Quantitative Structure-Activity Studies of Light-dependent Herbicidal Pyridone-Carboxanilides

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Contents

General Introduction

Recently, a number of computer-aided approaches have been flourishing in designing new agrochemicals and medicines rationally.[1] Ideally, if we could define or establish three-dimensional molecular architecture of the receptor site for particular bioactive compounds, we would be able to deduce on design other novel molecules the structures of which are complementary with the structure of this particular target. Quite a few computer-aided procedures have been developed for modeling such structures with use of theoretical calculations. In the area of herbicides, the receptor protein of a photosynthesis inhibitor, terbutryn, and its three-dimensional structure has been determined from isolated a photosynthetic bacterium has been determined by X-ray crystallography.[2] This bacterial receptor protein could be considered to be a first model for future studies of photosynthesis inhibitors in higher plants. However, the target proteins for many other types of herbicides have not always been isolated. Without detailed information about the three-dimensional nature of the receptor, this type of the "rational" approach are impossible.

In this situation, alternative approaches from the results of quantitative structure-activity (QSAR) analyses for a set of compounds belonging to a certain pharmacology are considered to be indispensable. Successful applications of traditional QSAR

analyses with the use of physicochemical free-energy related molecular descriptors to the herbicide design have been accumulated.[3,4,5] In most of these applications, the designed compounds are of the same type of structure as that of compounds included in the primary set for the analysis. In some cases, the QSAR information obtained from a set of compounds with a certain skeletal structure can be transposed to other skeletal types of compounds.[6,7,8].

Recently, Cramer et al. have succeeded to extend the QSAR approach.[9] In this procedure, the "active" conformation of a set of compounds not necessarily of the same skeleton is established by the molecular orbital calculations. After superposing active conformers in a lattice space, steric and electronic field parameters at every lattice points are calculated. With these field parameters and a newly developed statistical technique, PLS (partial least squares), the regression analysis is performed, but the results are more easily displayed as the graphics by the contours of the coefficients for electronic and steric field parameter terms allowing visualization of the regions where differences in observed activity are most strongly related to changes in electrostatic and steric fields. Such contour diagrams would hopefully be interpretable in terms of receptor structure. Results from the CoMFA procedure in which the three-dimensional structure of the receptor is not known, have been encouraging if the results could be able

to predict potencies of structurally diverse compounds not involved in the model derivation.

In this thesis, the traditional QSAR for the light-dependent herbicidal activity of a number of pyridone carboxanilides having various substitution patterns in the anilide as well as in pyridone moiety was first performed with use of free-energy-related physicochemical substituent parameters. Then, the CoMFA procedure was applied to a set of pyridone-carboxanilides and *ortho*-chlorinated diphenyl ethers of the same pharmacology to extract common structural requirements for the light-dependent herbicidal activity in terms of hydrophobic, steric and electronic characteristics.

In Chapter 1, the synthesis and light-dependent herbicidal activity of novel pyridone carboxanilides were described. In Chapter 2, physicochemical substituent effects in pyridone carboxanilides were analyzed quantitatively. In Chapter 3, three-dimensional (comparative molecular field) analysis of light-dependent pyridone-carboxanilides and diphenyl ethers was discussed. In Chapter 4, preparation of pyridone-carboxanilide derivatives was described.

Chapter 1 Light-dependent Herbicidal Activity of 4-Pyridone-3-Carboxanilide Derivatives against *Echinochloa oryzicola*

1-1 Introduction

The syntheses of 4-pyridone-3-carboxanilides including 1-benzyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilides have been carried out by Kato and his coworkers as one of the series studies on reactivity of ketene derivatives as synthons without referring to their utility[10]. Although antimicrobial[11-12] and plant chemical hybridizing[13] activities have been reported for related pyridone carboxylic acids, no herbicidal activity of pyridone-carboxylic acid derivatives has been reported sofar. With general screening procedures, we have found that their herbicidal activity is light-dependent.

Quite a few light-dependent herbicides of various chemical structures have been known. They are *ortho*-substituted diphenyl ethers including nitrofen[14-16], oxyfluorfen[17], cyclic imides such as chlorphthalim[18] and S-23142[19], and nitrogen heteroaromatic compounds such as M&B 39279[20] and TNPP-ethyl[21] (Fig.1-1). We have started the structural modification of 4-pyridone-3-carboxanilides expecting to optimize their light-dependent herbicidal activity.

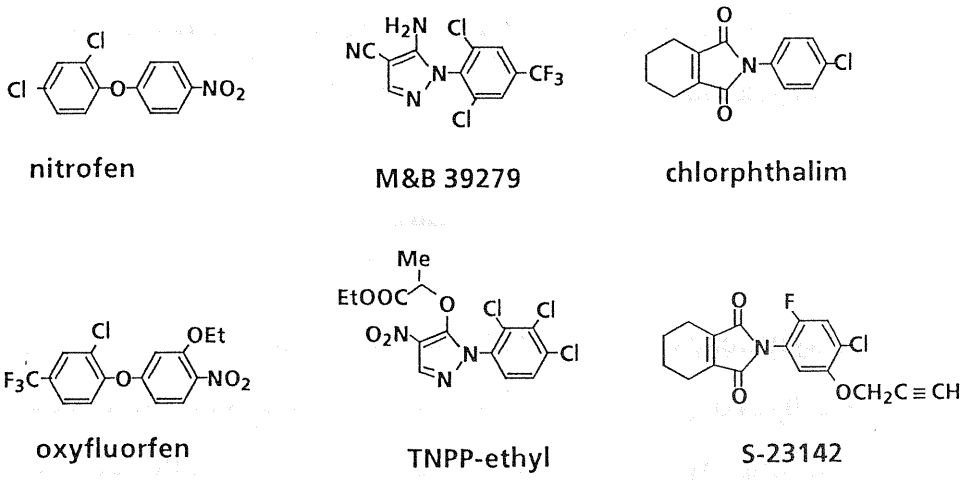


Fig.1-1 Light-dependent herbicides

This chapter will report the effect of structural modifications of the novel series of 4-pyridone-3-carboxanilide derivatives as light-dependent herbicides. The structural modifications were made at the X_n, R_1, R_2 and R_5 positions of the skeletal structure shown in Fig.1-2.

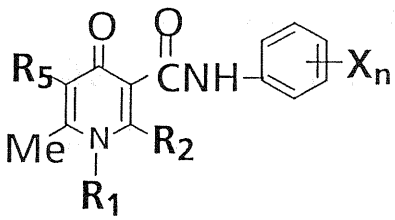


Fig 1-2. The general formula of herbicidal 4-pyridone-3-carboxanilides.

1-2 Experimental Procedures

1-2-1 Synthesis of 4-Pyridone-3-Carboxanilides

All 4-pyridone-3-carboxanilide derivatives listed in Tables 1-1 to 1-6 were prepared mainly by the following synthetic routes (Fig.1-3).

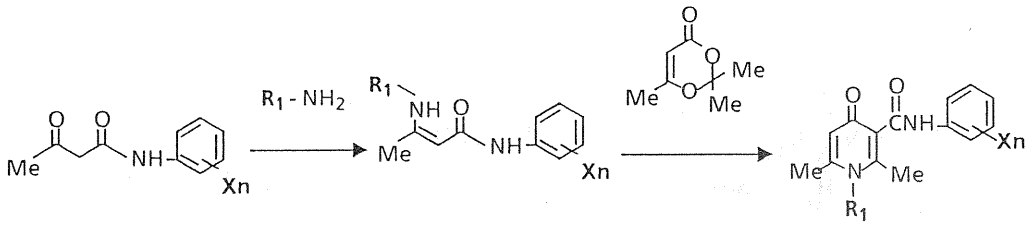


Fig. 1-3 Synthetic routes of 4-pyridone-3-carboxanilides

This method comprises reacting a acetoacetanilides with an amines to obtain 3-aminocrotonic acid anilides, finally reacting with 2,2,6-trimethyl-4*H*-1,3-dioxine-4-one in an appropriate solvent (e, g., toluene or xylene) under heating at a temperature of 100°C - 140°C to give 4-pyridone-3-carboxanilides.

1-2-2 Synthesis of 1,2-Oligomethylene-4-Pyridone-3-Carboxanilides

1,2-Oligomethylene-4-pyridone-3-carboxanilides listed in Table 1-7 were prepared mainly by the following method (Fig.1-4). This method is conducted by reacting a compounds of the formula (I) with compounds of the formula (II) without solvent or

in an appropriate solvent (such as toluene, xylene or mesitylene) under heating at 100°C to 170°C to obtain compounds of the formula (III), which were hydrolyzed by aq. NaOH to give compounds of the formula (IV), and halogenated with thionyl chloride to give the acid halide and finally reacting the acid halides were reacted with anilines to obtain 1,2-oligomethylene-4-pyridone-3-carboxanilides.

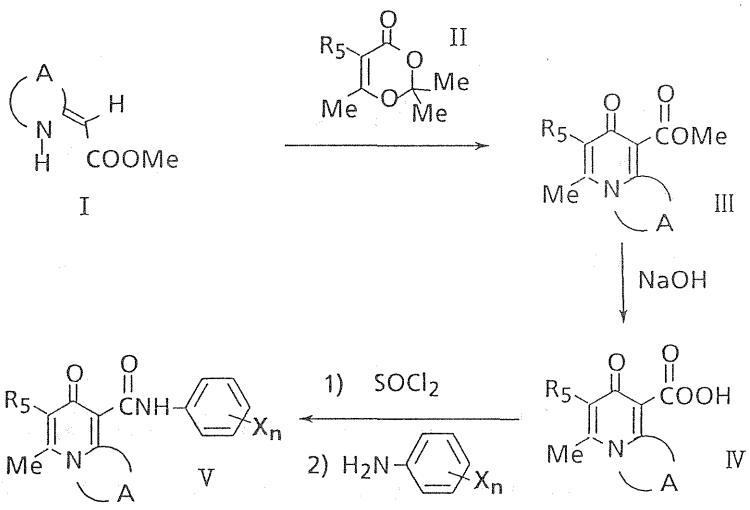


Fig. 1-4 Synthetic routes of 1-2oligomethylene-4-pyridone-3-carboxanilides. [In the formula, A is a straight or branched chain alkylene group having 3 to 5 carbon atoms]

1-2-3 Biological Tests

The herbicidal activity against *Echinochloa oryzicola* was measured using a series of dispersion solutions containing various amounts of each test compound. The test solution was prepared by dispersing a 20% wettable powder in distilled water. The 20%

wettable powder was prepared by mixing 20 parts (by weight) of each test compound, 50 parts of talc, 25 parts of bentonite, 2 parts of Solpole-9047 and 3 parts of Solpole-5039 (Toho Chemical Co., Ltd, Nihonbashikakigaracho, Chuo-ku, Tokyo, Japan). Four milliliters of each test solution were poured into a vial (ϕ3.5cm). Then, five grains of *Echinochloa oryzicola* were placed in the solution. The vials were kept at 25°C with 13 hr daylight at an intensity of 100 $\mu E\ m^{-2}sec^{-1}$ PAR for 7 days. The shoot length was measured for the five grains in each vial and averaged. The molar concentration of each compound required to inhibit the shoot elongation to half the length of the control (I_{50} value) was evaluated by the probit method[22]. The I_{50} measurements were repeated at least two times and the pI_{50} values were averaged over repeats, the standard deviation being ±0.20. The activity (pI_{50}) of each compound is listed in Tables 1-1 to 1-7.

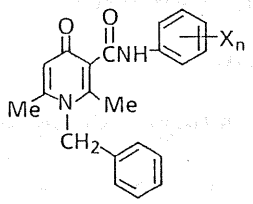
Their light-dependent effects were examined by comparing the shoot growth inhibitions between continuous light (100 $\mu E\ m^{-2}.sec^{-1}$ PAR) and dark conditions with a concentration close to I_{50} for each compound. The herbicidal effects were scored by the visual evaluation 7 days after starting the treatment.

1-3 Results and Discussion

First, we examined the effects of the benzene ring substitu-

ents of the anilide moiety(X_n) in Fig. 1-2 on its light-dependent and independent herbicidal activities fixing the R_1 substituent as benzyl, R_2 substituent as Me and R_5 as H (Fig.1-2). As shown in Table 1-1, the activity of the 1-*N*-benzyl derivatives was either light-dependent or independent. Among compounds, the activity of the unsubstituted (**1**), *ortho*-Cl(**2**), *ortho*-Me(**3**), *para*-F(**9**), *para*-Cl(**10**), *para*- Me(**11**), *para*-OMe(**12**), 2,3-Me_2(**13**), 2,4-Me_2(**14**), 2,6-Cl_2(**18**) and 2,6-Me_2(**19**) derivatives were light-independent. Among them, the unsubstituted derivative (**1**), with a pI_{50} value of 6.08, was selected as a lead compound for development of possible paddy field herbicides against *Echinochloa oryzicola*.[23] The *ortho*-Et(**4**), *ortho*-OPh(**5**), *ortho*-NO_2(**6**), *meta*-CF_3(**7**), *meta*-OMe(**8**), 2,5-disubstituted(**15-17**), 2-Me,6-Et(**20**), 2,6-Et_2(**21**) and 2,6-*iso*-Pr_2(**22**) derivatives were light-dependent. The criteria discriminating between light-dependent and independent compounds are not straightforward. There is a trend, however, that smaller substituents, regardless of their positions and substitution patterns, make the compounds light-independent more often than bulkier groups. The mono-*meta* and 2,5-disubstituted derivatives showed the light-dependent activity, whereas their mono-*para*, 2,4- and 2,6- disubstituted isomers were light-independent. The large *ortho* substituents tended to induce light-dependence as well as decrease in the net herbicidal activity. A somewhat similar specificity in substitution patterns governing the light-dependence has been observed in

Table 1-1 Structure and herbicidal activity of 1-benzyl-4-pyridone-3-carboxanilides.



