Structure-activity Relationship of Cyclic Imide Herbicides

I. *N*-Substituted Phenyl-3,4,5,6-tetrahydrophthalimides and Related CompoundsHiroki OHTA, Seiichi SUZUKI, Hisao WATANABE, Tetsuo JIKIHARA,
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Received October 27, 1975

In the course of the development of new herbicide (MK-616: *N*-(*p*-chlorophenyl)-3,4,5,6-tetrahydrophthalimide), the structure-activity relationship of cyclic imide herbicides was investigated. Sixty *N*-substituted phenyl-3,4,5,6-tetrahydrophthalimides and related compounds were prepared and their herbicidal activity were examined. The results indicate that, for high inhibitory activity, lipophilic tetramethylene moiety, double bond or nitrogen atom(s) in bridgehead position and *N*-(*p*-substituted)phenyl moiety are essential in these cyclic imides. New 4-(*p*-chlorophenyl)-1,2-tetramethylenurazole and 3-(*p*-chlorophenyl)-1,5-tetramethylenhydantoin were found to be herbicidally active.

In the previous paper,¹⁾ it has been reported that *N*-(*p*-chlorophenyl)-3,4,5,6-tetrahydrophthalimide (Fig. 1, R=*p*-Cl, MK-616) possesses potent herbicidal activity. Cyclic imide type compounds are well investigated in other pesticide field (*e.g.* captan as fungicide, tetramethrin as insecticide). However, no systematic study on the relationship between herbicidal activity and structure has yet been reported so far. In the detailed study of this type of compounds, attentions were paid to the four structural units shown in Fig. 1; the alkylene group (moiety A), the double bond which is

this type were synthesized in order to find what features in their structures are responsible for high activity. Some cyclic imide like compounds [4-(*p*-chlorophenyl)-1,2-tetramethylenurazole and 3-(*p*-chlorophenyl)-1,5-tetramethylenhydantoin] were highly active as a herbicide. We expect that these studies will suggest guidelines for the synthesis of more efficient herbicides.

MATERIALS AND METHODS

Synthesis

All melting points are uncorrected. NMR spectra were measured at 60 MHz (Hitachi-Perkin Elmer R-24) using tetramethylsilane as an internal reference. Singlet, doublet, and multiplet signals are abbreviated to s, d, and m, respectively.

Generally, most of *N*-substituted phenyl-3,4,5,6-tetrahydrophthalimides were prepared by the condensation reaction of 3,4,5,6-tetrahydrophthalic anhydride and the corresponding anilines in AcOH medium. A typical procedure is shown below.

1) *N*-(*p*-Chlorophenyl)-3,4,5,6-tetrahydrophthalimide (11). A mixture of 3,4,5,6-tetrahydrophthalic anhydride (3.04 g, 0.02 mole), *p*-chloroaniline (2.55 g, 0.02 mole) and 10 ml of AcOH was heated under reflux for 0.5 hr. After cooling, resulting crystals were collected, washed with water and dried to give 5.08 g of pale yellow needles. mp 166~7°C (EtOH). Anal. Found: C, 64.22; H, 4.75; N, 5.41; Cl, 13.73. Calcd.

FIG. 1. Structural Units of *N*-Substituted Phenyl-3,4,5,6-tetrahydrophthalimides.

conjugated with the carbonyl group (moiety B), the imide ring (moiety C) and the aryl ring (moiety D) and many kinds of compounds of

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TABLE I. ROOT GROWTH INHIBITORY AND HERBICIDAL ACTIVITIES OF *N*-SUBSTITUTED PHENYL-3,4,5,6-TETRAHYDROPHthalIMIDES AND RELATED COMPOUNDS

