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Structure-Activity Relationships of Herbicidal Nitrodiphenyl Ethers

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Thirty 4-(substituted phenoxy) nitrobenzenes were synthesized and examined for phytotoxicity against barnyard-grass in the light and dark. From the structure-activity relationships and light-requisition for the activity, they were classified into three groups. The diphenyl ethers of the first group, which required light for the activity, were characterized by *ortho* and *para* substitutions. The second group compounds having *meta* or *ortho* and *meta* substitutions were active even in the dark. The third group involved compounds substituted at both *meta* and *para* positions and their herbicidal activity was inhibited by light. *p*-Amino analog of nitrofen showed high herbicidal activity.

INTRODUCTION

Many *p*-nitrodiphenyl ethers (nitro DPE; **1**) have been developed to commercial herbicides. Matsunaka (1976) classified them into two groups by their requisition of light for the herbicidal activity. One of the groups requires light for the activity, whereas the other is active even in the dark. The former group including nitrofen (2, 4-dichlorophenyl *p*-nitrophenyl ether; 13) and chlornitrofen (2, 4, 6-trichlorophenyl *p*-nitrophenyl ether; 16) is characterized by having at least one *o*-substituent on the "A" benzene ring connecting to the *p*-nitrophenoxy group. The latter group herbicides exemplified by TOPE (*p*-nitrophenyl *m*-tolyl ether; 8) have no *o*-substituent. Major biochemical reactions related to light in plant may be the Hill reaction, photophosphorylation, and photoreduction. Moreland et al. (1970) have examined the effects of light-requiring DPE herbicides involving nitrofen, chlornitrofen, and fluorodifen (2-nitro-4-trifluoromethylphenyl *p*-nitrophenyl ether) on these reactions. However they did not test any DPE herbicides of another group. This paper deals with the structure-activity relationships of total 30 nitro DPEs having various pattern of chloro and/or methyl substituents on the "A" ring. There is evidently an additional group which is inhibited the herbicidal activity by light. The inhibition of the Hill reaction may not be the essential mode of action of light-requiring DPE herbicides.

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MATERIALS AND METHODS

Synthesis

The following two methods were employed for the Williamson synthesis of *p*-nitro DPEs (I).

Method a: To a fused mixture of a substituted phenol (1. 2 mole), KOH (1. 1 mole), and Al_2O_3 (0.05 mole) at 80–100°C was added *p*-chloronitrobenzene (1 mole). The reaction mixture was heated at 145°C for 4 hr and then poured into aq. alkaline solution. The precipitate was collected by filtration and recrystallized from ethyl acetate or ethanol. If necessary the product was purified with column chromatography on silicic acid eluted with benzene-hexane mixture (1:3).

Method b: To a mixture of a substituted phenol (1. 2 mole) and NaOH (1. 1 mole) in *N,N*-dimethylacetamide at 80–100°C was added *p*-chloronitrobenzene (1 mole). The reaction mixture was heated at 150–160°C until *p*-chloronitrobenzene disappeared and then poured into an aq. alkaline solution. The product was extracted with ether or benzene and purified by recrystallization or silicic acid column chromatography.

2, 4, 6-trichlorophenyl *p*-nitrophenyl ether (chlornitrofen; 16) was a gift from Mitsui-Toatsu Co.

p-Aminophenyl 2, 4 - dichlorophenyl ether

Nitrofen (1 g) in benzene (40 ml) was reduced by refluxing in the presence of active iron prepared from iron powder (10 g) and conc.HCl (2 ml). Basic fraction extracted with ether was converted to hydrochloride salt, mp 133–136°C. IR: 2800, 1580, 1500 (NH,+).

3-(3, 4-Dichlorophenyl)-1, 1-dimethylurea (DCMU)

To 3, 4-dichlorophenyl isocyanate (10.5 g) in dioxane (27 ml) was dropwise added dimethylamine (9.13 ml) at 20–30°C. The precipitate was collected by filtration and the filtrate was poured into water to get precipitate as the second crop. The combined products were recrystallized from ethyl acetate, mp 153–4°C, yield 87%. Anal. Found: C, 46.35; H, 4.29; N, 12.02. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{OCl}_2$: C, 46.20; H, 4.30; N, 11.76%.