No.	X_n	mp(°C)	Herbicidal effect[a] Light	Dark	pI_{50}[b]
1	H	176-177	+	+	6.08
2	*o*-Cl	179-180.5	+	+	6.02
3	*o*-Me	170.5-174	+	+	6.15
4	*o*-Et	166-169	+	−	4.30
5	*o*-OPh	213-214.5	+	−	2.27
6	*o*-NO_2	180-186	+	−	2.01
7	*m*-CF_3	174.5-176	+	−	2.76
8	*m*-OMe	175-176	+	−	3.38
9	*p*-F	198-203	+	+	5.88
10	*p*-Cl	169-170	+	+	5.72
11	*p*-Me	216-218.5	+	+	5.11
12	*p*-OMe	174-175	+	+	3.92
13	2,3-Me_2	201-205	+	+	5.77
14	2,4-Me_2	202.5-208.5	+	+	4.43
15	2,5-Cl_2	118-120	+	−	3.30
16	2,5-Me_2	171-175.6	+	−	4.29
17	2-Me,5-Cl	148-156	+	−	4.02
18	2,6-Cl_2	168-172.5	+	+	5.24
19	2,6-Me_2	184-188	+	+	5.47
20	2-Me,6-Et	150.5-153	+	−	4.03
21	2,6-Et_2	142-146.5	+	−	4.08
22	2,6-*iso*-Pr_2	216-219	+	−	2.58

a Scoring by visual evaluation against *Echinochloa oryzicola* (−; no effect , +; severe damage).

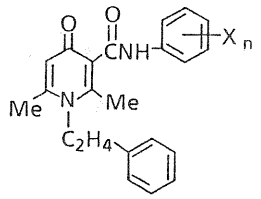
b Log of the reciprocal of the concentration required for the 50% shoot growth inhibition of *Echinochloa oryzicola*.

diphenyl ether type herbicides where *para* and/or *ortho* substituted derivatives are obviously light-dependent but the *meta* isomers are active in the dark as well.[16]

In contrast to 1-*N*-benzyl compounds, all of the 1-*N*-phenethyl and 1-*N*-*n*-butyl derivatives tested here were light-dependent, and their light-dependent activity were higher than that of the benzyl analogs(Tables 1-2, 1-3). Among 1-*N*-phenethyl and butyl derivatives, 2,3- and 2,6-disubstituted compounds such as 2,3-Me_2(**34**, **59**), 2-Me,3-Cl(**33**, **58**), 2-Me,6-Et(**40**, **65**), 2,6-Et_2(**41**, **66**) and 2,6-Cl_2(**37**, **64**) showed activities higher than others in each series with a similar structure-activity pattern. The position-specific effects of the benzene ring substituents were apparently highly important in determining the light-dependent herbicidal potency. In particular, the 1-*N*-phenethyl-2,6-Et_2 derivative (**41**) was most potent, the pI_{50} value being 6.06. At this point, the 2,6-Et_2 substitution was thought to be most favorable for the light-dependent activity.

Fixing the anilide substitution as 2,6-Et_2, the effect of the 1-*N*-substituents (R_1 in Fig.1-2) including fused ring structures (**86** - **88**) on the light-dependent activity was next examined (Table 1-4). The activity of the unsubstituted compound(**69**) was low, but the alkyl (**71** - **76**:from Et to *n*-Hex), phenethyl(**41**), benzyloxy(**85**) and fused ring derivatives(**87**,**88**) showed an activity greater than pI_{50}=4.50. The phenethyl derivative (**41**) was also shown to be

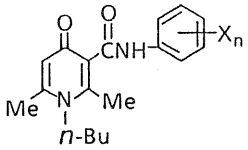
Table 1-2 **Structure and herbicidal activity of 1-phenethyl-4-pyridone-3-carboxanilides.**



No.	X_n	mp(°C)	Herbicidal effect[a]		pI_{50}[a]
			Light	Dark	
23	H	178-181.5	+	—	3.60
24	*o*-Cl	168-170	+	—	5.39
25	*o*-Me	158-159.5	+	—	5.14
26	*o*-Et	145-147	+	—	5.67
27	*o*-OMe	191-195	+	—	3.69
28	*m*-Cl	159.5-162.5	+	—	4.41
29	*m*-Br	171-174	+	—	3.27
30	*m*-CF_3	171-173	+	—	3.00
31	*p*-Cl	181-183.5	+	—	3.47
32	*p*-CH3	203-205	+	—	3.52
33	2-Me,3-Cl	186-188	+	—	5.58
34	2,3-Me_2	189-191.5	+	—	5.43
35	2-Me,5-Cl	177.5-179.5	+	—	4.82
36	2,5-Me_2	155-157	+	—	5.24
37	2,6-Cl_2	182-184.5	+	—	5.82
38	2-Me,6-Cl	173.5-175	+	—	5.44
39	2,6-Me_2	190-192	+	—	5.27
40	2-Me,6-Et	144-146	+	—	5.44
41	2,6-Et_2	113-115	+	—	6.06
42	3,4-Cl_2	196-201	+	—	2.07
43	3,4-Me_2	184-186	+	—	3.83
44	3,5-Me_2	210.3-212.5	+	—	3.31

a See footnotes to Table 1-1.

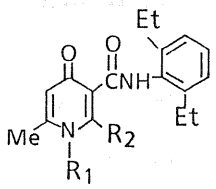
Table 1-3 **Structure and herbicidal activity of 1-butyl-4-pyridone-3-carboxanilides.**



No.	X_n	mp(°C)	Herbicidal effect[a] Light	Dark	pI_{50}[a]
45	H	146.5-148.5	+	−	4.16
46	*o*-Cl	185-187	+	−	4.60
47	*o*-Me	143-145	+	−	4.30
48	*o*-Et	161.5-163.5	+	−	4.21
49	*o*-OMe	158-160	+	−	2.95
50	*o*-NO_2	180-185	+	−	2.44
51	*m*-Cl	140-142	+	−	4.23
52	*m*-CF_3	150-152.5	+	−	3.14
53	*m*-OMe	131-133	+	−	3.26
54	*m*-NO_2	188-192	+	−	4.35
55	*p*-Cl	192-194.5	+	−	3.41
56	*p*-Me	210.5-215	+	−	3.50
57	2,3-Cl_2	197.5-200.5	+	−	3.97
58	2-Me,3-Cl	170-172	+	−	4.67
59	2,3-Me_2	137-139	+	−	4.26
60	2,4-Cl_2	213-215	+	−	4.53
61	2,4-Me_2	160-162	+	−	4.52
62	2,5-Cl_2	162-164	+	−	4.10
63	2,5-Me_2	169-170.5	+	−	4.01
64	2,6-Cl_2	169-171	+	−	4.36
65	2-Me,6-Et	133-135	+	−	4.19
66	2,6-Et_2	110-112	+	−	4.74
67	3,4-Cl_2	174-175.5	+	−	1.62
68	3,4-Me_2	174.8-176.5	+	−	3.24

a See footnotes to Table 1-1.

Table 1-4 **Structure and herbicidal activity of 2',6'-diethyl-4-pyridone-3-carboxanilides.**



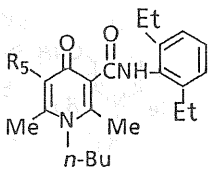
No.	R_1	R_2	mp(°C)	Herbicidal effect[a] Light	Dark	pI_{50}[a]
69	H	-Me	187-189	+	−	3.85
70	-Me	-Me	130-132	+	−	4.49
71	-Et	-Me	115-116	+	−	4.61
72	-*n*-Pr	-Me	116-118	+	−	4.71
66	-*n*-Bu	-Me	110-112	+	−	4.74
73	-*iso*-Bu	-Me	136.5-138	+	−	4.29
74	-*n*-Pent	-Me	96-98	+	−	5.31
75	-*iso*-Pent	-Me	128-130	+	−	5.07
76	-*n*-Hex	-Me	oil	+	−	4.87
77	-*n*-Oct	-Me	oil	+	−	4.01
78	-*n*-Dodecyl	-Me	75-80	+	−	3.25
21	$-CH_2Ph$	-Me	142-146.5	+	−	4.08
79	$-CH_2Ph(p\text{-}Cl)$	-Me	174-176.5	+	−	3.21
41	$-C_2H_4Ph$	-Me	113-115	+	−	6.06
80	$-CH=CH_2$	-Me	135.5-136	+	−	3.90
81	$-CH_2CH=CH_2$	-Me	154-155.8	+	−	3.88
82	$-CH_2C\equiv CH$	-Me	259-261	+	−	3.85
83	-OMe	-Me	126-127	+	−	4.02
84	-O-*n*-Pent	-Me	oil	+	−	4.34
85	$-OCH_2Ph$	-Me	60-62	+	−	4.52
86	$-(CH_2)_3-$		149-151	+	−	3.95
87	$-(CH_2)_4-$		134.5-137	+	−	4.56
88	$-(CH_2)_5-$		149.5-150.5	+	−	5.24

a See footnotes to Table 1-1.

most potent among other R_1-substituted derivatives.

The effects of R_5-substituents were compared for the 1-*N*-butyl derivatives (Table 1-5).

Table 1-5 **Structure and herbicidal activity of 1-butyl-2',6'-diethyl-4-pyridone-3-carboxanilides**



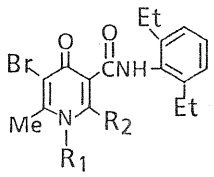
No.	R_3	mp(°C)	Herbicidal effect[a] Light	Dark	pI_{50}[a]
66	H	110-112	+	−	4.74
89	-Cl	125.5-126.5	+	−	5.74
90	-Br	161-162.5	+	−	6.23
91	-Me	111-112	+	−	5.72
92	-Et	117.5-120.5	+	−	5.69
93	$-CH_2Ph$	oil	+	−	2.11
94	-CN	189-191	+	−	5.58
95	-COOH	241-243	+	−	5.56

a See footnotes to Table 1-1.

Except for the benzyl substituent(**93**), the R_5-substitution was shown to enhance the activity of the unsubstituted derivative(**66**). The R_5-Br compound(**90**) was most potent, pI_{50}=6.23. The potency enhancement was about thirty times that of unsubstitued derivative. Since the 5(R_5)-Br substitution was thought to be most favorable for potentiation of the activity, a number of 5-Br substituted derivatives were synthesized (Table 1-6). Among these compounds, the activities of compounds (**97**), (**98**), (**90**), (**99**), (**101**), (**104**), (**105**),

(**106**) and (**107**) were very high, the pI_{50} value being close to 6.0 or above.

Table 1-6 Structure and herbicidal activity of 5-bromo-2',6'-diethyl-4-pyridone-3-carboxanilides



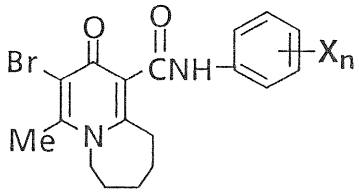
No.	R_1	R_2	mp(°C)	Herbicidal effect[a] Light	Dark	pI_{50}[a]
96	H	-Me	259-261	+	−	5.31
97	-Me	-Me	162-164	+	−	5.98
98	-*n*-Pr	-Me	123-125	+	−	5.94
90	-*n*-Bu	-Me	161-162.5	+	−	6.23
99	-*n*-Pent	-Me	140-141.5	+	−	6.31
100	-*iso*-Pent	-Me	153.5-154.5	+	−	5.46
101	-*n*-Hex	-Me	141-143	+	−	6.06
102	$-CH_2C{\equiv}CH$	-Me	211-214	+	−	5.79
103	$-CH_2Ph$	-Me	173.8-174.9	+	−	5.71
104	$-C_2H_4Ph$	-Me	108-110	+	−	6.82
105	$-(CH_2)_3-$		207-208.5	+	−	6.20
106	$-(CH_2)_4-$		207.5-210	+	−	6.11
107	$-(CH_2)_5-$		178-179.5	+	−	5.97

a See footnotes to Table 1-1.

Since the bicyclic derivatives(**105-107**) with the 5(R_5)-Br substituents were very active, we thought it worthwhile to reexamine the effect of substituents on the anilide moiety. The structural modifications made at positions other than the anilide moiety

might alter the "best" substitution patterns from that observed in the previous set of compounds. Quite a few fused ring compounds were synthesized with R_3=Br and R_1-R_2=$(CH_2)_5$ but with various anilide ring substitutions (Table 1-7).