No.	R	mp (°C)	pI ₅₀	Herbicidal activity			
				Foliar appl. A	B	Paddy appl. C	D
1	-H	139~40	3.81	—	—	4.5	0
2	2-Cl	91	3.49	2	0	3	4
3	2-CH ₃	136~7	4.64	3	0	1	5
4	2-OCH ₃	151~2	3.81	0	0	1	2
5	3-Cl	86	3.92	—	—	4	1
6	3-F	90~1	3.87	4	0	0	0
7	3-Br	103	4.22	3	1	1	4
8	3-CH ₃	106.5~7.5	3.78	2	0	1	1
9	3-CF ₃	120~1	3.00	1	0	1	1
10	4-F	152~4	4.96	5	4	3.5	4.5
11	4-Cl	166~7	5.25	5	5	5	5
12	4-Br	172~4	5.63	5	4	5	5
13	4-I	161~2	5.17	4	4	5	5
14	4-CH ₃	124~5	4.34	5	3	4	4
15	4-C ₂ H ₅	122.5~3	3.70	3	1	3	5
16	4-OCH ₃	100	4.90	5	5	2	5
17	4-OC ₂ H ₅	135	4.42	1	0	3	4
18	4-OC ₃ H ₇	98~100	3.22	0	0	0	5
19	4-SCH ₃	104~5	4.32	2	0	3	4.5
20	4-NO ₂	175~7	3.76	1	0	0	5
21	4-CN	144~5	5.16	4.5	5	2	5
22	4-CO ₂ H	254~6	3.28	0	0	1	0
23	4-N(CH ₃) ₂	202	<2.53	0	0	0	0
24	4-SCN	109~11	3.12	0	0	0	0
25	3, 4-Cl ₂	174	5.07	2	1	3	5
26	3-Cl,4-Br	182~3	4.36	3	0	3	5
27	3-Cl,4-F	130~1	4.69	5	2	5	5
28	3-Cl,4-CH ₃	181~2	<2.54	0	0	0	3
29	3-CH ₃ , 4-Cl	152~3	5.35	5	3	5	5
30	3-Br, 4-CH ₃	164~5	<2.60	0	0	0	0
31	3-CH ₃ , 4-Br	169~70	5.34	3	2	4.5	5
32	3, 4-(CH ₃) ₂	153~4	2.99	2	0	3	5
33	3, 5-Cl	95~6	2.62	0	0	4	4
34	2, 4-Cl	97~8	5.33	4	5	4	5

R'

35	-Methyl	52~3	3.01	0	0	0	0
36	-Cyclohexyl	77	2.87	0	0	0	0
37	-Benzyl	1.5620†	4.07	5	3	0	0

A, sawa millet 50 g/a; B, radish 50 g/a; C, barnyard grass 30 g/a; D, toothcup 30 g/a.

† n_D^{25} .

TABLE II. ROOT GROWTH INHIBITORY AND HERBICIDAL ACTIVITIES OF VARIOUS *N*-(*p*-CHLOROPHENYL) CYCLIC IMIDES (MOIETY A AND B)

No.	X	mp (°C)	pI ₅₀	Herbicidal activity			
				Foliar appl. A	B	Paddy appl. C	D
11		166~7	5.25	5	5	5	5
38		200	2.79	0	0	3	5
39		159~61	4.65	4.5	1	3	5
40		183~4	4.79	1	2	1	5
41		139~40	4.65	1	0	0	0
42		147~7.5	4.33	0	0	0	4
43		162~3.5	3.92	2	2	5	5
44		170~2	3.80	3	4	4	5
45		127~9	3.05	0	0	0	4
46		93~4	4.93	5	5	5	5
47		139.5~41	4.29	5	4	4	5
48		154~4.5	3.12	3	3	2	3
49		139~41	2.87	0	2	0	5
50		127~9	2.98	1	3	4	2
51		122	3.69	2	1	1	1
52		157	4.65	3	1	2	5

A, sawa millet 50 g/a; B, radish 50 g/a; C, barnyard grass 50 g/a; D, toothcup 50 g/a.

for $C_{14}H_{12}O_2NCl$: C, 64.25; H, 4.62; N, 5.35; Cl, 13.55%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1755, 1710, 880, 815. NMR δ (CDCl_3): 1.69 (4H, m), 2.31 (4H, m), 7.33 (4H, s).

By the similar method, 33 analogues were prepared (Table I). This method was also applicable for the synthesis of compounds in Table II except No. 48.