Herbicidal Activity

A test chemical dissolved in acetone was poured onto a sheet of filter paper placed on the bottom of a Petri dish. After evaporation of the solvent, water (10 ml) was poured and 40 seeds of barnyard-grass (*Echinochloa crus-galli*) were placed in the dish and kept at 30°C in the dark or light for 8 days. The light source was two 15W fluorescence lamps and the intensity was 700 lux on the surface of the dishes. The length of shoots and roots was measured and compared with that of the control.

Inhibition of Hill Reaction

Aqueous mixtures (5.0 ml) for the Hill reaction contained spinach chloroplasts containing approximately 80 μg of chlorophyll and following chemicals in μ moles: pH 8.0 tris buffer, 80; NaCl, 50; and potassium ferricyanide, 2. Centrifuge tubes containing the reaction mixture were kept in a thermostatted water bath. Reactions were performed at 25°C under 20,000 lux irradiated by a 150W incandescent reflectorized

lamp for 15 min and terminated by the addition of 10% trichloroacetic acid (1 ml). The precipitate was removed by centrifugation, and ferricyanide reduction in the supernatant was measured at 420 nm. Test chemicals were dissolved in acetone and the final concentration of acetone in all assays including controls was 1% by volume. Acetone in this concentration had no detectable effect on the Hill reaction.

RESULTS AND DISCUSSION

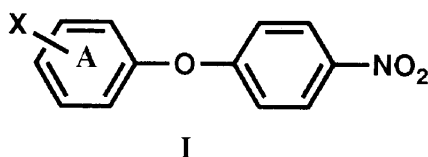
Seven types of *p*-nitro DPEs were synthesized from substituted phenols and *p*-chloronitrophenol: 1) *o*-type (indicating to have substitution(s) only at the *ortho* positions(s) of "A" ring. Other types are named in similar manner.); 2) *m*-type; 3) *p*-type; 4) *o*, *p*-type; 5) *m*, *p*-type; 6) *o*, *m* -type; 7) *o*, *m*, *p* -type. The Williamson synthesis for ethers was slightly modified by mixing aluminum oxide (method a) or N, N-dimethylacetamide (method b). The structures, physical and analytical data, and method for synthesis of thirty nitro DPEs, except chlornitrofen (**16**), studied in this paper are listed in Table 1. All the synthesized compounds show appropriate analytical data. Method b was superior to method a for readiness in separation and purification of products and higher yield. 2, 4, 6-Trimethylphenyl *p*-nitrophenyl ether (**18**) could not be synthesized with method a, but b. Methyl-substituted DPEs were synthesized with method b in relatively short reaction time but the synthesis of chloro derivatives took longer time.

Phyto toxic Activity

The effects of *p*-nitro DPEs on the growth of barnyard-grass shoots and roots are summarized in Tables 2 and 3, respectively. Table 2 includes also the half inhibitory molar concentrations (I_{50}) for shoot elongation. *p*-Nitro DPEs having no substituent and mono-chloro or methyl group at the *ortho* or *para* position of the "A" ring (**1**, **2**, **3**, **11**, **12**) showed little activity on the plant growth. *o*-Type DPEs with plural substitutions (**4-6**) had only poor activity. *o*, *p*-Type derivatives such as 2, 4-dichloro DPE (nitrofen; **13**) and 2, 4, 6-trichloro DPE (chlornitrofen; **16**) exerted high herbicidal activity in the light but not in the dark. Replacement of a chlorine atom by a methyl group caused decrease in the activity (compare **13** and **16** with **14** and **17**, respectively) and compounds having only methyl groups as substituents (**15**, **18**) were almost inactive. Thus, this type requires light and chlorine atoms in *ortho* and *para* positions for the exertion of herbicidal activity.

All *m*-type DPEs (**7-10**) including methyl-substituted compounds exerted high phytotoxicity both under the light and dark conditions. The activity was slightly lower in the light than in the dark. *o*,*m*-Type DPEs (**24-28**) showed similar tendency with *m*-type DPEs. In this series, however, methyl substituents decrease the activity, except 2,3-dimethyl derivative (**25**).

In contrast to the above-mentioned types, *m*,*p*-type DPEs (**19-23**) were not or weakly active in the light, but considerably active in the dark. Thus, light appears inhibit the phytotoxicity of this type DPEs. Further introduction of another chlorine substituent to the *m*-position of 2,4-dichloro DPE (*o*,*p*-type **13**), the *o*-position of 3,4-dichloro DPE (*m*,*p*-type **19**), or the *p*-position of 2,5-dichloro DPE (*o*,*m*-type **26**) made the DPE inactive (**29**). Another *o*,*m*,*p*-type DPE, **30**, was also inactive.