Table 1-7 Structure and herbicidal activity of 3-bromo-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxanilides



			Herbicidal effect[a]		
No.	X_n	mp(°C)	Light	Dark	pI_{50}[a]
108	H	218.5-220	+	−	4.66
109	o-Cl	252-255	+	−	5.51
110	o-Me	219-221.5	+	−	5.30
111	2,3-Cl_2	228-229	+	−	5.56
112	2-Me,3-Cl	234.5-238	+	−	6.30
113	2,3-Me_2	239-245.5	+	−	6.15
114	2,6-Br_2	207-212	+	−	6.07
115	2,6-Me_2	111-112	+	−	5.43
116	2-Me,6-Et	179.5-180	+	−	6.27
107	2,6-Et_2	178-179.5	+	−	5.97

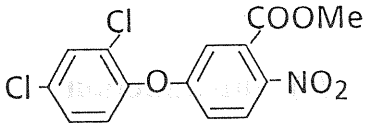
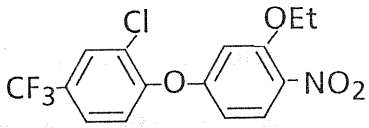
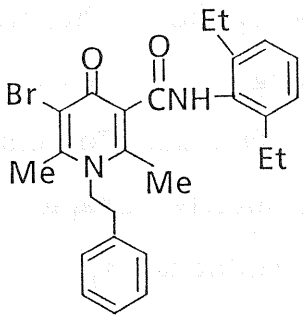
a See footnotes to Table 1-1.

The 2-Me,3-Cl(**112**), 2,3-Me_2(**113**), 2,6-Br_2(**114**), 2-Me,6-Et(**116**) and 2,6-Et_2(**107**) derivatives were among the most potent. The pattern of the activity variations was similar to that observed for the

1-*N*-butyl and phenethyl series.

Among a number of 4-pyridone-3-carboxanilides examined here, 5-bromo-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-1-phenethyl-3-pyridinecarboxanilide(**104**) showed the highest light-dependent herbicidal activity of pI_{50}=6.82. As shown in Table 1-8, the activity was about 10 times higher than that of bifenox and close to that of oxyfluorfen.

Table 1-8 The pI_{50} value of diphenyl ether herbicides and No. 104

Compound	Structure	pI_{50}[a]
bifenox		5.78
oxyfluorfen		7.18
104		6.82

a See footnotes to Table 1-1.

Bifenox and oxyfluorfen are widely used light-dependent herbicides possessing wide spectra. Thus, we selected the compound **104** as a candidate for detailed field trials. The selection of this candidate compound was justified by the quantitative structure-activity analyses, which will be discussed in Chapter 2.

Chapter 2 Quantitative Structure-Activity Relationships of Light-dependent Herbicidal 4-Pyridone-3-Carboxanilides

2-1 Introduction

In chapter 1, we have showed that a number of substituted 4-pyridone-3-carboxanilide derivatives drawn as Fig.2-1 exhibit various degrees of light-dependent herbicidal activity against *Echinochloa oryzicola*. Among various substitution patterns, the 2,6-Et_2 substitution is the most favorable for the light-dependent herbicidal activity at the anilide moiety (Chapter 1). One of the 2,6-Et_2 anilides, where the 1-*N*-substituent (R_1) is phenethyl, R_2=Me and R_5=Br, has been selected as a candidate for the field trials. We have examined as to whether this selection is appropriate by analyzing their structure-activity relationships quantitatively so as to

understand the physicochemical background of the substituent effects. In this chapter, we describe the detail of the analyses based on physicochemical substituent effect on the light-dependent herbicidal activity of a number of compounds having various substitution patterns in the anilide as well as in the pyridone moiety. The variations in the activity were governed by position-specific steric effects of the 4-pyridone ring substituents as well as the inductive electronic effect of the 1-*N*-substituent besides the hydrophobicity and the *ortho* steric effect of the anilide ring substituents. The selection of the above-mentioned candidate compound was confirmed to be relevant in terms of physicochemical substituent effects in this novel series of herbicidal compounds.

2-2 Experimental Procedures

2-2-1 Substituent Parameters

For the hydrophobicity of substituents (X_n in Fig.2-1) at the anilide moiety, the overall π value of substituents estimated from experimentally measured *logP* values of corresponding substituted acetanilides[24] were used. Preliminary examinations showed that the hydrophobicity of pyridone ring substituents was insignificant in governing the herbicidal potency.

For the steric effect of substituents, we preliminarily examined various sets of parameters. Depending on their positions in

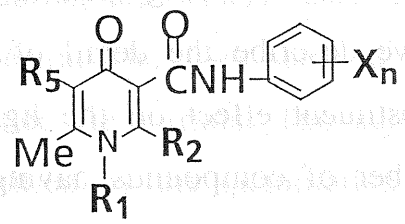


Fig 2-1. The general formula of herbicidal 4-pyridone-3-carboxanilides.

the molecule, different sets of parameters should be used to describe the steric effect on the activity properly. For the steric effect of *ortho* substituents at the anilide moiety, the E_s parameter defined by Taft[25] for alkyl groups and extended by Kutter and Hansch[26] to hetero-atom substituents was used. The E_s parameter is defined so that the greater the size, the more negative is the value. For the effect of 1-*N* substituents, we selected the STERIMOL parameters L and B_5 defined by Verloop[27]. L is the length parameter and B_5 is the "maximum" width parameter. For 1-*N*-substituents cyclized with the R_2-position, the conformation was fixed so that their "maximum width" is somewhat difficult to be defined while the length is well simulated by Et. Unless the "maximum width" of 1-*N*-substituents was estimated as that from the 1-*N*-C_α axis toward the direction perpendicular to the 4-pyridone ring, no relevant correlation was found out. Thus, for the R_1, R_2, $-(CH_2)_n-$ substituents, the "maximum" width to the above defined direction was approximated as the "maximum" width of Me

for $-(CH_2)_3-$ and of Et for $-(CH_2)_{4,5}-$ and regarded as B_5. For the steric effect of substituents at the 5-position of the 4-pyridone ring, MR[28] (molecular refractivity) was found to be the best parameter. In the analyses, the values of L, B_5 and MR relative to those of H were used as ΔL, ΔB_5 and ΔMR. To make the size similar to those of others, the ΔMR parameter was multiplied by 0.1.

The electronic effect of 1-*N* substituents was significant for which the σ_I value defined by Charton[29] was used. σ_I stands for the inductive components of the total electronic effect of substituents.

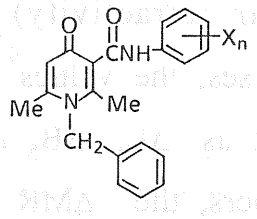
2-3 RESULTS

2-3-1 Effect of Anilide-ring Substituents

First, we analyzed the effect of anilide-ring substituents for compounds where the 1-*N* substituent (R_1) is fixed as benzyl listed in Table 2-1. As shown in Eq.2-1, the light-dependent herbicidal activity was parabolically related to the hydrophobicity in terms of the overall π parameter.

$$pI_{50} = -3.03\,\pi^2 + 3.38\pi + 3.24 \qquad [2\text{-}1]$$
$$(1.44) \quad (1.93) \quad (0.54)$$
$$n=11, \quad s=0.45, \quad r=0.88, \quad F_{2,8}=13.3.$$

Table 2-1 **Structure and herbicidal activity of 1-benzyl-4-pyridone-3-carboxanilides.**



No.	X_n	π	Eso	pI_{50}[a] obsd.	Eq. 2-1 calcd.	Eq. 2-1 (Δ)[b]	Eq.2-13 calcd.	Eq.2-13 (Δ)[b]
4	*o*-Et	0.16	-1.31	4.30	3.70	0.60	3.99	0.31
5	*o*-OPh	1.21	-0.55	2.27	2.90	-0.63	3.14	-0.87
6	*o*-NO_2	-0.22	-2.52	2.01	2.35	-0.34	2.02	-0.01
7	*m*-CF_3	1.40	0.00	2.76	2.04	0.72	2.00	0.76
8	*m*-OMe	0.14	0.00	3.38	3.65	-0.27	2.98	0.40
15	2,5-Cl_2	1.03	-0.97	3.30	3.51	-0.21	3.68	-0.38
16	2,5-Me_2	0.31	-1.24	4.29	4.00	0.29	4.08	0.21
17	2-Me,5-Cl	0.69	-1.24	4.02	4.13	-0.11	4.02	0.00
20	2-Me,6-Et	0.25	-1.31	4.03	3.89	0.14	4.04	-0.01
21	2,6-Et_2	0.69	-1.31	4.08	4.13	-0.05	4.00	0.08
22	2,6-*iso*-Pr_2	1.25	-1.71	2.58	2.73	-0.15	3.06	-0.48

a Log of the reciprocal of the concentration required for the 50% shoot growth inhibition of *Echinochloa oryzicola*.

b Δ, the difference between observed and calculated values.

In Eq.2-1 and the following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, the figures in parentheses are 95 % confidence intervals and

F is the ratio of regression and residual variances. Among 1-*N*-benzyl derivatives, unsubstituted and some substituted derivatives such as *ortho*-Cl, *para*-F, *para*-Me, 2,3-Me_2, 2,6-Me_2 and 2,6-Cl_2 compounds are herbicidal light-independently (Chapter 1). Since the mechanism of action is different from those listed in Table 2-1, they were not included in Eq.2-1. If they were included, the correlation quality was much poorer. Eq.2-1 indicates that there is an optimal hydrophobicity at around 0.56 for the activity.

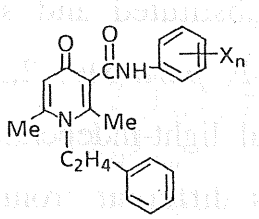
For the effect of anilide-ring substituents of compounds where R_1=phenethyl listed in Table 2-2, Eq.2-2 was formulated, showing that the activity is also related parabolically with the hydrophobic parameter π, although the quality of correlation was not satisfactory. The addition of the π term did not improve the correlation at this stage.

$$pI_{50} = -\underset{(0.42)}{1.04}\,\pi^2 + \underset{(0.42)}{5.11} \qquad [2\text{-}2]$$

$$n=22,\quad s=0.76,\quad r=0.75,\quad F_{1,20}=26.1.$$

The situation is illustrated in Fig.2-2. In elaborating the correlations, we noticed that the activity of most compounds where at least one of the *ortho* positions is occupied are higher than that expressed by the parabola according to Eq.2-2, irrespective of the hydrophobic and electronic properties of substituents.

Table 2-2 **Structures and herbicidal activity of 1-phenethyl-4-pyridone-3-carboxanilides.**



No.	X_n	π	Eso	pI_{50}[a] obsd.	Eq.2-3 calcd.	Eq.2-3 (Δ)[a]	Eq.2-13 calcd.	Eq.2-13 (Δ)[a]
23	H	0.00	0.00	3.60	3.70	-0.10	4.10	-0.50
24	*o*-Cl	0.12	-0.97	5.39	5.11	0.28	5.20	0.19
25	*o*-Me	-0.30	-1.24	5.14	5.06	0.08	4.70	0.44
26	*o*-Et	0.16	-1.31	5.67	5.60	0.07	5.22	0.45
27	*o*-OMe	-0.49	-0.55	3.69	3.82	-0.13	4.07	-0.38
28	*m*-Cl	0.99	0.00	4.41	3.61	0.80	3.96	0.45
29	*m*-Br	1.15	0.00	3.27	3.42	-0.15	3.72	-0.45
30	*m*-CF_3	1.40	0.00	3.00	3.04	-0.04	3.23	-0.23
31	*p*-Cl	0.96	0.00	3.47	3.64	-0.17	4.00	-0.53
32	*p*-CH3	0.47	0.00	3.52	3.88	-0.36	4.32	-0.80
33	2-Me,3-Cl	0.66	-1.24	5.58	5.54	0.04	5.27	0.31
34	2,3-Me_2	0.19	-1.24	5.43	5.52	-0.09	5.26	0.17
35	2-Me,5-Cl	0.69	-1.24	4.82	5.52	-0.70	5.25	-0.43
36	2,5-Me_2	0.31	-1.24	5.24	5.56	-0.32	5.31	-0.07
37	2,6-Cl_2	0.16	-0.97	5.82	5.13	0.69	5.23	0.59
38	2-Me,6-Cl	0.06	-1.24	5.44	5.44	0.00	5.16	0.28
39	2,6-Me_2	-0.09	-1.24	5.27	5.31	-0.04	5.01	0.26
40	2-Me,6-Et	0.25	-1.31	5.44	5.64	-0.20	5.27	0.17
41	2,6-Et_2	0.69	-1.31	6.06	5.62	0.44	5.23	0.83
42	3,4-Cl_2	1.84	0.00	2.07	2.07	0.00	2.02	0.05
43	3,4-Me_2	0.94	0.00	3.83	3.66	0.17	4.02	-0.19
44	3,5-Me_2	1.01	0.00	3.31	3.59	-0.28	3.93	-0.62

a See footnotes to Table 2-1.

