N-アリール-4-カルボキシ-およびN-アリール-4-ヒドロキシ-フタルイミド類の構造と根こぶ病防除活性

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Original Article

Structure-activity Relationships of *N*-Aryl-4-carboxy- and *N*-Aryl-4-hydroxy-phthalimides in Control of *Plasmodiophora* Disease*

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Sixty-five *N*-aryl-4-carboxy- and *N*-aryl-4-hydroxy-phthalimides having various substituents on the *N*-aryl moiety were prepared, and their preventive activity against clubroot of Chinese cabbage caused by *Plasmodiophora brassicae* was examined. Among these compounds, only 2,6-dialkyl derivatives showed high preventive activity, which depended on the position-specific substituent effect, and both the presence of the α-branching and the number of carbon atoms in the alkyl groups on the *N*-aryl ring.

INTRODUCTION

In the previous papers,[1,2] we have reported that *N*-(2,6-dialkylphenyl)phthalimides having substituents such as carboxy, ester, amide and hydroxy at the 4-position of phthalimide moiety exhibited potent preventive activity against *Plasmodiophora brassicae*, the causal fungus of clubroot of cruciferous crops.

For further extension of the studies on structure-activity relationships of *N*-aryl-4-substituted phthalimide, modification of substituents of the *N*-aryl moiety was investigated by fixing a substituent at the 4-position to either the carboxy or the hydroxy group. In this paper, we discuss the structure-activity relationships of *N*-aryl-4-substituted phthalimides having alkyl, alkoxy and halogeno groups on the *N*-aryl ring.

* Studies on *N*-Arylphthalimides (Part 4). See Ref. 2) for Part 3.

MATERIALS AND METHODS

1. *Synthesis*

1.1 *Anilines*

2,6-Dimethoxy-,[3-5] 2,6-diethoxy-,[3-5] 2,5-diisopropyl-,[3,4,6] 4-isopropyl-3-methyl-,[7,8] 2-*s*-butyl-6-methyl-,[9,10] 2-ethyl-6-*n*-propyl-,[9,10] 2,6-di-*s*-butyl-,[9,11] and 2,4,6-triisopropyl-[3,4,6] anilines were prepared according to the reported methods. 2-*s*-Butyl-4-chloro-6-methylaniline (n_D^{21} 1.5731) and 2-*s*-butyl-4,6-dimethylaniline (n_D^{24} 1.5327) were synthesized in the same manner as reported.[9]

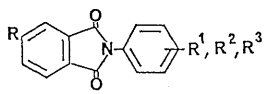
1.2 *Phthalimides*

Phthalimides were prepared from anilines and 4-substituted phthalic anhydrides.[1] The structures were determined by IR and NMR spectra and elementary analyses for C, H and N.

2. *Preventive Activity*

Preventive activity against clubroot of Chinese cabbage (*Plasmodiophora brassicae*) was examined by the method reported pre-

Table 1 Structure, physical properties and preventive activity of *N*-aryl-4-carboxy- and *N*-aryl-4-hydroxy-phthalimides.