Table 1. Structures and Physical and Analytical Data of *p*-Nitrodiphenyl Ethers (I)

No.	Substituent	mp	Elemental Analysis						Method
			Found %			Calcd. %			
			C	H	N	C	H	N	
	X	(°C)							
1	H	55-7	66.92	4.19	6.57	66.97	4.22	6.51	a
0 -type									
2	2-Cl	75-7	57.68	3.29	5.62	57.73	3.23	5.61	a
3	2-Me	160*	68.13	4.86	5.97	68.11	4.84	6.11	a
4	2,6-Cl ₂	122	50.96	2.70	4.87	50.73	2.49	4.93	a
5	2-Cl-6-Me	80-1	59.19	3.80	5.23	59.21	3.83	5.35	a
6	2,6-Me ₂	59-60	69.23	5.49	5.78	69.12	5.39	5.76	b
m-type									
7	3-Cl	58-9	57.62	3.10	5.51	57.73	3.23	5.61	a
8	3-Me	61-2	68.28	4.83	6.00	68.11	4.84	6.11	a
9	3,5-Cl ₂	80	50.68	2.48	4.90	50.73	2.49	4.93	a
10	3,5-Me ₂	80-1	69.17	5.35	5.72	69.12	5.39	5.76	a
p-type									
11	4-Cl	75-6	57.71	3.15	5.41	57.73	3.23	5.61	a
12	4-Me	66-7	68.16	4.84	6.24	68.11	4.84	6.11	a
o,p-type									
13	2,4-Cl ₂	71	50.67	2.48	4.90	50.73	2.49	4.93	a
14	2-Me-4-Cl	61-3	59.40	3.81	5.36	59.21	3.83	5.35	a
15	2,4-Me ₂	59-61	69.20	5.37	5.77	69.12	5.39	5.76	a
16	2,4,6-Cl ₃	105-6	—	—	—	—	—	—	—
17	2,4-Cl ₂ -6-Me	93-4	52.53	3.08	4.63	52.37	3.05	4.70	a
18	2,4,6-Me ₃	86-7	70.16	5.98	5.50	70.02	5.88	5.44	b
m,p-type									
19	3,4-Cl ₂	79-80	50.84	2.68	4.68	50.73	2.49	4.93	a
20	3-Me-4-Cl	111	59.36	3.86	5.26	59.21	3.83	5.35	a
21	3,4-Me ₂	87-8	69.19	5.37	5.73	69.12	5.39	5.76	a
22	3,4,5-Me ₃	100-1	70.01	5.69	5.46	70.02	5.88	5.44	a
23	3,5-Me ₂ -4-Cl	121	60.57	4.36	5.00	60.54	4.36	5.04	a
o,m-type									
24	2,3-Cl ₂	123	50.74	2.48	4.96	50.73	2.49	4.93	b
25	2,3-Me ₂	76-7	69.16	5.40	5.78	69.12	5.39	5.76	b
26	2,5-Cl ₂	95-6	50.74	2.49	4.87	50.73	2.49	4.93	b
27	2,5-Me ₂	128**	68.95	5.44	5.76	69.12	5.39	5.76	a
28	2,3,5-Me ₃	98-9	70.29	6.02	5.61	70.02	5.88	5.44	b
o,m,p-type									
29	2,4,5-Cl ₃	115	45.47	2.17	4.41	45.42	1.91	4.41	b
30	2,4,5-Me ₃	72-3	70.07	5.84	5.44	70.02	5.88	5.44	b

*bp at 3 mmHg **bp at 0.2 mmHg

Table 2. Effect of p-Nitrodiphenyl Ethers (I) on Growth of Barnyard-grass Shoots.

