000	>8000
22	2-Cl	2-Cl	>8000	>8000	>8000	>8000
23	2-Me	2-Me	>8000	>8000	>8000	>8000
24	2-Me	3-Cl	2000	8000	<500	<500
25	2-Me	3-CF <sub>3</sub>	8000	>8000	2900	2000
26	2-Cl	3-CF <sub>3</sub>	4500	8000	1000	2000
27	2-Me	4-F	700	2000	<500	<500
28	2-Me	4-Cl	2000	8000	<500	<500
29	2-Me	4-Br	2000	5200	<500	<500
30	2-Me	4-CF <sub>3</sub>	2000	4500	<500	<500
31	2-CF <sub>3</sub>	4-F	700	2000	<500	<500
32	2-CF <sub>3</sub>	4-CF <sub>3</sub>	700	900	<500	<500
33	3-Cl	4-OMe	>8000	>8000	>8000	>8000
34	3-CF <sub>3</sub>	4-F	1200	2000	<500	<500
35	3-CF <sub>3</sub>	4-Cl	8000	1500	<500	<500
36	3-CF <sub>3</sub>	4-CF <sub>3</sub>	3800	2000	<500	<500
37	4-Cl	4-Me	>8000	>8000	>8000	>8000
38	4-Cl	4-Cl	>8000	>8000	>8000	>8000
39	4-OMe	4-OMe	>8000	>8000	>8000	>8000

and velvetleaf. The plants were grown in a greenhouse for 10 days. A designed amount of test compound formulated in an emulsifiable concentrate was diluted with water containing a spreader, and the dilution was sprayed over the foliage of the test plants by means of a small sprayer at a spray volume of 10 L/are. After the treatment, the plants were grown in a greenhouse for 20 days and the herbicidal effects were observed by visual observation of the treated plants in comparison with the untreated controls.

**Preemergent Tests** (Table II). Cylindrical plastic pots (diameter 10 cm, height 10 cm) were filled with upland field soil, and the seeds of Japanese millet, oat, morning glory, and velvetleaf were sowed therein and covered with soil. A designed amount of the test compound formulated in an emulsifiable concentrate was diluted with water, and the dilution was sprayed onto the soil surface by means of a small hand sprayer at a spray volume of 1000 L/ha. The test plants were grown in a greenhouse for 20 days, and the herbicidal activity of the compound was determined by visual observation of the treated plants in comparison with the untreated controls. Doses giving 50% phototoxicity were determined by interpolation of control rating plots plotted against the log of the test doses.

**Table II. Preemergence Herbicidal Activities of 2,6-Diphenyl-4-(methylthio)pyridines**

no.	X <sub>n</sub>	Y	dose giving 50% phototoxicity, g/ha			
			Japanese millet	oat	morning glory	velvetleaf
1	H	H	>8000	>8000	>8000	>8000
2	2-Me	H	6000	>8000	>8000	>8000
7	3-F	H	5000	>8000	>8000	>8000
10	3-CF <sub>3</sub>	H	5000	>8000	>8000	>8000
12	4-Me	H	>8000	>8000	>8000	>8000
23	2-Me	2-Me	>8000	>8000	>8000	>8000
32	2-CF <sub>3</sub>	4-CF <sub>3</sub>	2000	6300	7800	>8000
34	3-CF <sub>3</sub>	4-F	5000	6000	6000	6000
36	3-CF <sub>3</sub>	4-CF <sub>3</sub>	>8000	>8000	3000	8000
38	4-Cl	4-Cl	>8000	>8000	>8000	>8000