2) *N*-(*p*-Chlorophenyl)cyclopentene-1,2-dicarboximide (48). A mixture of cyclopentene-1,2-dicarboxylic anhydride²³ (1.38 g, 0.01 mole), *p*-chloroaniline (1.28 g, 0.01 mole) and 10 ml of benzene was refluxed for 0.5 hr. The precipitated product was collected and dried to yield carboxylic acid amide (mp 173.5~174.5°C). A mixture of carboxylic acid amide (1.33 g, 0.005 mole), anhyd. NaOAc (0.2 g) and 10 ml of Ac_2O was heated under reflux for 3 hr with stirring. The reaction mixture was poured into cold water with stirring and the precipitated material was collected and dried. Recrystallization from EtOH-EtOAc yielded 0.99 g of *N*-(*p*-chlorophenyl)cyclopentene-1,2-dicarboximide (48). mp 154~154.5°C. *Anal.* Found: C, 63.17; H, 4.20; N, 5.62; Cl, 14.37; Calcd. for $C_{15}H_{10}O_2NCl$: C, 63.04; H, 4.07; N, 5.66; Cl, 14.31%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1774, 1708, 835, 780. NMR δ (CDCl_3): 2.60 (6H, m), 7.25, and 7.44 (4H, quartet, $J=9$ Hz).

By the similar method, *N*-(*p*-chlorophenyl)pyridine-2,3-dicarboximide (53) (mp 221°C) (EtOH-EtOAc) and *N*-(*p*-chlorophenyl)pyrazine-2,3-dicarboximide (54) (mp 298~300°C) were prepared.

3) *N*-(*p*-Chlorophenyl)-3,4,5,6-tetrahydropyrazine-2,3-dicarboximide (55). *N*-(*p*-Chlorophenyl)pyrazine-2,3-dicarboximide (5.19 g, 0.02 mole) was hydrogenated over 5% Pd-C in 100 ml of dioxane at 70°C at the atmospheric pressure. After 30 min hydrogen absorption was ceased (2 mole eq.). The catalyst was removed from dark brown colored reaction mixture by filtration, and dioxane was evaporated *in vacuo*. The residue was recrystallized from EtOH-EtOAc to give 3.6 g of reddish brown needles. mp 258~260°C. *Anal.* Found: C, 54.50; H, 3.91; N, 15.80; Cl, 13.32. Calcd. for $C_{12}H_{10}O_2N_2Cl$: C, 54.66; H, 3.82; N, 15.94; Cl, 13.45%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3350, 1755, 1665, 825. NMR δ (CDCl_3 -DMSO- d_6): 3.25 (4H, s), 5.10 (2H, broad s), 7.31 (4H, s).

4) *N*-(*p*-Chlorophenyl)pyridazine-4,5-dicarboximide (56). To a suspension of pyridazine-4,5-dicarboxylic acid (6.72 g, 0.04 mole) in 100 ml of dry ether was added $(\text{CF}_3\text{CO}_2)_2\text{O}$ (10.08 g, 0.048 mole) dropwise with stirring. Stirring was continued further 3 hr at room temperature, and concentration yielded 5.82 g of pyridazine-4,5-dicarboxylic anhydride. mp 184~186°C (dec.). *Anal.* Found: C, 48.12; H, 1.44; N, 18.34. Calcd. for $C_8H_2O_4N_2$: C, 48.01; H, 1.34; N, 18.67%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1870, 1818, 1795, 1120.