		Average length of shoots (% of control)									
		10ppm		50ppm		100ppm		200ppm		I ₅₀ (x10 ⁻⁵ M)	
No.	X	L	D	L	D	L	D	L	D	L	D
1	H	112	67	111	105	114	84	—	—	—	—
o-type											
2	2-Cl	108	108	91	90	81	73	—	—		
3	2-Me	123	79	91	100	114	90	—	—		
4	2,6-Cl ₂		—	67	109	78	74	52	116		
5	2-Cl-6-Me		—	78	95	70	74	65	63		
6	2,6-Me ₂		—	81	84	89	84	74	65	—	—
m-type											
7	3-Cl	62	50	15	0	0	0	—	—	7.2	4.0
8	3-Me	66	55	0	0	0	0	—	—	6.1	4.8
9	3,5-Cl*	87	52	40	0	0	12	—	—	14.0	3.7
10	3,5-Me ₂	59	5	18	0	33	0	—	—	6.4	1.2
p-type											
11	4-Cl	101	86	67	100	77	74	—	—		
12	4-Me	110	100	98	72	74	73	—	—	—	—
o,p-type											
13	2,4-Cl ₂	62	100	27	96	22	93	—	—	7.0	—
14	2-Me-4-Cl	116	84	76	98	63	88	—	—	102.0	—
15	2,4-Me ₂	94	102	97	92	86	89	—	—	—	—
16	2,4,6-Cl ₃	64	110	23	89	15	92	—	—	6.0	—
17	2,4-Cl ₂ -6-Me	79	98	70	102	60	105	—	—	50.0	—
18	2,4,6-Me ₃		—	81	88	97	126	88	92		
m,p-type											
19	3,4-Cl ₂	82	52	62	28	55	11	—	—	57.0	4.6
20	3-Me-4-U	75	82	73	37	69	0	—	—	—	14.0
21	3,4-Me ₂	92	65	86	18	81	16	—	—	—	5.8
22	3,4,5-Me ₃	88	47	102	12	89	0	—	—	—	3.1
23	3,5-Me ₂ -4-Cl	104	62	80	4	105	0	—	—	—	4.3
o, m-type											
24	2,3-Cl ₂	79	79	52	0	48	0	—	—	21.5	9.9
25	2,3-Me ₂	98	54	51	0	21	0	—	—	18.1	4.5
26	2,5-Cl ₂	86	63	64	44	52	37	51	28	44.0	12.3
27	2,5-Me ₂	—	—	91	76	93	79	85	64		
28	2,3,5-Me ₃				—	101	110	99	97	—	—
o,m,p-type											
29	2,4,5-Cl ₃				—	104	82	80	72		
30	2,4,5-Me ₃	—	—	—	—	110	126	104	90		

L: light D: dark

The present relationships of *o,p*- and *m*-type DPEs to light in phytotoxicity exertation support Matsunaka's classification of DPEs in which the light-requiring DPEs have at least one *o*-substituent on the "A" benzene ring (Matsunaka, 1976). However, *o,m*-type DPEs are out of this classification. They have an *o*-substituent, but require no light for the activity. Thus, the light-requiring DPEs should have substituents at both *o*- and *p*-positions. *m,p*-Type DPEs whose phytotoxicity was inhibited by light should be classified into additional new group.

p-Aminophenyl 2,4-dichlorophenyl ether, which may be formed from nitrofen by photochemical or metabolic reduction in plants, almost completely killed barnyard-grass at 500 ppm and inhibit the growth more than 80% at 100 ppm under the dark conditions. Nitrofen itself did not show any effect to the growth of barnyard-grass at 500 ppm under the dark conditions.

Inhibition of Hill Reaction

The inhibitory activity of *p*-nitroDPEs toward the Hill reaction is listed in Table

Table 3. Effect of *p*-Nitrodiphenyl Ethers (I) on Growth of Barnyard-grass Roots.

No.	X	Average length of roots (% of control)							
		10ppm		50ppm		100ppm		200ppm	
		L	D	L	D	L	D	L	D
1	H	85	135	83	129	84	89	—	—
<i>o</i> -type									
2	2-Cl	118	114	114	87	76	65	—	—
3	2-Me	105	62	105	93	110	133	—	—
4	2,6-Cl ₂	—	—	111	106	110	62	105	86
5	2-Cl-6-Me	—	—	117	101	105	120	99	88
6	2,6-Me ₂	—	—	97	101	87	110	97	106
<i>m</i> -type									
7	3-Cl	35	32	11	0	0	0	—	—
8	3-Me	66	106	0	0	0	0	—	—
9	3,5-Cl ₂	84	46	8	0	0	0	—	—
10	3,5-Me ₂	71	10	6	0	5	0	—	—
<i>p</i> -type									
11	4-Cl	112	118	42	99	69	110	—	—
12	4-Me	136	127	121	122	109	94	—	—
<i>o,p</i> -type									
13	2,4-Cl ₂	94	98	26	100	24	117	—	—
14	2-Me-4-Cl	134	53	77	98	90	101	—	—
15	2,4-Me ₂	121	135	120	51	114	108	—	—
16	2,4,6-Cl ₃	67	100	11	71	9	93	—	—
17	2,4-Cl ₂ -6-Me	123	126	63	82	71	69	—	—
18	2,4,6-Me ₃	—	—	109	26	108	77	—	—
<i>m,p</i> -type									
19	3,4-Cl ₂	50	47	12	20	89	0	—	—
20	3-Me-4-Cl	113	91	23	34	47	0	—	—
21	3,4-Me ₂	79	56	50	25	48	12	—	—
22	3,4,5-Me ₃	93	50	61	11	71	0	—	—
23	3,5-Me ₂ -4-Cl	108	82	62	40	61	0	—	—
<i>o,m</i> -type									
24	2,3-Cl ₂	52	40	31	0	27	0	—	—
25	2,3-Me ₂	110	62	35	0	15	0	—	—
26	2,5-Cl ₂	73	23	32	8	29	22	43	15
27	2,5-Me ₂	—	—	135	101	111	76	161	49
28	2,3,5-Me ₃	—	—	—	—	121	128	175	122
<i>o,m,p</i> -type									
29	2,4,5-Cl ₃	—	—	—	—	109	70	43	75
30	2,4,5-Me ₃	—	—	—	—	100	159	145	107