R							Substituent parameter			
COOH			OH							
Compd. No.	mp (°C)	Activity (%) 6.3 ppm	Compd. No.	mp (°C)	Activity (%) 6.3 ppm	R^1,R^2,R^3	$\sum\pi$[a]	$\sum E_s$[b]	$\sum\sigma$[c,d]	X[e]
1	266–268	0	**38**	257–258	0	H	0	0	0	0
2	236–237	0	**39**	236–237	0	2-Me	0.23	−1.24	−0.17	0
3	272–274	0	**40**	198–199	0	2-*i*-Pr	0.88	−1.71	−0.15	1
4	255–256	0	**41**	220–222	0	2-CF_3	0.70	−2.40	0.54	0
5	248–250	0		—		2-OMe	−0.08	−0.55	−0.27	0
6	241–242	0	**42**	310–312	0	2-CN		−0.51	0.66	0
7	219–220	0		—		2-NO_2	0.30	−1.01	0.78	0
8	234–236	0		—		3-Me	0.51	−1.24	−0.07	0
9	312–313	0	**43**	295–297	0	3-NO_2	0.32	−1.01	0.71	0
10	255–256	0	**44**	254–256	0	4-Me	0.52	−1.24	−0.17	0
11	250–251	0	**45**	229–231	0	4-*i*-Pr	1.34	−1.71	−0.15	1
12	298–299	0	**46**	247–248	0	4-F	0.23	−0.46	0.06	0
13	297–298	0		—		4-NO_2	0.40	−1.01	0.78	0
14	264–265	0		—		2,6-Cl_2	1.00	−1.94	0.46	0
15	276–277	0	**47**	164–165	0	2,6-Br_2	1.18	−2.30	0.46	0
16	269–272	0		—		2,6-F_2	0.32	−0.92	0.12	0
17	238–239	0		—		2,6-$(OMe)_2$	−0.16	−1.10	−0.54	0
18	208–209	0		—		2,6-$(OEt)_2$	0.84	−1.10[f]	−0.48	0
	—		**48**	102–109	0	2-*s*-Bu,4-Et	2.42	−3.68	−0.30[g]	1
19	198–201	0	**49**	161–162	0	2,5-$(i\text{-Pr})_2$	2.16	−3.42	−0.22	1
20	197–200	0	**50**	244–245	0	4-*i*-Pr,3-Me	1.85	−2.95	−0.22	1
21	224–225	0	**51**	205–207	0	2,6-$(Me)_2$	0.46	−2.48	−0.34	0
22	183–185	0	**52**	164–165.5	0	2-Et,6-Me	0.81	−2.55	−0.32	0
23	224–225	40	**53**	175.5–176	24	2,6-$(Et)_2$	1.16	−2.62	−0.30	0
24	250–255	0		—		2-Me,6-*n*-Pr	1.31	−2.84	−0.30	0
25	214–215	72	**54**	220–222	60	2-*i*-Pr,6-Me	1.11	−2.95	−0.32	1
26	105–107	84	**55**	119–123	80	2-*s*-Bu,6-Me	1.61	−3.61	−0.32	1
27	200–201	60	**56**	vitreous	44	2-*i*-Bu,6-Me	1.41	−4.02	−0.37	1

28	228–230	100	**57**	156–157	92	2-Et,6-*i*-Pr	1.46	−3.02	−0.30	1
29	210–211	100	**58**	155–156	100	2-*s*-Bu,6-Et	1.96	−3.68	−0.30	1
30	271–272	0	**59**	122–125	<20	2-Et,6-*n*-Pr	1.66	−2.91	−0.28	0
31	270–272	100	**60**	202–205	60	2,6-(*i*-Pr)$_2$	1.76	−3.42	−0.30	1
32	171–174	0	**61**	127–128	0	2-*s*-Bu,6-*n*-Pr	2.46	−3.97	−0.28	1
33	108–111	0	**62**	160–164	0	2,6-(*s*-Bu)$_2$	2.76	−4.74	−0.30	1
34	297.5–298.5	0		—		2,4,6-(*i*-Pr)$_3$	3.10	−5.13	−0.45	1
35	118–120	36	**63**	88–93	28	2-*s*-Bu,6-Me,4-Cl	2.51	−4.58	−0.09	1
36	252–253	36		—		2,6-(*i*-Pr)$_2$,4-Cl	2.66	−4.39	−0.07	1
37	198–201	0	**64**	82–85	<20	2-*s*-Bu,5,6-(Me)$_2$	2.12	−4.85	−0.39	1
	—		**65**	90–94	<20	2-*s*-Bu,4,6-(Me)$_2$	2.13	−4.85	−0.49	1

a) Unless otherwise noted, taken from Ref. 12).
b) Unless otherwise noted, taken from Refs. 13)–15).
c) Unless otherwise noted, taken from Refs. 16) and 17).
d) The σ value of the ortho-substituents was taken as the σ value of the corresponding para-substituents (Ref. 18)).
e) Indicator variable for the α-branching in substituents.
f) Taken as E_s(OMe).
g) Estimated assuming that σ (*s*-butyl) = σ (isopropyl).

viously.[1] The results are summarized in Table 1.