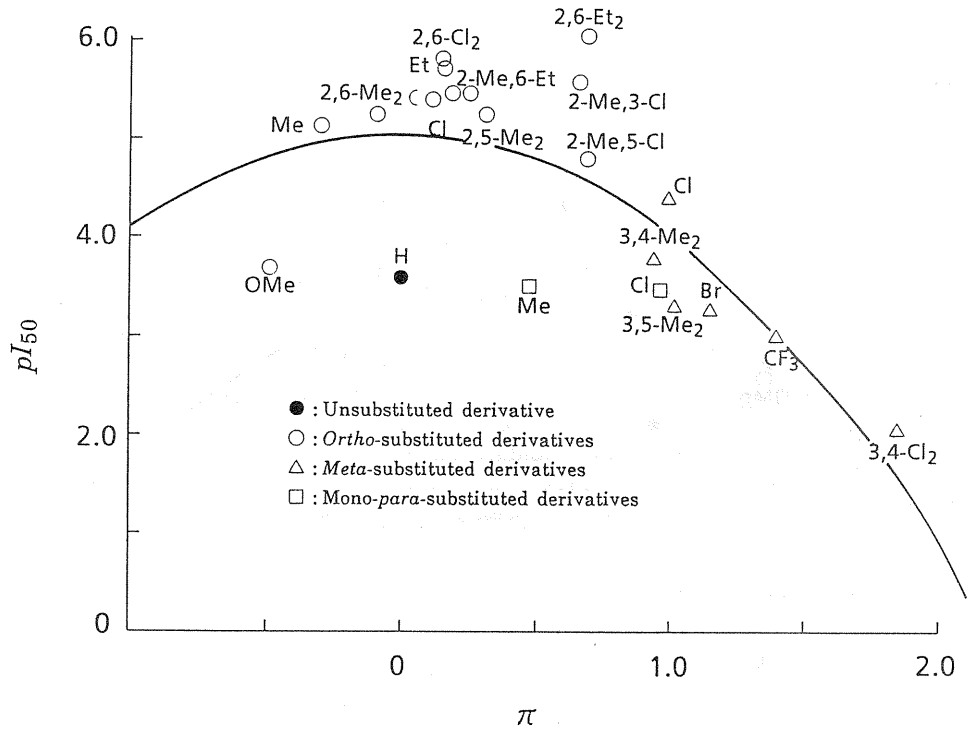


Fig. 2-2 Relationship of pI_{50} of 1-*N*-phenethyl compounds with the π value of anilide substituents.

Thus, participation of steric effects of *ortho* substituents was examined. We found that the addition of the Taft-Kutter-Hansch E_s parameter term for just the bulkier *ortho* substituent, Es^o, fit the situation best as shown in Fig.2-3. In Fig.2-3, the coefficient, 1.4, of the E_s^o term was selected and added to the pI_{50} value so that the plots for the *ortho*-substituted derivatives are aligned parabolically as well as possible. The correlation was formulated as shown in Eq.2-3, the quality of which was much improved from that of Eq.2-2.

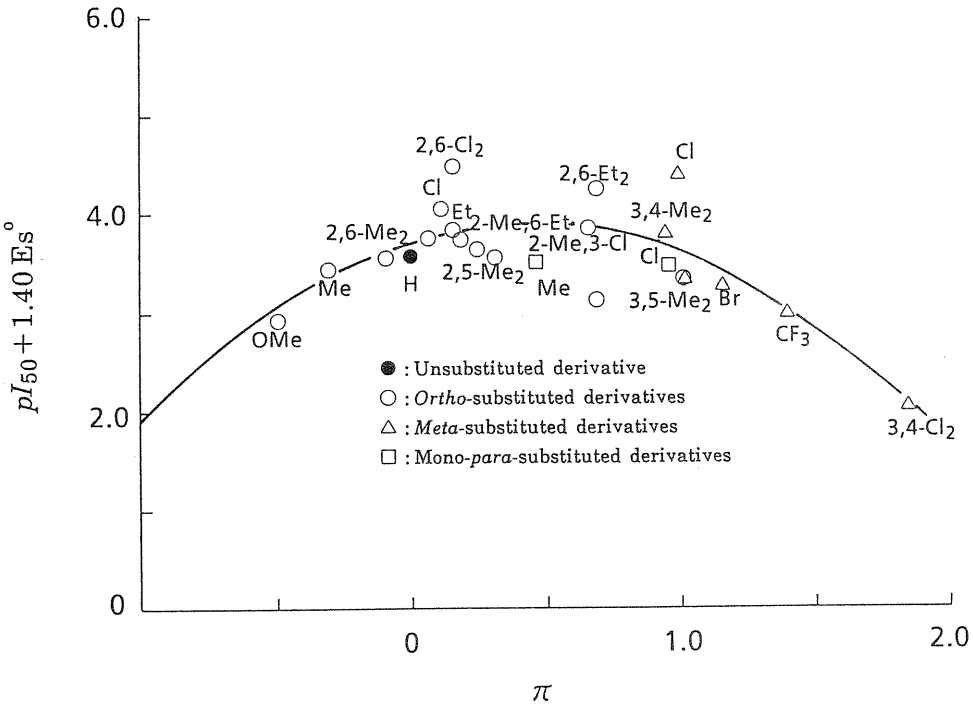


Fig. 2-3 Relationship of pI_{50} of 1-*N*-phenethyl compounds with the π and E_s^o parameters for anilide substituents.

$$pI_{50} = -0.93\,\pi^2 + 0.83\,\pi - 1.37\,E_s^o(\text{large}) + 3.70 \qquad [2\text{-}3]$$

(0.43) (0.61) (0.35) (0.41)

n=22, s=0.36, r=0.95, $F_{3,18}$=62.0.

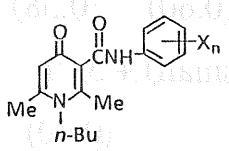
The addition of the E_s^o term for the smaller *ortho*-substituents was not significant as indicated in Eq.2-4.

$$pI_{50} = - 0.92\ \pi^2 + 0.81\ \pi - 1.27\ E_s^{o}(\text{large}) \qquad [2\text{-}4]$$
$$(0.43) \quad (0.60) \quad (0.38)$$
$$- 0.24 E_s^{o}(\text{small}) + 3.71$$
$$(0.38) \qquad (0.40)$$
$$n=22,\ \ s=0.35,\ \ r=0.96,\ \ F_{4,17}=49.0.$$

Eq.2-3 indicates that the bulk of the larger one of *ortho*-substituents is favorable to the activity and the optimum overall hydrophobicity of substituents is about 0.45.

The activity of compounds where the R_1 substituent is *n*-butyl listed in Table 2-3 was analyzed similarly. As shown in Fig.2-4, the pI_{50} seemed also to be parabolically related with overall π value of anilide substituents. The positive deviations of the pI_{50} value for most *ortho*-substituted derivatives from the best fit parabola are similar to those for 1-*N*-phenethyl compounds. The steric effect specific to *ortho*-substituents was expected to be favorable to the activity also in this series. The activity of the *ortho*-NO_2 compound (**50**) having the bulkiest NO_2 group in terms of E_s (-2.52) was, however, lower than predicted. There could be an optimum in the bulk of *ortho* substituents. With these observations, Eq.2-5 was formulated for which Fig.2-5 was drawn.

Table 2-3 **Structure and herbicidal activity of 1-butyl-4-pyridone-3-carboxanilides.**



No.	X_n	π	Es^o	pI_{50}[a] obsd.	Eq.2-5 calcd.	Eq.2-5 (Δ)[a]	Eq.2-13 calcd.	Eq.2-13 (Δ)[a]
45	H	0.00	0.00	4.16	3.63	0.53	3.45	0.71
46	*o*-Cl	0.12	-0.97	4.60	4.38	0.22	4.55	0.05
47	*o*-Me	-0.30	-1.24	4.30	3.77	0.53	4.05	0.25
48	*o*-Et	0.16	-1.31	4.21	4.35	-0.14	4.57	-0.36
49	*o*-OMe	-0.49	-0.55	2.95	3.29	-0.34	3.43	-0.48
50	*o*-NO_2	-0.22	-2.52	2.44	2.47	-0.03	2.61	-0.17
51	*m*-Cl	0.99	0.00	4.23	3.61	0.62	3.31	0.92
52	*m*-CF_3	1.40	0.00	3.14	2.93	0.21	2.59	0.55
53	*m*-OMe	0.14	0.00	3.26	3.76	-0.50	3.57	-0.31
54	*m*-NO_2	0.31	0.00	4.35	3.87	0.48	3.65	0.70
55	*p*-Cl	0.96	0.00	3.41	3.64	-0.23	3.35	0.06
56	*p*-Me	0.47	0.00	3.50	3.91	-0.41	3.67	-0.17
57	2,3-Cl_2	0.93	-0.97	3.97	4.31	-0.34	4.39	-0.42
58	2-Me,3-Cl	0.66	-1.24	4.67	4.47	0.20	4.62	0.05
59	2,3-Me_2	0.19	-1.24	4.26	4.40	-0.14	4.61	-0.35
60	2,4-Cl_2	1.02	-0.97	4.53	4.20	0.33	4.27	0.26
61	2,4-Me_2	0.30	-1.24	4.52	4.46	0.06	4.66	-0.14
62	2,5-Cl_2	1.03	-0.97	4.10	4.19	-0.09	4.26	-0.16
63	2,5-Me_2	0.31	-1.24	4.01	4.46	-0.45	4.66	-0.65
64	2,6-Cl_2	0.16	-0.97	4.36	4.41	-0.05	4.58	-0.22
65	2-Me,6-Et	0.25	-1.31	4.19	4.41	-0.22	4.62	-0.43
66	2,6-Et_2	0.69	-1.31	4.74	4.43	0.31	4.59	0.15
67	3,4-Cl_2	1.84	0.00	1.62	1.76	-0.14	1.37	0.25
68	3,4-Me_2	0.94	0.00	3.24	3.67	-0.43	3.37	-0.13

a See footnotes to Table 2-1.

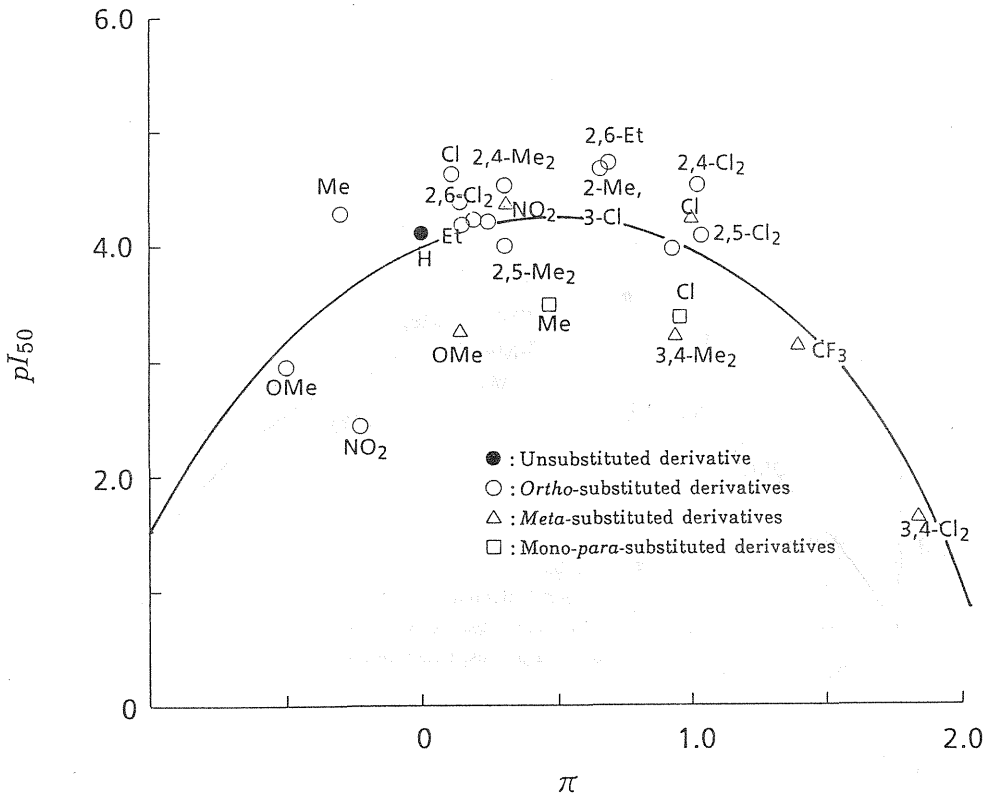


Fig. 2-4 Relationship of pI_{50} of 1-*N*-butyl compounds with the π value of anilide substituents

$$pI_{50} = -1.17\,\pi^2 + 1.15\,\pi - 0.64\,Es^{o2} - 1.27\,Es^{o} + 3.63 \qquad [2\text{-}5]$$

(0.44) (0.62) (0.29) (0.59) (0.36)

n=24, s=0.38 r=0.90, $F_{4,19}$=19.1.