**Table III. Postemergence Herbicidal Activities of 4-Substituted 2,6-Diphenylpyridines**

no.	Z	dose giving 70% phototoxicity, g/ha			
		common chickweed	Persian speedwell	field pansy	cleavers
36	SMe	<63	<63	<63	<63
40	SEt	>500	>500	>500	>500
41	Sn-Pr	>8000	>8000	>8000	>8000
42	OMe	125	<63	<63	125
43	OEt	500	<63	<63	500
44	On-Pr	>8000	>8000	>8000	>8000
45	Oi-Pr	>8000	>8000	>8000	>8000
46	OCH <sub>2</sub> CH=CH <sub>2</sub>	>8000	>8000	>8000	>8000
47	OCH <sub>2</sub> CCH	>8000	>8000	>8000	>8000

**Postemergent Tests** (Tables III and IV). Upland field soil filled in a vat measuring 33 by 23 cm and 11 cm deep was sown with wheat, barley, cleavers, common chickweed, field pansy, rounded chamomile, field pennycress, and Persian speedwell. The plants were grown in a greenhouse for 18 days. The grown plants (1–4 leaf stage and 2–12 cm long) were subjected to foliage treatment from above, using a small sprayer with a dilute liquid (10 L/are) containing a prescribed amount of sample emulsifiable concentrate. Twenty days after treatment, the herbicidal effect and phototoxicity were observed. Doses giving 70% phototoxicity were determined by interpolation of control rating plots plotted against the log of the test doses.

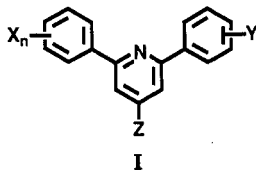
## RESULTS AND DISCUSSION

In general, these compounds exhibit moderate preemergent herbicidal activity at 8000 g/ha and good postemergent activity on broadleaf weeds at 500 g/ha (Tables I and II). At postemergence application, the bleaching appeared on the treated leaves, especially growing ones, 2–3 days after application. The bleaching symptoms observed resulted in severe necrosis, leading to plant death after 25–30 days. To examine the structure–activity relationships, we synthesized a variety of diphenylpyridines in this study.

First, we synthesized the diphenylpyridines that possess one substituent with a variety of natures and on various positions in one phenyl ring, shown by structure I (Y = H, Z = SMe), to examine the substituent effect in the

Table IV. Postemergence Herbicidal Activities of Compound 36

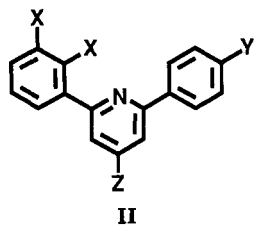
g/ha	mean phototoxicity, % control							
	wheat	barley	cleavers	common chickweed	field pansy	Persian speedwell	rounded chamomile	field pennycress
63	20	25	90	75	100	100	100	100
250	38	30	90	85	100	100	100	100



phenyl ring on the herbicidal activity. The postemergent herbicidal activities of 2-(monosubstituted)phenyl-4-(methylthio)-6-phenylpyridines are summarized in Table I (2-17). The results show that the substituents in one phenyl ring are very important for the herbicidal activity. Especially when the phenyl ring is substituted by an appropriate substituent such as a halogen, methyl, or trifluoromethyl group, the herbicidal activity is increased irrespective of the positions of the substituents. When an electron-withdrawing substituent such as a trifluoromethyl group is introduced in the meta or para position (10 or 16), the activity is greatest. Also, substitution by methyl and trifluoromethyl groups at the ortho position resulted in a sharp increase in activity (2 and 5). In contrast to these results, the diphenylpyridines that possess multiple substituents in one phenyl ring showed decreased herbicidal activity (18-21).

Second, diphenylpyridine derivatives with one substituent in each phenyl ring (structure I; Z = SMe) were prepared to search for the best combination of substituent patterns in two phenyl moieties. Herbicidal activities of disubstituted diphenylpyridines are indicated in Table I (22-39). Two combinations of 3- and 4'- or 2- and 4'-positions on each phenyl ring showed higher herbicidal activity than the corresponding 2-(monosubstituted)phenyl-4-(methylthio)-6-phenylpyridines (2-17). On the other hand, the derivatives with ortho substituents in both phenyl moieties showed reduced herbicidal activity (22 and 23). Also, the introduction of para substituents in both phenyl rings resulted in a complete loss of activity (37-39). Other substitution patterns such as 2- and 3'- or 3- and 3'-substitution appeared to have only a modest effect on herbicidal activity.