RESULTS AND DISCUSSION

1. Structure-activity Relationship

Among *N*-aryl-4-carboxyphthalimides (A series), only 2,6-dialkyl series (**25**–**29** and **31**) showed preventive activity. Both unsubstituted (**1**) and monosubstituted derivatives (**2**–**13**) were inactive. The activity of disubstituted derivatives varied with the physicochemical properties and positions of substituents on the *N*-aryl ring. The dihalogeno (**14**–**16**) and dialkoxy (**17** and **18**) derivatives showed no activity. The 2,6-diisopropyl (**31**) and 2-isopropyl-6-methyl (**25**) derivatives showed strong and moderate activity, respectively, whereas the 2,5-diisopropyl (**19**) and 4-isopropyl-3-methyl (**20**) derivatives showed no activity. The result suggests that position-specific substituent effect determines the preventive activity. The activity of 2,6-dialkyl derivatives varied with both the presence of α-branching and the number of carbon atoms in the alkyl substituents. The 2-isopropyl-6-methyl (**25**) and 2-ethyl-6-isopropyl (**28**) derivatives showed moderate and strong activity, respectively, whereas the 2-methyl-6-*n*-propyl (**24**) and 2-ethyl-6-*n*-propyl (**30**) derivatives showed no activity. The result indicates the importance of α-branching effect. The 2,6-diethyl derivative (**23**) showed only a slight activity, whereas the other 2,6-dialkyl derivatives (**21**, **22**, **32** and **33**) were inactive. The result indicates the significance of the number of carbon atoms in two alkyl groups.

An introduction of additional substituents to the meta- or para-position of active 2,6-dialkyl derivatives made the compounds inactive, as seen in the 2,4,6-triisopropyl (**34**), 2-*s*-butyl-5,6-dimethyl (**37**), 2,6-diisopropyl-4-chloro (**36**) and 2-*s*-butyl-4-chloro-6-methyl (**35**) derivatives.

In *N*-aryl-4-hydroxyphthalimides (B series), the structure-activity relationship was very similar to that of A series. The positions of alkyl groups, the α-branching effect, and the number of carbon atoms in the 2,6-dialkyl groups were significant for the activity. The 2-*s*-butyl-6-methyl (**55**), 2-ethyl-6-isopropyl (**57**) and 2-*s*-butyl-6-ethyl (**58**) derivatives

showed strong activity, whereas the other derivatives were weakly active or inactive. The similarity in structure-activity relationships between the two series suggests that the critical site of the putative receptor and mode of action do not differ between the 4-carboxy- and 4-hydroxy-phthalimides.

2. *Parameter Focusing*

Parameter focusing[19] was employed in order to determine which substituent effects are related to the activity of the di- and tri-substituted derivatives having substituents at both ortho-positions. This approach has been used for identifying key parameters which control bioactivity. The analysis was made using $\sum\pi$, $\sum E_s$, and $\sum\sigma$ for substituents on the *N*-aryl ring, which are the sums of π (the Hansch-Fujita's hydrophobic substituent constants[12]), E_s (the Taft's steric substituent constants[13-15]), and σ values (the Hammett's electronic substituent constants[16]), respectively. The results are listed in Table 1.

The $\sum\pi$ values of A series are plotted against the $\sum E_s$ values in Fig. 1. The plots of six active compounds having the activity of more than 40% seemed to form a good focus. However, with a high collinearity between the two variables taken into account, it is not clear which variable is significant. Three plots of inactive compounds (**23**, **24** and **30**) with no α-branched substituents were observed close to the focused area. The α-branching effect seemed to be related to the activity. Parameter focusing of B series was very similar to that of A series (Fig. 2). Two plots of the inactive compounds (**53** and **59**) with no α-branched substituents were also observed close to the focused area of active compounds, suggesting the importance of the α-branching effect. The other parameter focusing using the $\sum\sigma$ values did not afford any significant result.

3. *Discriminant Analysis*

In order to clarify the substituent effects, the linear discriminant analysis[20] was performed using the 2,6-disubstituted derivatives. Eighteen 4-carboxyphthalimides (A series) and thirteen 4-hydroxyphthalimides (B series) were divided into two groups (inactive-group 1 and active-group 2) with the cutting point at 40% of the activity, since the preventive activity of equal to or less than 40% seemed to be practically inactive. The two series were separately subjected to discriminant analysis using the UCLA Biomedical Program BMDP7M.[21]

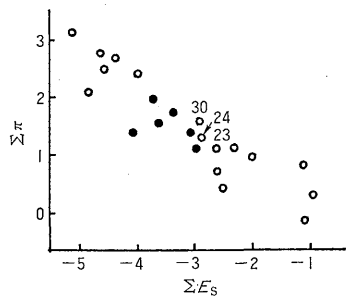


Fig. 1 Parameter focusing in preventive activity of *N*-aryl-4-carboxyphthalimides against *Plasmodiophora* disease.
●: Active compound.