To a stirred solution of the anhydride (3.00 g, 0.02-mole) in 30 ml of hot AcOH was added a solution of

p-chloroaniline (2.55 g, 0.02 mole) in 8 ml of AcOH. The reaction mixture was heated on a steam bath for 15 min, then cooled. The resulting precipitate was filtered to yield 4.72 g of carboxylic acid amide. mp 198~199°C (EtOH-EtOAc). *Anal.* Found: C, 51.53; H, 2.84; N, 15.10; Cl, 12.64. Calcd. for $C_{12}H_8O_2N_2Cl$: C, 51.90; H, 2.90; N, 15.14; Cl, 12.77%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3370, 1720, 1670, 830. NMR δ (CDCl_3 -DMSO- d_6): 7.33, and 7.69 (4H, quartet, $J=8.5$ Hz), 9.48 (1H, d, $J=1$ Hz), 9.59 (1H, d, $J=1$ Hz), 10.79 (1H, s). A mixture of the resulting carboxylic acid amide (1.39 g, 0.005 mole) and 1 g of Ac_2O was heated to 50~60°C for 5 hr. The resulting dark brown colored product was triturated with ether, washed with EtOAc to yielded 0.3 g of *N*-(*p*-chlorophenyl)pyridazine-4,5-dicarboximide (56). Further purification was difficult. mp 213~214°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1775, 1720, 830.

5) *N*-(*p*-Chlorophenyl)-3,6-dithia-3,4,5,6-tetrahydrophthalimide (57). A mixture of 3,6-dithia-tetrahydrophthalic anhydride²³ (1.12 g, 0.006 mole) and *p*-chloroaniline (0.76 g, 0.006 mole) and 4 ml of AcOH was heated under reflux for 15 min, then cooled. The resulting crystals were collected and recrystallization from EtOH-EtOAc yielded 1.2 g of *N*-(*p*-chlorophenyl)-3,6-dithia-3,4,5,6-tetrahydrophthalimide (57). mp 182~183°C. *Anal.* Found: C, 48.51; H, 2.70; N, 4.61; S, 21.33; Cl, 11.88. Calcd. for $C_{12}H_8O_2NS_2Cl$: C, 48.40; H, 2.71; N, 4.70; S, 21.54; Cl, 11.91%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1768, 1710, 832. NMR δ (CDCl_3): 3.29 (4H, s), 7.34 (4H, s).

6) 3-(*p*-Chlorophenyl)-1,5-tetramethylenehydantoin (58). To a solution of pipecolic acid (1.94 g, 0.015 mole) and sodium hydroxide (0.60 g, 0.015 mole) in 25 ml of water was added *p*-chlorophenyl isocyanate (2.30 g, 0.015 mole) in 20 ml of chlorobenzene. After stirring for 1 hr at room temperature, the reaction mixture was extracted with ether. Then, conc. HCl was added to the aqueous phase to pH 2, and the mixture was heated under reflux for 1 hr with stirring. After cooling at room temperature, the resulting crystals were collected, washed with water and recrystallized from EtOH to yield 3.22 g of 3-(*p*-chlorophenyl)-1,5-tetramethylenehydantoin (58). mp 157~158°C. *Anal.* Found: C, 59.11; H, 4.96; N, 10.42; Cl, 13.46. Calcd. for $C_{13}H_{13}O_2N_2Cl$: C, 58.98; H, 4.95; N, 10.58; Cl, 13.40%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3100, 1770, 1710, 835, 750. NMR δ (CDCl_3): 1.55 (4H, broad m), 2.10 (2H, broad m), 2.85 (1H, sextet, $J=ca.$ 12,12, and 6 Hz), 3.80 (1H, quartet, $J=12$, and 5 Hz), 4.20 (1H, m), 7.40 (4H, s).

7) 4-(*p*-Chlorophenyl)-1,2-tetramethylenurazole (59). The preparation of 4-(*p*-chlorophenyl)urazole was accomplished according to the method of Cookson *et al.*⁴⁾

From 10.4 g of ethyl hydrazinecarboxylate and 15.4g of *p*-chlorophenyl isocyanate was obtained 25.1 g of

the semicarbazide derivative. mp 205~207°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3290, 1740, 1690, 1640, 840. The semicarbazide was cyclized to the 4-(*p*-chlorophenyl)urazole with hot 4*N* potassium hydroxide solution and subsequent acidification. mp 235~236°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3200, 1795, 1700, 832, 790.