On the basis of the limited structure-activity relationships found here, great enhancement of activity was only achieved by the introduction of an ortho or meta substituent in one phenyl ring and the introduction of a para substituent in the other as presented in structure II.



Finally, the substitution effect at the pyridine 4-position on the herbicidal activity was investigated. A variety of substituents was introduced in the pyridine nucleus of diphenylpyridines with optimum substitution in each phenyl ring (structure II; X = 3-CF<sub>3</sub>, Y = 4-CF<sub>3</sub>). The substitution requirements at the pyridine 4-position were quite specific. The introduction of a methylthio (36),

methoxy (42), or ethoxy (43) group enhanced the herbicidal activity, and the 4-methylthio derivative (36) showed the highest herbicidal activity. On the other hand, the introduction of other substituents reduced the herbicidal activity. In the case of 42 and 36, the activities fell off rapidly with increasing length of the alkyl chain in the alkoxy or alkylthio group (40, 41, and 44).

One of these compounds, 2-[3-(trifluoromethyl)phenyl]-4-(methylthio)-6-[4-(trifluoromethyl)phenyl]pyridine (36), provided complete control on a large number of weed species at 63 g/ha in postemergence application (Table IV). Several weeds, such as field pansy, Persian speedwell, rounded chamomile, and field pennycress, were completely controlled, while wheat and barley were tolerant at 63 g/ha.

Biochemical studies on diphenylpyridines are under investigation and will be reported in future publications.

#### LITERATURE CITED

- Bartels, P. G.; Watson, C. W. Inhibition of carotenoid synthesis by Fluridone and Norflurazon. *Weed. Sci.* 1978, 26, 198-203.
- Boger, P.; Sandmann, G. Inhibition of carotenoid biosynthesis by herbicides. In *Target Sites of Herbicide Action*; Boger, P., Sandmann, G., Eds.; CRC Press: Boca Raton, FL, 1989.
- Cramp, M.; Gilmour, J.; Hatton, L.; Hewett, R.; Nolan, C.; Parnell, E. Design and Synthesis of N-(2,4-difluorophenyl)-2-(3-trifluoromethylphenoxy)-3-Pyridinecarboxamide (difufenican), a novel pre- and early post-emergence herbicide for use in winter cereals. *Pestic. Sci.* 1987, 18, 15-28.
- Kawamura, S.; Hamada, T.; Yoshida, R.; Sanemitsu, Y. U.S. Patent 4849011, 1989.
- Martin, R. T. U.S. Patent 3249419, 1966; *Chem. Abstr.* 1966, 65, 4570g.
- Mizutani, M.; Yoshida, R.; Sanemitsu, Y. Novel herbicidal compounds, 3-Dimethylamino-4H-(1,2,4)Triazino(5,6-b)indoles. *Agric. Biol. Chem.* 1987, 51, 3173-3175.
- Potts, K. T.; Cipullo, J. M.; Ralli, P.; Theodoridis, G. Synthesis of 2,6-Disubstituted Pyridines, Polypyridinyls, and Annulated Pyridines. *J. Org. Chem.* 1982, 47, 3027-3038.
- Sanemitsu, Y.; Mizutani, M.; Satoh, R. Novel Herbicidal Compounds, 3-Methylthio-4-Amino-1,6-Dihydro-1,2,4-triazin-5(4H)-ones. *Agric. Biol. Chem.* 1985, 49, 555-557.
- Sanemitsu, Y.; Nakayama, Y.; Tanabe, Y.; Matsumoto, H.; Hashimoto, S. 5-Substituted amino-3,6-Dichloro-1,2,4-triazines as New Potential Herbicides. *Agric. Biol. Chem.* 1990, 54, 3367-3369.

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