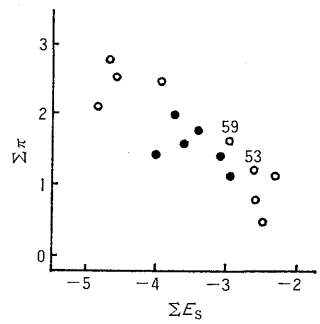


Fig. 2 Parameter focusing in preventive activity of *N*-aryl-4-hydroxyphthalimides against *Plasmodiophora* disease.
●: Active compound.

The variables examined are $\sum\pi$, $(\sum\pi)^2$, $\sum E_s$, $(\sum E_s)^2$, $\sum\sigma$, and an indicator variable X, which takes one for the compounds having α-branched substituents or zero for the others. All combinations of the variables were analyzed for the best combination. The squared correlation matrix for the variables is shown in Table 2.

The best classification functions for the two series are:

A series:

inactive compounds, group 1

$$1.34(\sum\pi)^2-6.22X-1.49 \quad (1)$$

active compounds, group 2

$$-4.54(\sum\pi)^2+36.15X-13.13 \quad (2)$$

Table 2 The squared correlation matrix for variables used in discriminant analysis.

	$\sum\pi$	$\sum E_s$	$\sum\sigma$	X[a]	$(\sum\pi)^2$	$(\sum E_s)^2$
A Series[b]						
$\sum\pi$	1.00	0.74	0.00	0.46	0.88	0.75
$\sum E_s$		1.00	0.06	0.59	0.61	0.96
$\sum\sigma$			1.00	0.09	0.02	0.07
X				1.00	0.42	0.64
$(\sum\pi)^2$					1.00	0.70
$(\sum E_s)^2$						1.00
B series[c]						
$\sum\pi$	1.00	0.67	0.01	0.38	0.95	0.66
$\sum E_s$		1.00	0.17	0.62	0.65	0.99
$\sum\sigma$			1.00	0.13	0.02	0.14
X				1.00	0.30	0.57
$(\sum\pi)^2$					1.00	0.66
$(\sum E_s)^2$						1.00

a) Indicator variable for the α-branching in substituents.
b) *N*-(2,6-Disubstituted phenyl)-4-carboxyphthalimide derivatives.
c) *N*-(2,6-Disubstituted phenyl)-4-hydroxyphthalimide derivatives.

Table 3 Observed and calculated class of *N*-(2,6-disubstituted phenyl)phthalimides.

4-Carboxyphthalimide[a]						4-Hydroxyphthalimide[b]					
Compd. No.	Class					Compd. No.	Class				
	Obsd.[c]	Calcd.[d]	Calcd.[e]	Calcd.[f]	Calcd.[g]		Obsd.[c]	Calcd.[d]	Calcd.[e]	Calcd.[f]	Calcd.[g]
14	1	1	1	1	1	**47**	1	1	1	1	1
15	1	1	1	1	1	**51**	1	1	1	1	1
16	1	1	1	1	1	**52**	1	1	1	1	1
17	1	1	1	1	1	**53**	1	1	1	1	1
18	1	1	1	1	1	**54**	2	2	2	2	2
21	1	1	1	1	1	**55**	2	2	2	2	2
22	1	1	1	1	1	**56**	2	2	2	1	1
23	1	1	1	1	1	**57**	2	2	2	2	2
24	1	1	1	1	1	**58**	2	2	2	2	2
25	2	2	2	2	2	**59**	1	1	1	1	1
26	2	2	2	2	2	**60**	2	2	2	2	2
27	2	2	2	2	1	**61**	1	1	1	2	2
28	2	2	2	2	2	**62**	1	1	1	1	2
29	2	2	2	2	2						
30	1	1	1	1	1						
31	2	2	2	2	2						
32	1	1	1	2	2						
33	1	1	1	1	2						

a) *N*-(2,6-Disubstituted phenyl)-4-carboxyphthalimide derivatives.
b) *N*-(2,6-Disubstituted phenyl)-4-hydroxyphthalimide derivatives.
c) Observed class of compounds.
d) Calculated class using discriminant functions (1)–(4).
e) Calculated class according to the leave-one-out procedure based on the corresponding discriminant functions (1)–(4).
f) Calculated class using discriminant functions (5)–(8).
g) Calculated class according to the leave-one-out procedure based on the corresponding discriminant functions (5)–(8).