Cycloalkylation of the 4-(*p*-chlorophenyl)urazole was accomplished according to the modified Zinner's method.⁵⁾

4-(*p*-Chlorophenyl)urazole (2.12 g, 0.01 mole) was dissolved in 30 ml of DMF, to this was added powdered potassium hydroxide (1.32 g, 0.02 mole) and allowed to stir for 1 hr. A sticky greenish salt was formed. Tetramethylene bromide (2.16 g, 0.01 mole) was added to the above salt and the mixture was heated under reflux for 1 hr with stirring. Precipitated potassium bromide was filtered off and DMF was evaporated *in vacuo*. The residue was recrystallized from EtOH to give 2.2 g of 4-(*p*-chlorophenyl)-1,2-tetramethyleneurazole (**59**). mp 192~193°C. Anal. Found: C, 54.38; H, 4.40; N, 15.91; Cl, 13.33. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_3\text{Cl}$: C, 54.24; H, 4.55; N, 15.82; Cl, 13.35%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1770, 1700, 820. NMR δ (CDCl_3): 1.84 (4H, m), 3.62 (4H, m), 7.51 (4H, s).

8) 4-(*p*-Chlorophenyl)-1,2-(2'-butenyl)urazole (**60**). The preparation of the compound was accomplished according to the method of Gillis and Hagarty.⁶⁾

From 4.87 g of 4-(*p*-chlorophenyl)urazole and butadiene in the presence of $\text{Pb}(\text{OAc})_4$ was obtained 4.30 g of a Diels Alder adduct. mp 176~177°C. Anal. Found: C, 54.40; H, 3.70; N, 15.71; Cl, 13.31. Calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_2\text{N}_3\text{Cl}$: C, 54.66; H, 3.82; N, 15.94; Cl, 13.45%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1765, 1695, 820. NMR δ (CDCl_3): 4.17 (4H, d, $J=0.9$ Hz), 5.94 (2H, t, $J=0.9$ Hz), 7.39, and 7.60 (4H quartet, $J=9$ Hz).

Biological test

1) *Inhibition of root growth (Petri dish test)*. Twenty five seeds of sawa millet (*echinocloa utilis*) were placed on a filter paper laid on a bottom of a petri dish of 9 cm diameter, and soaked with 10 ml of a test solution containing a fixed amount of test compound and surfactant (Tween 20). Each dish was kept in a humid glass house conditioning temperature (25°C at day time and 20°C at night) for 7 days. Root growth inhibitory indices are presented as pI_{50} , negative logarithm of the molar concentration which produces a 50% inhibition.

2) *Foliar application test*. The post-emergence herbicidal activities were evaluated by spraying first leaf stage of sawa millet and radish grown in a 1/5000a Wagner pot with a liquid formulation of the test compound which was prepared by dilution of 50% wettable powder at the rate of 50 g/a. The sprayed plants were held in the greenhouse for a month and the effects of the test compounds on the plants were then evaluated

visually, the result being rated at 0 (no effect) to 5 (plants dead) scale relative to the control.

3) *Submerged pot test (paddy application test)*. Wagner pots (1/5000a) were packed with paddy soil (alluvial clayish loam) and to this were sown seeds of barnyard grass (*echinocloa crus-galli*) and toothcup (*rotala indica*). Then the pots were watered and kept in a greenhouse. After 5 days solution of the test compounds formulated as a wettable powder were applied at the rate of 30 g/a or 50 g/a. Herbicidal activities were evaluated after a month and the results were determined in the same way as that described in the case of foliar application test.

RESULT AND DISCUSSION

1) Effect of the benzene ring substituents of the root growth inhibitory and herbicidal activities among *N*-substituted phenyl-3,4,5,6-tetrahydrophthalimides and related compounds (Moiety D)

As shown in Table I, the highest root growth inhibitory activity in the series of the compounds was found in the 4-chloro (**11**) and 4-bromo (**12**) compounds. The 4-methyl (**14**), 4-methoxy (**16**), 4-methylthio (**19**), and 4-cyano (**21**) compounds showed also high activity, while the substitution at ortho or meta position gave relatively low activity. *N*-Methyl (**35**), *N*-cyclohexyl (**36**), and *N*-benzyl (**37**) compounds which have no *N*-aryl group also showed lower activity.