The optimal π and E_s^o values are estimated as 0.49 and -0.99 respectively. The addition of the E_s^{o2} term to Eq.2-3 for the 1-*N*-phenethyl compounds did not improve the correlation. This

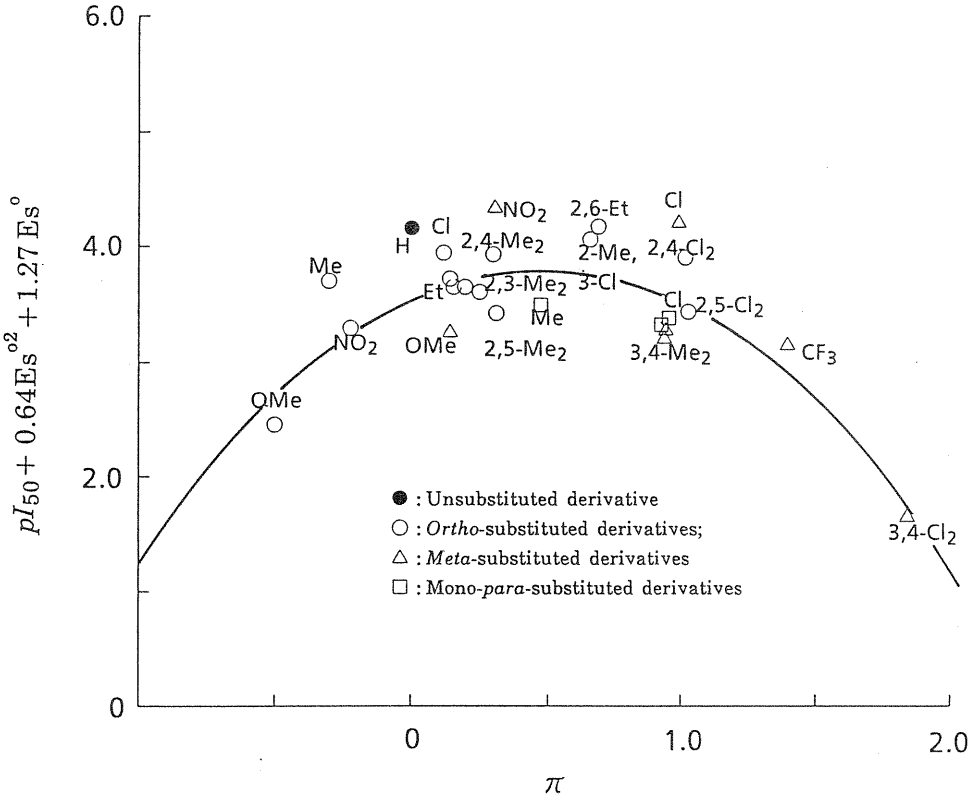
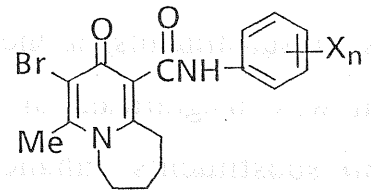


Fig. 2-5 Relationship of pI_{50} of 1-*N*-butyl compounds with the π and E_s^{o} parameters for anilide substituents.

could be due to the fact that variations in the E_s^{o} value is narrower that in 1-*N*-butyl compounds.

For the activity of bicyclic pyridone derivatives with Br at the R_5-position (Fig.2-1) listed in Table 2-4, the same combination of parameters as that in Eq.2-3 afforded the best correlation as Eq.2-6.

Table 2-4 **Structure and herbicidal activity of 3-bromo-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxanilides.**



No.	X_n	π	Eso	pI_{50}[a] obsd.	Eq.2-6 calcd.	Eq.2-6 (Δ)[a]	Eq.2-13 calcd.	Eq.2-13 (Δ)[a]
108	H	0.00	0.00	4.66	4.62	0.04	4.78	-0.12
109	o-Cl	0.12	-0.97	5.51	5.70	-0.19	5.89	-0.38
110	o-Me	-0.30	-1.24	5.30	5.18	0.12	5.38	-0.08
111	2,3-Cl_2	0.93	-0.97	5.56	5.58	-0.02	5.72	-0.16
112	2-Me,3-Cl	0.66	-1.24	6.30	6.11	0.19	5.95	0.35
113	2,3-Me_2	0.19	-1.24	6.15	6.03	0.12	5.94	0.21
114	2,6-Br_2	0.37	-1.16	6.07	6.07	0.00	6.01	0.06
115	2,6-Me_2	-0.09	-1.24	5.43	5.64	-0.21	5.69	-0.26
116	2-Me,6-Et	0.25	-1.31	6.27	6.14	0.13	5.95	0.32
107	2,6-Et_2	0.69	-1.31	5.97	6.16	-0.19	5.92	0.05

a See footnotes to Table 2-1.

$$pI_{50} = -1.62\,\pi^2 + 1.55\,\pi - 0.95\,Es^o + 4.62 \qquad [2\text{-}6]$$

$$(1.05) \quad (0.79) \quad (0.38) \quad (0.43)$$

$$n=10, \quad s=0.18, \quad r=0.96, \quad F_{3,6}=22.9.$$

The optimum π value was estimated as 0.48.

The correlations represented by Eqs.2-1, 2-3, 2-5 and 2-6 are similar to each other in that they have an optimum π value in a very narrow range of 0.45-0.56 for the anilide substituents irrespective of variations in substituents at the 1-*N* and R_5 positions. Although the E_s^o term was insignificant in Eq.2-1, there is a trend that the bulkier *ortho* substituents enhance the activity up to a certain point beyond which the activity decreases as observed in the *ortho*-NO_2 derivative (**6**) from the residuals in Table 2-1. The low activity of the *ortho*-OPh compound (**5**) may be attributed to its overall bulk which is not represented by the E_s value appropriately. The similarity in structure-activity pattern among the four series of compounds suggested that the correlations could be combined and analyzed together. Accordingly, Eq.2-13 was formulated, using I-ben, I-phe and I-ring as the indicator variables to differentiate the compound series. I-ben is equal to unity for R_1=benzyl, as is I-phe for R_1=phenethyl, and I-ring for bicyclic pyridone derivatives where R_1-R_2=$(CH_2)_5$ and R_5=Br, respectively; the 1-*N*- butyl series was used as the reference (I values for the 1-*N*-butyl compounds are zero). The stepwise development of Eq.[13] justified statistically is shown in Table 2-5.

Table 2-5 Development of Eq.2-13 for the Light-dependent Herbicidal Activity of 4-Pyridone-3-carboxanilides

Eq.No.	π^2	l-ring	l-phe	π	Eso	Eso^2	l-ben	Const	n[a]	s[b]	r[c]	$F_{X,Y}$[d]
2-7	-0.88							4.74	67	0.94	0.57	$F_{1,65} = 31.28$
	(0.32)[e]							(0.28)				
2-8	-0.76	1.42						4.46	67	0.80	0.72	$F_{1,64} = 25.94$
	(0.27)	(0.56)						(0.26)				
2-9	-0.76	1.74	0.81					4.15	67	0.72	0.79	$F_{1,63} = 17.34$
	(0.24)	(0.52)	(0.39)					(0.28)				
2-10	-1.53	1.76	0.84	1.20				3.95	67	0.65	0.83	$F_{1,62} = 14.54$
	(0.46)	(0.47)	(0.35)	(0.63)				(0.27)				
2-11	-1.45	1.73	0.90	1.27	-0.33			3.58	67	0.62	0.85	$F_{1,61} = 6.00$
	(0.62)	(0.46)	(0.60)	(0.61)	(0.27)			(0.40)				
2-12	-1.15	1.51	0.81	0.92	-1.78	-0.84		3.37	67	0.46	0.92	$F_{1,60} = 50.17$
	(0.35)	(0.35)	(0.26)	(0.46)	(0.46)	(0.24)		(0.31)				
2-13	-1.16	1.33	0.65	1.01	-1.82	-0.81	-0.58	3.45	67	0.42	0.94	$F_{1,59} = 13.17$
	(0.32)	(0.33)	(0.25)	(0.43)	(0.42)	(0.22)	(0.32)	(0.28)				

a) Number of compounds used for correlations. b) Standard deviation. c) Correlation coefficient. d) F statistic for significance of the addition of variables. X: The number of independent variables added at each step of the development, Y: n-m-1, m being the total number of independent variables in the developed equation. $F_{1,60}(\alpha = 0.025) = 5.29$, $F_{1,60}(\alpha = 0.005) = 8.49$. e) Figures in parentheses are 95% confidence intervals.

$$pI_{50} = -1.16\,\pi^2 + 1.01\,\pi - 0.81\,E_s^{o2} - 1.82\,E_s^{o} \qquad [2\text{-}13]$$
$$(0.32) \quad (0.43) \quad (0.22) \quad (0.42)$$
$$-0.58\ \text{I-ben} + 0.65\ \text{I-phe} + 1.33\ \text{I-ring}$$
$$(0.32) \quad (0.25) \quad (0.33)$$
$$+3.45$$
$$(0.28)$$
$$n=67,\ s=0.42,\ r=0.94,\ F_{7,59}=59.7.$$

The π and E_s^o parameter terms are all significant. In Table 2-6, the internal correlation among independent variables for sixty-seven derivatives was shown to be insignificant.

Table 2-6 Correlation coefficient matrix (r) for the parameters used in Eq. 2-13.

	π^2	π	Es^{o2}	Es^{o}	I-ben	I-phe	I-ring
π^2	1.00						
π	0.88	1.00					
Es^{o2}	-0.34	-0.37	1.00				
Es^{o}	0.44	0.42	-0.90	1.00			
I-ben	0.08	0.12	0.23	-0.19	1.00		
I-phe	0.05	0.03	-0.17	0.16	-0.31	1.00	
I-ring	-0.18	-0.16	0.06	-0.15	-0.19	-0.29	1.00

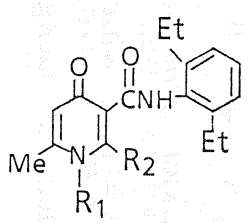
The calculated pI_{50} value of each derivative is listed in Tables 2-1, 2-2, 2-3 and 2-4. The negative I-ben term indicates that the 1-

N-benzyl substitution is unfavorable to the activity relative to the 1-*N*-butyl substitution, but positive I-phe and I-ring terms show that the 1-*N*-phenethyl substitution and the cyclization of the 1-*N*-substituent with the R_2-position are more favorable to the activity than the 1-*N*-butyl. From the π and π^2 terms, the optimum hydrophobicity of anilide-ring substituents is evaluated as 0.44. Since the π value does not include the hydrophobicity of "1-*N*-substituents" and R_5-Br, it does not represent the molecular hydrophobicity. In this respect, the parabolic π terms are unlikely to be connected with the transport process to the site of action in the plant body. An optimal steric condition for the bulkier *ortho* substituent at the anilide moiety is located at about E_s=-1.12 which nearly corresponds to that of Et. But the physicochemical background of the indicator variable terms was obscure and the effects of 1-*N* and R_5 substituents were not separated.

2-3-2 Effect of Pyridone-ring Substituents

The effect of 1-*N* substituents were analyzed with use of compounds where the anilide-ring substitution was fixed as 2,6-Et_2 and the R_5 position was unoccupied listed in Table 2-7. In this series of compounds, the 1-*N* phenethyl compound (**41**) showed the highest activity. With single parameters, We did not find out any correlation significant above the 95% level. At the best, the activity is slightly related with the STERIMOL length parameter

Table 2-7 Structures and herbicidal activity of 2',6'-diethyl-4-pyridone-3-carboxanilides



			Substituent Parameters							pI_{50}				
			X n		R1			R5	obsd	Eq.2-16		Eq.2-26	
No.	R_1	R_2	π	Es°	σ_I	ΔB_5	ΔL[a]	ΔMR		calcd	(△)[b]	calcd	(△)[b]
69	H	Me	0.69	-1.31	0.00	0.00	0.00	0	3.85	4.36	-0.51	4.39	-0.54
70	Me	Me	0.69	-1.31	-0.01	1.04	0.81	0	4.49	4.35	0.14	4.37	0.12
71	Et	Me	0.69	-1.31	-0.01	2.17	2.05	0	4.61	4.44	0.18	4.41	0.20
72	*n*-Pr	Me	0.69	-1.31	-0.01	2.49	2.86	0	4.71	4.62	0.09	4.52	0.19
66	*n*-Bu	Me	0.69	-1.31	-0.01	3.54	4.11	0	4.74	4.74	0.00	4.58	0.16
73	*iso*-Bu	Me	0.69	-1.31	-0.01	3.45	2.86	0	4.29	4.32	-0.03	4.33	-0.04
74	*n*-Pent	Me	0.69	-1.31	-0.03[c]	3.94	4.91	0	5.31	4.95	0.36	4.70	0.61
75	*iso*-Pent	Me	0.69	-1.31	-0.03[c]	3.54	4.11	0	5.07	4.79	0.28	4.61	0.46
76	*n*-Hex	Me	0.69	-1.31	-0.03	4.96	6.16	0	4.87	5.07	-0.20	4.77	0.10
77	*n*-Octyl	Me	0.69	-1.31	-0.04[d]	5.85	3.76	0	4.01	3.96	0.05	4.08	-0.07
78	*n*-Dodecyl	Me	0.69	-1.31	-0.04[d]	8.39	5.23	0	3.25	3.69	-0.44	3.89	-0.64

21	CH_2Ph	Me	0.69	-1.31	0.03	5.02	2.56	0	4.08	3.63	0.45	3.89	0.19
79	CH2Ph(*p*-Cl)	Me	0.69	-1.31	0.04	6.44	3.23	0	3.21	3.40	-0.19	3.74	-0.53
41	C_2H_4Ph	Me	0.69	-1.31	0.02	2.58	6.27	0	6.06	5.74	0.32	5.20	0.86
80	$CH=CH_2$	Me	0.69	-1.31	0.11	2.09	2.23	0	3.90	4.24	-0.34	4.30	-0.40
81	CH2CH=CH2	Me	0.69	-1.31	0.02	3.20	3.29	0	3.88	4.48	-0.60	4.43	-0.55
82	CH2CCH	Me	0.69	-1.31	0.14	3.49	1.93	0	3.85	3.62	0.23	3.91	-0.06
83	OMe	Me	0.69	-1.31	0.30	2.07	1.92	0	4.02	3.68	0.34	3.97	0.05
84	O-*n*-Pent	Me	0.69	-1.31	0.28	4.81	6.05	0	4.34	4.34	0.00	4.35	-0.01
85	O-CH2Ph	Me	0.69	-1.31	0.43	2.50	6.14	0	4.52	4.74	-0.22	4.62	-0.10
86	$-(CH2)_3-$		0.69	-1.31	-0.01[e]	1.04[f]	2.05[d]	0	3.95	4.79	-0.84	4.64	-0.69
87	$-(CH2)_4-$		0.69	-1.31	-0.01[e]	2.17[g]	2.05[d]	0	4.56	4.44	0.13	4.41	0.15
88	$-(CH2)_5-$		0.69	-1.31	-0.01[e]	2.17[g]	2.05[d]	0	5.24	4.44	0.80	4.41	0.83

a) Taken from a brochure distributed by Dr. Verloop. b) Δ, the difference between observed and calculated values. c) Taken as being equivalent to the value of *n*-Hex. d) Taken as being equivalent to the value of *n*-Hep. e) Taken as being equivalent to the value of Et. f) Taken as being equivalent to the maximum width of Me g) Taken as being equivalent to the maximum width of Et

L, as shown in Eq.2-14.

$$pI_{50} = 0.13\,\Delta L + 3.95 \qquad [2\text{-}14]$$

(0.16) (0.60)

n=23, s=0.64, r=0.35, $F_{1,21}$=2.88

The situation is illustrated in Fig.2-6.