L: light D: dark

4. Only the weak activity was found in P-type DPEs which showed no phytotoxicity, *m,p*-type DPEs which were not phytotoxic in the light, and m-type DPEs which were phytotoxic independently of light. In contrary the *o,p*-type DPEs which require light for phytotoxicity showed the high inhibitory activity. However, difference in the inhibitory activity between the *o,p*-type and the three other types is not very distinctive.

On the other hand, *o,m*-type DPEs which were classified into the same group as m-type, exerting herbicidal activity both in the light and dark, inhibited the Hill reaction more strongly than m-type DPEs. Furthermore, both *o*- and *o,m,p*-type DPEs which were non-phytotoxic rather strongly inhibited the Hill reaction. The

Table 4. Inhibition of Hill Reaction by P-Nitrodiphenyl Ethers (I).

No.	X	Inhibition % (at 10^{-4}M)	I_{50} ($\times 10^{-5}\text{M}$)
1	H	39	—
0-type			
2	2-Cl	31	—
3	Z-Me	42	—
4	2,6-Cl ₂	56	7.7
5	2-Cl-6-Me	60	8.0
6	2,6-Me ₂	59	8.3
m-type			
7	3-Cl	41	—
8	3-Me	35	—
9	3,5-Cl ₂	45	—
10	3,5-Me ₂	39	—
p-type			
11	4-Cl	47	—
12	4-Me	45	—
o,p-type			
13	2,4-Cl ₂	66	7.7
14	2-Me-4-Cl	55	8.8
15	2,4-Me ₂	61	8.3
16	2,4,6-Cl ₃	77	4.5
17	2,4-Cl ₂ -6-Me	72	7.0
18	2,4,6-Me ₃	73	5.6
m,p-type			
19	3,4-Cl ₂	38	—
20	3-Me-4-Cl	37	—
21	3,4-Me ₂	36	—
22	3,4,5-Me ₃	48	—
23	3,5-Me ₂ -4-Cl	44	—
o, m-type			
24	2,3-Cl ₂	56	8.5
25	2,3-Me ₂	60	7.1
26	2,5-Cl ₂	66	6.7
27	2,5-Me ₂	67	8.0
28	2,3,5-Me ₃	61	5.6
o,m,p-type			
29	2,4,5-Cl ₃	68	1.0
30	2,4,5-Me ₃	64	6.0

inhibitory activity of the present DPEs, even the most active one, was several hundreds time less than that of the herbicide DCMU, the well known Hill reaction inhibitor. In view of these data, the inhibition of the Hill reaction is not considered as the essential mode of action of the light-requiring DPE herbicides.

An action mechanism for the light-requiring DPE herbicides has been presented by studies on acifluorfen-methyl [methyl 5-(2-chloro-4-trifluoromethylphenoxy)-2-nitrobenzoate] and related DPEs that they accumulate tetrapyrroles such as protoporphyrin IX and protochlorophyllide by stimulating 5-aminolevulinic acid synthesis and tetrapyrroles-sensitized photoperoxidation of membrane lipids causes eventual death of plant cells (Duke et al., 1991; Haworth and Dan Hess, 1988; Kouji et al., 1988; Matringe and Scalla, 1988). The action mechanism for other DPEs which do not require light for the herbicidal activity must be studied in other direction.

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