B series:

inactive compounds, group 1

$$1.53(\sum\pi)^2-6.34X-1.98 \quad (3)$$

active compounds, group 2

$$-3.72(\sum\pi)^2+28.38X-10.27 \quad (4)$$

F matrix confidence levels for the two series are more than 99.9% ($F_{2,15}=60.52>F_{2,15,0.999}=11.34$ for A series and $F_{2,10}=39.35>F_{2,10,0.999}=14.91$ for B series). F matrix contains F values computed from the Mahalanobis distances D^2 statistics that test the equality of group means for each pair of the groups. The results of reclassification by Eqs. (1), (2), (3), and (4) are summarized in Table 3. All compounds of both A and B series were correctly classified. No compound was misclassified according to the leave-one-out procedure.[22] Replacing the $\sum\pi$ by the $\sum E_s$, a discriminant analysis was repeated, since the degree of collinearity between them was high (Table 2). The classification functions obtained are as below. Although these functions were statistically justified by F matrix confidence levels ($F_{3,14}=17.21>F_{3,14,0.995}=6.68$ for A series and $F_{2,10}=13.43>F_{2,10,0.995}=9.43$ for B series), A and B series functions misclassified one compound (**32**) and two (**56** and **61**), respectively.

A series:

inactive compounds, group 1

$$-6.70(\sum E_s)^2-34.51\sum E_s+11.82X-20.59 \quad (5)$$

active compounds, group 2

$$-10.03(\sum E_s)^2-47.06\sum E_s+33.99X-39.29 \quad (6)$$

B series:

inactive compounds, group 1

$$1.41(\sum E_s)^2-11.76X-5.71 \quad (7)$$

active compounds, group 2

$$0.36(\sum E_s)^2+4.13X-4.85 \quad (8)$$

The leave-one-out procedure increased the number of misclassified compounds (Table 3).

From these results, the analysis using the $\sum\pi$ can be regarded more reliable than that using the $\sum E_s$. The activity of these two series seemed to depend on the hydrophobic and α-branching effects of substituents on the N-aryl ring.

4. *Conclusion*

The structure-activity relationship study would allow us to define at least four structural requirements for high preventive activity of the N-aryl-4-carboxy- and N-aryl-4-hydroxyphthalimide series: (1) existence of hydrophobic groups such as alkyl groups at both of the ortho-positions, (2) total four to six carbon atoms in two alkyl groups, (3) presence of the α-branch moiety at least in one of the alkyl groups and (4) absence of additional substituents on the meta- and/or para-positions. Therefore, N-aryl-4-carboxy- and N-aryl-4-hydroxyphthalimides having alkyl groups such as *s*-butyl-methyl, ethyl-isopropyl, isopropyl-isopropyl, and *s*-butyl-ethyl at both of the ortho-positions of the N-aryl ring should be preferable for the fungicidal activity.

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要　　約

N-アリール-4-カルボキシ- および *N*-アリール-4-ヒドロキシ-フタルイミド類の構造と根こぶ病防除活性*

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N-アリール環上に種々の置換基を有する 4-カルボキシおよび 4-ヒドロキシフタルイミド誘導体 65 種を合成し，アブラナ科野菜根こぶ病防除活性を検討した．2, 6 両位にアルキル基を導入した化合物群には高い活性が認められたが，これらの活性は両アルキル基の炭素原子数と α-branching 効果とに支配されていた．高い活性発現に必要と考えられる条件として，1) 両オルソ位にアルキル基のような疎水基が存在すること，2) 両アルキル基中の炭素原子の合計数が 4～6 個であること，3) 少なくとも一方のアルキル基に α-分岐が存在すること，4) 2, 6 両アルキル置換体のメタおよび，またはパラ位への置換基の導入は望ましくないことの四つの構造的特徴を提示した．

* *N*-アリールフタルイミド類の研究（第 4 報）