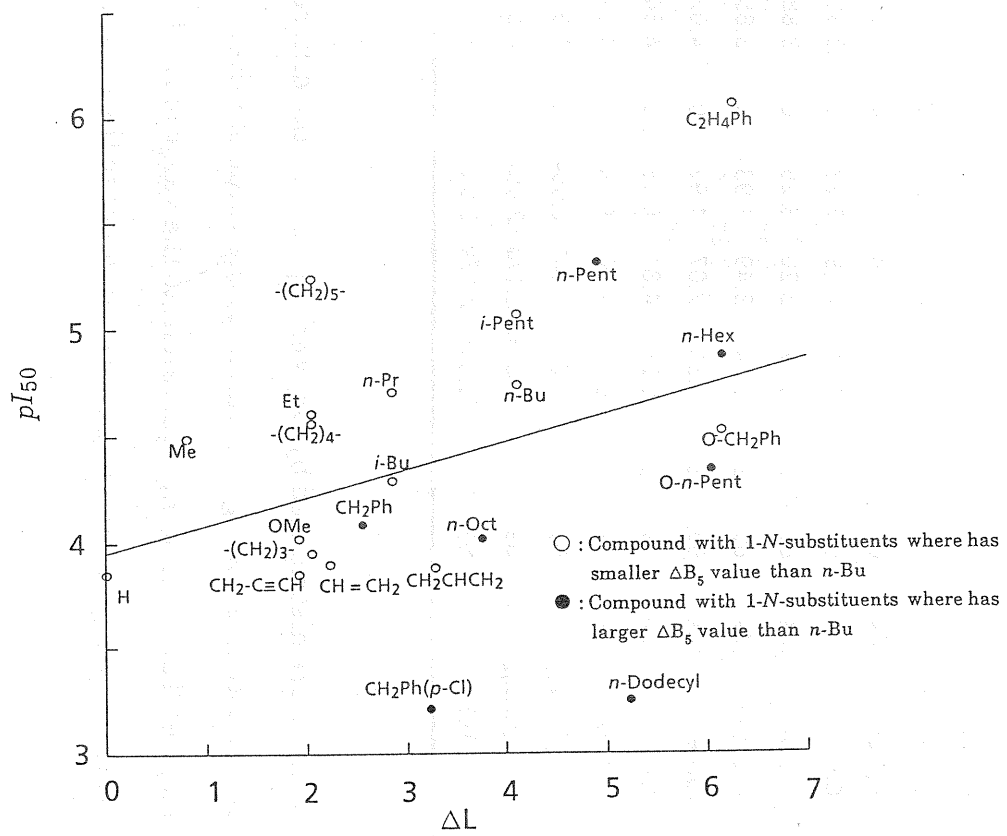


Fig. 2-6 Relationship of pI_{50} of 3-(2',6'-diethylanilide) compounds with the ΔL value of 1-*N*-Substituents.

It was noted that the activity of most compounds having 1-*N* substituents the B_5 value for the maximum width of which is smaller than that of *n*-butyl such as phenethyl and R_1,R_2=-$(CH_2)_5$- are higher than that expressed by the line according to Eq.2-14, irrespective of the hydrophobic property of the substituents. On the other hand, the activity of the compounds having substituents with the ΔB_5 value greater than that of *n*-butyl such as -CH_2Ph(*para*-Cl) and -*n*-dodecyl are lower than predicted by Eq.2-14. Thus, the participation of the steric width effect of R_1 substituents was examined. The correlation was formulated as shown in Eq.2-15. The quality was much improved from that of Eq.2-14, although it is still not satisfactory.

$$pI_{50} = 0.29\,\Delta L - 0.26\,\Delta B_5 + 4.34 \qquad [2\text{-}15]$$
$$\qquad\quad (0.14) \quad (0.14) \quad (0.47)$$
$$n=23,\ s=0.49,\ r=0.71,\ F_{2,21}=10.09$$

Fig.2-7 illustrates the correlation where the pI_{50} value is plotted against the value of [ΔL- ΔB_5] of 1-*N*-substituents. Fig.2-7 suggests that the activity of compounds having alkyl and aralkyl is higher but that with alkoxy, vinyl and propargyl is lower than expected. To discriminate between these two types of substituents, the σ_I parameter for the inductive electronic effect was selected.

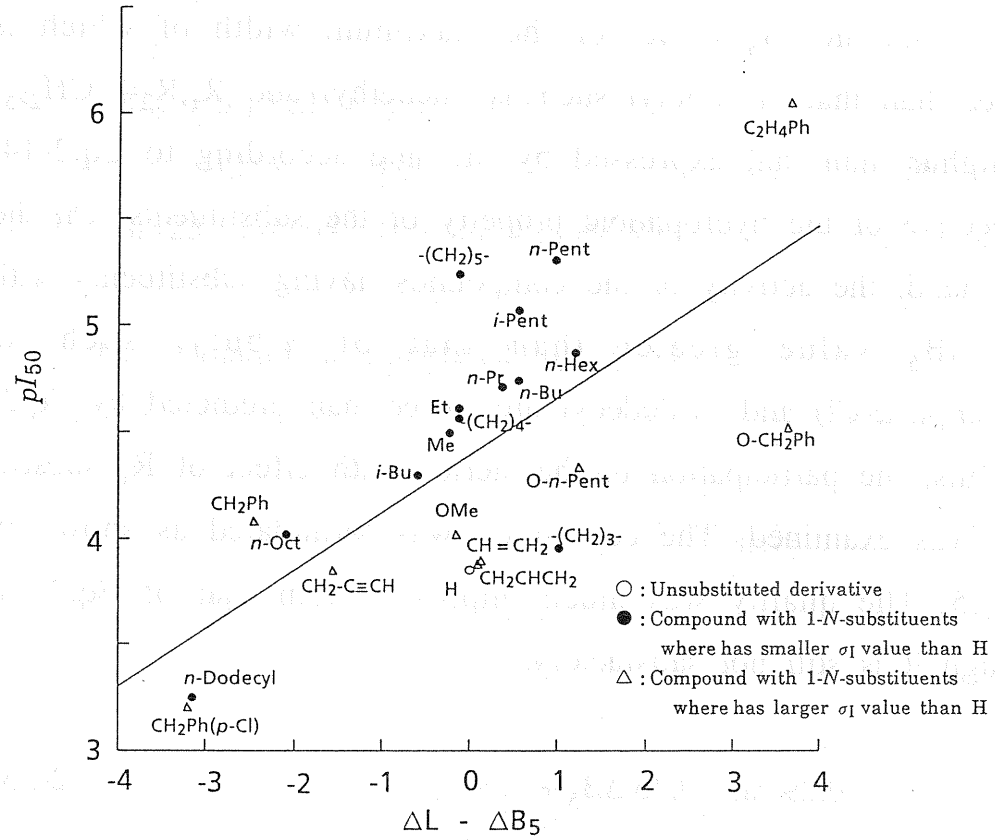


Fig. 2-7 Relationship of pI_{50} of 3-(2',6'-diethylanilide) compounds with the ΔL and ΔB_5 parameters for 1-*N*-Substituents.

With addition of the σ_I term, the correlation was satisfactory as shown in Eq.2-16.

$$pI_{50} = 0.36\,\Delta L - 0.31\,\Delta B_5 - 2.38\,\sigma_I + 4.36 \qquad [2\text{-}16]$$

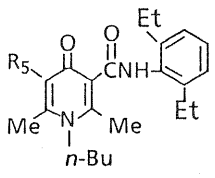
$$(0.13) \quad (0.12) \quad (1.57) \quad (0.42)$$

$$n=23, \quad s=0.41, \quad r=0.82, \quad F_{3,19}=13.10$$

Eq.2-16 shows that electron donating 1-*N* substituents having longer and narrower dimensions are favorable to the activity. The phenethyl group with $\Delta L=6.27$, $\Delta B_5=2.58$ and $\sigma_I=0.02$ was confirmed to be the most suitable 1-*N*-substituent within the range of structures covered in this study.

For compounds in Table 2-8 where R_1 is fixed as *n*-butyl with the 2,6-diethyl anilide structure, the activity was best correlated parabolically with the ΔMR parameter.

Table 2-8 Structures and herbicidal activity of 1-butyl-2',6'-diethyl-4-pyridone-3-carboxanilides.



		Substituent Parameters						pI_{50}				
		X_n		R_1			R_5	obsd	Eq.2-17	Eq.2-26		
No.	R_5	π	Eso	σ_I	ΔB_5[a]	ΔL[a]	ΔMR		calcd	(Δ)[a]	calcd	(Δ)[a]
66	H	0.69	-1.31	-0.01	3.54	4.11	0.000	4.74	4.78	-0.04	4.58	0.16
89	Cl	0.69	-1.31	-0.01	3.54	4.11	0.500	5.74	5.64	0.10	5.69	0.05
90	Br	0.69	-1.31	-0.01	3.54	4.11	0.785	6.23	5.89	0.34	6.04	0.19
91	Me	0.69	-1.31	-0.01	3.54	4.11	0.462	5.72	5.60	0.12	5.63	0.09
92	Et	0.69	-1.31	-0.01	3.54	4.11	0.927	5.69	5.94	-0.25	6.14	-0.45
93	CH_2Ph	0.69	-1.31	-0.01	3.54	4.11	2.898	2.11	2.11	0.00	2.11	0.00
94	CN	0.69	-1.31	-0.01	3.54	4.11	0.530	5.58	5.68	-0.10	5.74	-0.16
95	COOH	0.69	-1.31	-0.01	3.54	4.11	0.590	5.56	5.74	-0.18	5.83	-0.27

a See footnotes to Table 2-7.

$$pI_{50} = -1.10\,\Delta MR^2 + 2.27\,\Delta MR + 4.78 \qquad [2\text{-}17]$$

(0.33) (1.09) (0.52)

n=8, s=0.22, r=0.99, $F_{2,5}$=116.91

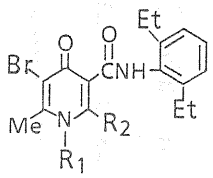
Eq.2-17 indicates that the optimal ΔMR is about 1.00 which is not far apart from that of Br (ΔMR=0.785).

2-3-3 Analysis for Entire Series of Pyridone-carboxanilides

The effects of 1-*N* and R_5 substituents were analyzed with only physicochemical substituent parameters as shown in Eqs.2-16 and 2-17. They and the effects of anilide substituents were expected to be additive since some compounds were included in both Eq.2-13 and Eq.2-16 or -17, simultaneously. The correlation could be combined and analyzed together for the whole series of 4-pyridone-3-carboxanilides by use of only physicochemical substituent parameters with additional compounds listed in Table 2-9 not included in the above analyses.

As expected, Eq.2-26 was formulated with the same physicochemical parameters as those included in Eq.2-13, 2-16 and 2-17 for the combined set of compounds.