Among the 4-alkyl and 4-alkoxy derivatives, increasing the alkyl chain length decreased the activity. Substitution at para position by nitro (**20**), carboxyl (**22**) and dimethylamino (**23**) group caused loss of activity in whole or in part. Among the disubstituted compounds, the 3,4-dihalogeno and 3-alkyl,4-halogeno compounds showed as high activity as the 4-halogeno compounds. On the contrary, the 3-halogeno, 4-alkyl compounds showed loss of activity. The root growth inhibitory activity of the series of the compounds was closely correlated with the results of pot tests.

In conclusion, 4-halogeno substitution seems to be favorable to the root growth inhibitory and herbicidal activities of this type of compounds. It was difficult to characterize

TABLE III. ROOT GROWTH INHIBITORY AND HERBICIDAL ACTIVITIES OF HETERO ATOM(S) CONTAINING *N*-(*p*-CHLOROPHENYL) CYCLIC IMIDS (MOIETY A AND B)

No.	X	mp (°C)	pI ₅₀	Herbicidal activity			
				Foliar appl. A	B	C	Paddy appl. D
53		221	2.94	0	0	0	3
54		298~300	2.80	0	0	0	2
55		258~60	2.59	0	0	0	0
56		213~4	2.60	0	0	0	0
57		184~5	2.57	0	0	0	4
58		157~8	5.68	5	5	5	5
59		192~3	5.15	5	5	5	5
60		176~7	4.99	1	1	5	5

A, sawa millet 50 g/a; B, radish 50 g/a; C, barnyard grass 50 g/a; D, toothcup 50 g/a.

these substituent effects in monistic conception; for example, the root growth inhibitory activity correlated poorly with the Hammett σ constants.

2) *Effect of the modification of the phthalimide moiety (Moiety A and B) on the root growth inhibitory and herbicidal activities among the N-(p-chlorophenyl)cyclic imides*

As shown in Table II, the highest activities were observed in the parent 3,4,5,6-tetrahydrophthalimide compound (**11**), while shift of a double bond, introduction of another double bond or hydrogenation of a double bond of the compound (**11**) lead to the less active compounds. Introduction of a methyl group to the tetramethylene group of the compound (**11**) lead to the less active com-

pounds except one (**46**) which possesses a methyl group at 3-position. The fact that the open chain maleimide analogues (**50**), (**51**) and (**52**) reduced activities indicated clearly necessity of the tetramethylene moiety. The alkylene group increases the lipophilicity in many cases and the double bond conjugating with the imide carbonyl group may enhance the polarity of the compounds. Thus, it is suggested that a proper balance of the lipophilicity of the tetramethylene group and the hydrophilicity of the imide ring is responsible for high activity.

3) *Effect of the hetero atom(s) introduction into the phthalimide moiety (Moiety A and B) in the root growth inhibitory and herbicidal activities among the N-(p-chlorophenyl)cyclic imides*

As shown in Table III, both root growth inhibitory activity and herbicidal activity were greatly reduced by introduction of the nitrogen or sulfur atom(s) into the tetramethylene group of the (11). On the other hand, these high activities were maintained by the introduction of the nitrogen atom(s) at the bridgehead position (58), (59), and (60). As shown in Fig. 2, it is suggested that the tetramethylene

The fact that the morphological effect of three types of compounds mentioned above are quite similar to each other suggests that the double bond and the bridgehead nitrogen atom(s) play an equivalent role in mechanism of action.

Acknowledgement. The authors wish to thank Professor Tetsuo Takematsu in Utsunomiya University and Dr. Syoichi Matsunaka in National Institute of Agricultural Science for their valuable suggestions. They are also grateful to Mitsubishi Chemical Industries Limited for permission to publish this work.

FIG. 2. Essential Moiety for Herbicidal Activity.

chain is essential for high activity as a lipophilic site and a double bond or nitrogen atom(s) capable of conjugating with the imide carbonyl group which activates the polar imide ring is also necessary for high activity.

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