Table 2-9 Structures and herbicidal activity of 5-bromo-2',6'-diethyl-4-pyridone-3-carboxanilides



			Substituent Parameters						pI_{50}		
			X n			R_1		R_5	obsd	Eq.2-26	
No.	R_1	R_2	π	Eso	σ_I	ΔB_5[a]	ΔL[a]	ΔMR		calcd	(Δ)[a]
96	H	Me	0.69	-1.31	0.00	0.00	0.00	0.785	5.31	5.85	-0.54
97	Me	Me	0.69	-1.31	-0.01	1.04	0.81	0.785	5.98	5.83	0.15
98	*n*-Pr	Me	0.69	-1.31	-0.01	2.49	2.86	0.785	5.94	5.98	-0.04
99	*n*-Pent	Me	0.69	-1.31	-0.03[a]	3.94	4.91	0.785	6.31	6.16	0.15
100	*iso*-Pent	Me	0.69	-1.31	-0.03[a]	3.54	4.11	0.785	5.46	6.07	-0.61
101	*n*-Hex	Me	0.69	-1.31	-0.03	4.96	6.16	0.785	6.06	6.23	-0.17
102	CH_2CCH	Me	0.69	-1.31	0.14	3.49	1.93	0.785	5.79	5.37	0.42
103	CH_2Ph	Me	0.69	-1.31	0.03	5.02	2.56	0.785	5.71	5.35	0.36
104	C_2H_4Ph	Me	0.69	-1.31	0.02	2.58	6.27	0.785	6.82	6.66	0.16
105	$-(CH_2)_3-$		0.69	-1.31	-0.01[a]	1.04[a]	2.05[a]	0.785	6.20	6.10	0.10
106	$-(CH_2)_4-$		0.69	-1.31	-0.01[a]	2.17[a]	2.05[a]	0.785	6.11	5.87	0.24

a See footnotes to Table 2-7.

$$pI_{50} = -1.13\,\pi(X)^2 + 0.96\,\pi(X) - 0.80\,Es^{o}(X)^2 - 1.79\,E_s^{o}(X)$$
$$(0.29) \qquad (0.37) \qquad (0.20) \qquad (0.38)$$
$$+ 0.22\,\Delta L(R_1) - 0.20\,\Delta B_5(R_1) - 1.38\,\sigma_I(R_1)$$
$$(0.052) \qquad (0.066) \qquad (1.28)$$
$$-1.28\,\Delta MR(R_5)^2 + 2.87\,\Delta MR(R_5) + 3.29 \qquad [2\text{-}26]$$
$$(0.18) \qquad (0.38) \qquad (0.39)$$
$$n=105,\ s=0.40,\ r=0.94,\ F_{9,95}=82.76$$

The stepwise development of Eq.2-26 justified statistically for 105 derivatives devoid of duplications is shown in Table 2-10. The physicochemical parameters of each substituent used in the analyses are included in Tables 2-7 to 2-9 and 2-11. As summarized in Table 2-12, the intercorrelation between the independent variables for 105 derivatives is shown to be insignificant except for that between singular and squared parameters. The calculated pI_{50} value of each derivative is listed in Tables 2-7 to 2-9 and 2-11.

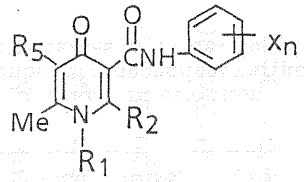
In Eq. 2-26, the signs X, R_1 and R_5 mean that the parameter terms concerned are specific to substituents on the benzene ring (X_n) and 4-pyridone ring (R_1, R_5), respectively. The fact that the regression coefficient value of each term in Eq.2-26 approximately coincides with that of corresponding term in Eqs.2-13, 2-16 and 2-17 shows that the indicator variable terms in Eq.2-13 are indeed replaced by and separated into parameter terms for position

Table 2-10 Development of Eq.2-26 for the Light-dependent Herbicidal Activity of 4-Pyridone-3-carboxanilides

Eq.No	$\pi(X)^2$	$\Delta MR(R_5)$	$\Delta MR(R_5)2$	$\pi(X)$	$\Delta L(R_1)$	$\Delta B_5(R_1)$	$Es^o(X)$	$Es^o(X)^2$	$\sigma_I(R_1)$	Const	n[a]	s[b]	r[c]	$F_{X,Y}$[d]
2-18	-0.90									4.98	105	1.02	0.46	$F_{1,103} = 27.80$
	(0.34)[e]									(0.26)				
2-19	-0.83	0.93								4.74	105	0.95	0.57	$F_{1,102} = 17.67$
	(0.32)	(0.44)								(0.27)				
2-20	-0.75	3.14	-1.33							4.51	105	0.71	0.79	$F_{1,101} = 79.42$
	(0.24)	(0.59)	(0.30)							(0.21)				
2-21	-1.49	3.00	-1.30	1.14						4.27	105	0.67	0.82	$F_{1,100} = 15.91$
	(0.43)	(0.56)	(0.28)	(0.57)						(0.23)				
2-22	-1.60	3.43	-1.45	1.30	0.18					3.46	105	0.60	0.86	$F_{1,99} = 23.59$
	(0.39)	(0.53)	(0.26)	(0.52)	(0.075)					(0.39)				
2-23	-1.63	3.19	-1.37	1.37	0.19	-0.19				4.06	105	0.56	0.88	$F_{1,98} = 18.58$
	(0.36)	(0.50)	(0.24)	(0.48)	(0.069)	(0.089)				(0.45)				
2-24	-1.43	3.09	-1.35	1.30	0.22	-0.22	-0.41			3.56	105	0.52	0.90	$F_{1,97} = 14.84$
	(0.35)	(0.47)	(0.23)	(0.45)	(0.066)	(0.084)	(0.21)			(0.49)				
2-25	-1.12	2.94	-1.30	0.92	0.21	-0.20	-1.76	-0.80		3.30	105	0.41	0.94	$F_{1,96} = 58.55$
	(0.29)	(0.38)	(0.18)	(0.37)	(0.052)	(0.067)	(0.39)	(0.21)		(0.40)				
2-26	-1.13	2.87	-1.28	0.96	0.22	-0.20	-1.79	-0.80	-1.38	3.29	105	0.40	0.94	$F_{1,95} = 4.57$
	(0.29)	(0.38)	(0.18)	(0.37)	(0.052)	(0.066)	(0.38)	(0.20)	(1.28)	(0.39)				

a) Number of compounds used for correlations. b) Standard deviation. c) Correlation coefficient. d) F statistic for significance of the addition of variables. X: The number of independent variables added at each step of the development, Y: n-m-1, m being the total number of independent variables in the developed equation. $F_{1,120}(\alpha = 0.05) = 3.92$ e) Figures in parentheses are 95% confidence intervals

Table 2-11 Structures and herbicidal activity of 4-pyridone-3-carboxanilides



					Substituent Parameters						pI_{50}				
					Xn		R1			R5	obsd	Eq.2-13		Eq.2-26	
No.	R_1	R_2	R_5	Xn	π	Eso	σ_I	ΔB_5[a]	ΔL[a]	ΔMR		calcd	(Δ)[a]	calcd	(Δ)[a]
4	CH_2Ph	Me	H	o-Et	0.16	-1.31	0.03	5.02	2.56	0	4.30	3.99	0.31	3.89	0.41
5	CH_2Ph	Me	H	o-OPh	1.21	-0.55	0.03	5.02	2.56	0	2.27	3.14	-0.87	3.04	-0.77
6	CH_2Ph	Me	H	o-NO_2	-0.22	-2.52	0.03	5.02	2.56	0	2.01	2.02	-0.01	1.96	0.05
7	CH_2Ph	Me	H	m-CF_3	1.40	0.00	0.03	5.02	2.56	0	2.76	2.00	0.76	1.92	0.84
8	CH_2Ph	Me	H	m-OMe	0.14	0.00	0.03	5.02	2.56	0	3.38	2.98	0.40	2.91	0.47
15	CH_2Ph	Me	H	2,5-Cl_2	1.03	-0.97	0.03	5.02	2.56	0	3.30	3.68	-0.38	3.57	-0.27
16	CH_2Ph	Me	H	2,5-Me_2	0.31	-1.24	0.03	5.02	2.56	0	4.29	4.08	0.21	3.97	0.32
17	CH_2Ph	Me	H	2-Me,5-Cl	0.69	-1.24	0.03	5.02	2.56	0	4.02	4.02	0.00	3.91	0.11
20	CH_2Ph	Me	H	2-Me,6-Et	0.25	-1.31	0.03	5.02	2.56	0	4.03	4.04	-0.01	3.94	0.09
21	CH_2Ph	Me	H	2,6-Et_2	0.69	-1.31	0.03	5.02	2.56	0	4.08	4.00	0.08	3.89	0.19
22	CH_2Ph	Me	H	2,6-iso-Pr_2	1.25	-1.71	0.03	5.02	2.56	0	2.58	3.06	-0.48	2.95	-0.37
23	C_2H_4Ph	Me	H	H	0.00	0.00	0.02	2.58	6.27	0	3.60	4.10	-0.50	4.11	-0.51
24	C_2H_4Ph	Me	H	o-Cl	0.12	-0.97	0.02	2.58	6.27	0	5.39	5.20	0.19	5.19	0.20
25	C_2H_4Ph	Me	H	o-Me	-0.30	-1.24	0.02	2.58	6.27	0	5.14	4.70	0.44	4.70	0.44
26	C_2H_4Ph	Me	H	o-Et	0.16	-1.31	0.02	2.58	6.27	0	5.67	5.22	0.45	5.20	0.47

27	C_2H_4Ph	Me	H	*o*-OMe	-0.49	-0.55	0.02	2.58	6.27	0	3.69	4.07	-0.38	4.10	-0.41
28	C_2H_4Ph	Me	H	*m*-Cl	0.99	0.00	0.02	2.58	6.27	0	4.41	3.96	0.45	3.95	0.46
29	C_2H_4Ph	Me	H	*m*-Br	1.15	0.00	0.02	2.58	6.27	0	3.27	3.72	-0.45	3.71	-0.44
30	C_2H_4Ph	Me	H	*m*-CF_3	1.40	0.00	0.02	2.58	6.27	0	3.00	3.23	-0.23	3.23	-0.23
31	C_2H_4Ph	Me	H	*p*-Cl	0.96	0.00	0.02	2.58	6.27	0	3.47	4.00	-0.53	3.99	-0.52
32	C_2H_4Ph	Me	H	*p*-Me	0.47	0.00	0.02	2.58	6.27	0	3.52	4.32	-0.80	4.31	-0.79
33	C_2H_4Ph	Me	H	2-Me,3-Cl	0.66	-1.24	0.02	2.58	6.27	0	5.58	5.27	0.31	5.24	0.35
34	C_2H_4Ph	Me	H	2,3-Me_2	0.19	-1.24	0.02	2.58	6.27	0	5.43	5.26	0.17	5.24	0.19
35	C_2H_4Ph	Me	H	2-Me,5-Cl	0.69	1.24	0.02	2.58	6.27	0	4.82	5.25	-0.43	5.22	-0.40
36	C_2H_4Ph	Me	H	2,5-Me_2	0.31	-1.24	0.02	2.58	6.27	0	5.24	5.31	-0.07	5.28	-0.04
37	C_2H_4Ph	Me	H	2,6-Cl_2	0.16	-0.97	0.02	2.58	6.27	0	5.82	5.23	0.59	5.21	0.61
38	C_2H_4Ph	Me	H	2-Me,6-Cl	0.06	-1.24	0.02	2.58	6.27	0	5.44	5.16	0.28	5.15	0.29
39	C_2H_4Ph	Me	H	2,6-Me_2	-0.09	-1.24	0.02	2.58	6.27	0	5.27	5.01	0.26	5.00	0.27
40	C_2H_4Ph	Me	H	2-Me,6-Et	0.25	-1.31	0.02	2.58	6.27	0	5.44	5.27	0.17	5.25	0.19
41	C_2H_4Ph	Me	H	2,6-Et_2	0.69	-1.31	0.02	2.58	6.27	0	6.06	5.23	0.83	5.20	0.86
42	C_2H_4Ph	Me	H	3,4-Cl_2	1.84	0.00	0.02	2.58	6.27	0	2.07	2.02	0.05	2.04	0.03
43	C_2H_4Ph	Me	H	3,4-Me_2	0.94	0.00	0.02	2.58	6.27	0	3.83	4.02	-0.19	4.01	-0.18
44	C_2H_4Ph	Me	H	3,5-Me_2	1.01	0.00	0.02	2.58	6.27	0	3.31	3.93	-0.62	3.92	-0.61
45	*n*-Bu	Me	H	H	0.00	0.00	-0.01	3.54	4.11	0	4.16	3.45	0.71	3.48	0.68
46	*n*-Bu	Me	H	*o*-Cl	0.12	-0.97	-0.01	3.54	4.11	0	4.60	4.55	0.05	4.57	0.03
47	*n*-Bu	Me	H	*o*-Me	-0.30	-1.24	-0.01	3.54	4.11	0	4.30	4.05	0.25	4.08	0.22
48	*n*-Bu	Me	H	*o*-Et	0.16	-1.31	-0.01	3.54	4.11	0	4.21	4.57	-0.36	4.58	-0.37
49	*n*-Bu	Me	H	*o*-OMe	-0.49	-0.55	-0.01	3.54	4.11	0	2.95	3.43	-0.48	3.48	-0.53
50	*n*-Bu	Me	H	*o*-NO_2	-0.22	-2.52	-0.01	3.54	4.11	0	2.44	2.61	-0.17	2.65	-0.21

Table 2-11 (continued)

					Substituent Parameters						pI_{50}				
					X_n		R_1			R_5	obsd	Eq.2-13		Eq.2-26	
No.	R_1	R_2	R_5	Xn	π	Eso	σ_I	ΔB_5[a]	ΔL[a]	ΔMR		calcd	(Δ)[a]	calcd	(Δ)[a]
51	*n*-Bu	Me	H	*m*-Cl	0.99	0.00	-0.01	3.54	4.11	0	4.23	3.31	0.92	3.33	0.90
52	*n*-Bu	Me	H	*m*-CF_3	1.40	0.00	-0.01	3.54	4.11	0	3.14	2.59	0.55	2.61	0.53
53	*n*-Bu	Me	H	*m*-OMe	0.14	0.00	-0.01	3.54	4.11	0	3.26	3.57	-0.31	3.60	-0.4
54	*n*-Bu	Me	H	*m*-NO_2	0.31	0.00	-0.01	3.54	4.11	0	4.35	3.65	0.70	3.67	0.68
55	*n*-Bu	Me	H	*p*-Cl	0.96	0.00	-0.01	3.54	4.11	0	3.41	3.35	0.06	3.36	0.05
56	*n*-Bu	Me	H	*p*-Me	0.47	0.00	-0.01	3.54	4.11	0	3.50	3.67	-0.17	3.69	-0.19
57	*n*-Bu	Me	H	2,3-Cl_2	0.93	-0.97	-0.01	3.54	4.11	0	3.97	4.39	-0.42	4.38	-0.41
58	*n*-Bu	Me	H	2-Me,3-Cl	0.66	-1.24	-0.01	3.54	4.11	0	4.67	4.62	0.05	4.62	0.06
59	*n*-Bu	Me	H	2,3-Me_2	0.19	-1.24	-0.01	3.54	4.11	0	4.26	4.61	-0.35	4.62	-0.36
60	*n*-Bu	Me	H	2,4-Cl_2	1.02	-0.97	-0.01	3.54	4.11	0	4.53	4.27	0.26	4.27	0.26
61	*n*-Bu	Me	H	2,4-Me_2	0.30	-1.24	-0.01	3.54	4.11	0	4.52	4.66	-0.14	4.66	-0.14
62	*n*-Bu	Me	H	2,5-Cl_2	1.03	-0.97	-0.01	3.54	4.11	0	4.10	4.26	-0.16	4.26	-0.16
63	*n*-Bu	Me	H	2,5-Me_2	0.31	-1.24	-0.01	3.54	4.11	0	4.01	4.66	-0.65	4.66	-0.65
64	*n*-Bu	Me	H	2,6-Cl_2	0.16	-0.97	-0.01	3.54	4.11	0	4.36	4.58	-0.22	4.59	-0.23
65	*n*-Bu	Me	H	2-Me,6-Et	0.25	-1.31	-0.01	3.54	4.11	0	4.19	4.62	-0.43	4.63	-0.44
66	*n*-Bu	Me	H	2,6-Et_2	0.69	-1.31	-0.01	3.54	4.11	0	4.74	4.59	0.15	4.58	0.16
67	*n*-Bu	Me	H	3,4-Cl_2	1.84	0.00	-0.01	3.54	4.11	0	1.62	1.37	0.25	1.42	0.20
68	*n*-Bu	Me	H	3,4-Me_2	0.94	0.00	-0.01	3.54	4.11	0.785	3.24	3.37	-0.13	3.39	-0.15

108	-$(CH_2)_5$-	Br	H	0.00	0.00	-0.01[a]	2.17[a]	2.05[a]	0.785	4.66	4.78	-0.12	4.77	-0.11
109	-(CH2)$_5$-	Br	o-Cl	0.12	-0.97	-0.01[a]	2.17[a]	2.05[a]	0.785	5.51	5.89	-0.38	5.86	-0.35
110	-(CH2)$_5$-	Br	o-Me	-0.30	-1.24	-0.01[a]	2.17[a]	2.05[a]	0.785	5.30	5.38	-0.08	5.37	-0.07
111	-(CH2)$_5$-	Br	2,3-Cl_2	0.93	-0.97	-0.01[a]	2.17[a]	2.05[a]	0.785	5.56	5.72	-0.16	5.67	-0.11
112	-(CH2)$_5$-	Br	2-Me,3-Cl	0.66	-1.24	-0.01[a]	2.17[a]	2.05[a]	0.785	6.30	5.95	0.35	5.90	0.40
113	-(CH2)$_5$-	Br	2,3-Me_2	0.19	-1.24	-0.01[a]	2.17[a]	2.05[a]	0.785	6.15	5.94	0.21	5.90	0.25
114	-(CH2)$_5$-	Br	2,6-Br_2	0.37	-1.16	-0.01[a]	2.17[a]	2.05[a]	0.785	6.07	6.01	0.06	5.97	0.10
115	-(CH2)$_5$-	Br	2,6-Me_2	-0.09	-1.24	-0.01[a]	2.17[a]	2.05[a]	0.785	5.43	5.69	-0.26	5.67	-0.24
116	-(CH2)$_5$-	Br	2-Me,6-Et	0.25	-1.31	-0.01[a]	2.17[a]	2.05[a]	0.785	6.27	5.95	0.32	5.92	0.36
107	-(CH2)$_5$-	Br	2,6-Et_2	0.69	-1.31	-0.01[a]	2.17[a]	2.05[a]	0.785	5.97	5.92	0.05	5.87	0.10

a) See footnotes to Table 2-7.

Table 2-12 Correlation coefficient matrix (r) for the parameters used in Eq. 2-26.

	$\pi(X)^2$	$\pi(X)$	$Es^o(X)^2$	$Es^o(X)$	$\Delta L(R_1)$	$\Delta B_5(R_1)$	$\sigma_l(R_1)$	$\Delta MR(R_5)^2$	$\Delta MR(R_5)$
$\pi(X)^2$	1.00								
$\pi(X)$	0.85	1.00							
$Es^o(X)^2$	-0.34	-0.28	1.00						
$Es^o(X)$	0.42	0.29	-0.91	1.00					
$\Delta L(R_1)$	0.08	-0.02	-0.24	0.28	1.00				
$\Delta B_5(R_1)$	0.07	0.08	0.09	-0.05	0.15	1.00			
$\sigma_l(R_1)$	0.02	0.06	0.06	-0.07	0.08	-0.02	1.00		
$\Delta MR(R_5)^2$	-0.05	0.01	0.08	-0.12	-0.10	-0.06	-0.09	1.00	
$\Delta MR(R_5)$	-0.11	-0.01	0.13	-0.21	-0.28	-0.19	-0.15	0.83	1.00

specific electronic and steric effects of substituents on the pyridone ring. Requiring no additional parameter term, the structural change at the position R_2 substituent from Me to polymethylene bridge does not seem to induce significant effect on the activity.

2-4 Discussion

Above analyses are believed to reveal most favorable structural requirements for light-dependent herbicidal activity of pyridonecarboxanilides. Our previous selection of 5-bromo-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-1-phenethyl-3-pyridinecarboxanilide (**104**) as the candidate for further trials was justified in terms of physicochemical substituent effects. This compound has optimum stereo-hydrophobic characteristics in the anilide moiety and holds most favorable stereo-electronic conditions position-specifically for the pyridone ring substituents. The width of the phenethyl group in terms of ΔB_5 is smaller than those of *n*-butyl and benzyl. This is one of the reasons why the phenethyl as the 1-*N* substituent is favorable to the activity. The ΔB_5 value of phenethyl has been estimated from a conformation in which the C_α-C_β-bond is perpendicular to the pyridone ring and the end benzene ring is parallel with the pyridone ring. Molecular orbital calculations searching for the most stable conformation of a selected 1-*N*-phenethyl analog of the present series of compounds showed that

this is indeed the case (Chapter 3).

The fact that the hydrophobicity of the pyridone moiety was insignificant in governing the herbicidal potency shows that the overall molecular hydrophobicity of the pyridone-carboxanilides is unlikely to participate in the transport process to the site of action inside the plant cell. This seems to be somewhat peculiar without reasonable explanation at the moment. In other subsets of 4-pyridone-3-carboxanilides, we have found that the 2,4-Cl_2 substitution (**60**, π=1.02, E_s^o=-0.97) and 2,4,6-Cl_3 (not included in this study, π=1.12[4], E_s^o=-0.97) are also favorable to the light-dependent herbicidal activity. The 2,4-Cl_2 and 2,4,6-Cl_3 substitution patterns are known to be favorable to the light-dependent herbicidal activity in such diphenyl ether type herbicides[31] as nitrofen (2,4-dichlorophenyl 4-nitrophenyl ether), chlomethoxynil [5-(2,4-dichlorophenoxy)-2-nitroanisole] and chlornitrofen(2,4,6-trichlorophenyl 4-nitrophenyl ether). On the other hand, the *meta*-Me and 3,5-Me_2 substitutions are known to make the herbicidal activity light-independent in such diphenyl ethers[31] as DMNP(3,5-dimehyl-4'-nitro-diphenyl ether)[32]. In 4-pyridone-3-carboxanilides, 3,5-Me_2 (**44**, π=1.01, E_s^o=0) substitutions was also unfavorable to the light-dependent herbicidal activity because of the luck of the bulk of the *ortho* substituent. Thus, the effects of substituents on the anilide-benzene ring of 4-pyridone-3-carboxanilides and those on one of the benzene ring in diphenyl ethers are similar and the corresponding

benzene ring moieties might interact with a common site of light-dependent herbicidal action in the plant cells. To examine this hypothesis, one of the next projects could be to estimate the three-dimensional similarity between 4-pyridone-3-carboxanilides and diphenyl ethers to fit the common "receptor site" in terms of the stable conformations with use of molecular orbital calculations.

Chapter 3 Three-Dimensional Structure-Activity (Comparative Molecular Field) Analysis of Light-dependent 4-Pyridone-3-Carboxanilides and Diphenyl Ether Herbicides.

3-1 Introduction

We have described that a number of substituted 4-pyridone-3-carboxanilide derivatives (Fig.3-1) show various degrees of light-dependent herbicidal activity against *Echinochloa oryzicola* (Chapter 1).

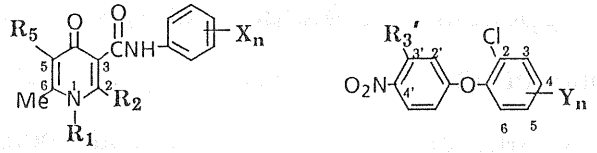


Fig.3-1 The general formula of herbicidal 4-pyridone-3-carboxanilides and *ortho*-chlorinated diphenyl ethers (Numerals represent substituent positions).

The symptoms of the treated plants are common to the symptoms induced by light-dependent diphenyl ether herbicides (Fig.3-1). Moreover, one of the derivatives DLH-1777, (5-bromo-2',6'-diethyl-1,4-dihydro-1,6-dimethyl-4-oxo-2-propyl-3-pyridinecarboxanilide) (Fig.3-1:X_n=2,6-Et_2, R_1=Me, R_2=Pr, R_5=Br), exhibits photobleaching and peroxidizing effects similar to those induced by oxyfluorfen (Fig.3-1:Y_n=4-CF_3, R'_3=OEt) with an abnormal accumulation of protoporphyrin IX in treated plant tissues by interfering with their porphyrin biosynthesis.[33]

We have examined the structure-activity relationships quantitatively (QSAR) for a number of 4-pyridone-3-carboxanilides, in which various substituents are introduced to the anilide-benzene and pyridone rings, with physicochemical substituent parameters and regression analysis (Chapter 2). For substituents in the anilide-benzene ring, the steric effect of *ortho*-substituents and the hydrophobicity are important in governing the herbicidal activity. Besides the 2,6-Et_2 in DLH-1777, such substitution patterns as 2,4-Cl_2 and 2,4,6-Cl_3 are favorable for potentiating the activity (Chapter 2). These substitution patterns are also favorable to or essential for the light-dependent herbicidal activity of diphenyl ethers as patterns in one of the two benzene rings.[31] Because the substitution pattern is similar between the anilide-benzene ring of pyridone-carboxanilides and the *ortho*-chlorinated benzene ring of diphenyl ether herbicides, we postulated that the two series of

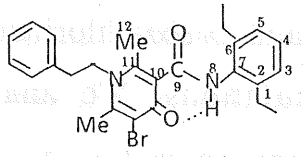
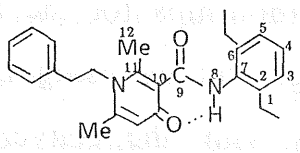
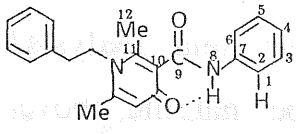
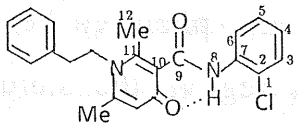
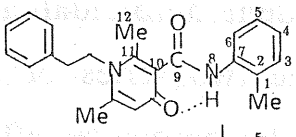
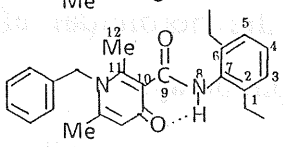
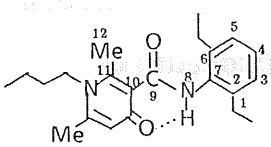
compounds may work so that the anilide-benzene and the *ortho*-chlorinated benzene rings in respective series of compounds recognize a common region of the receptor site for the light-dependent herbicidal activity (Chapter 2). To examine this hypothesis, we determined the most stable three-dimensional structures of some representative pyridone-carboxanilides and *ortho*-chlorinated diphenyl ethers by molecular orbital calculations. We analyzed the three-dimensional structure- activity relationships for the two series of compounds quantitatively as a single set by using the stereoelectronic and hydrophobic parameters with the conventional regression and the comparative molecular field analysis[9] (CoMFA) procedures. In this Chapter, we describe that the above hypothesis seems to be valid. With the anilide and phenoxy benzene rings interacting similarly with the receptor region, the stereoelectronic factors required for the light-dependent herbicidal activity are suggested to be common between the two series of compounds three-dimensionally. The potency of the herbicidal effect is also governed by the (sub)molecular hydrophobicity.

3-2 Experimental Procedures

3-2-1 Set of Compounds

4-Pyridone-3-carboxanilide derivatives (**21**, **23** - **25**, **41**, **66**, and **104**) used for the analyses are shown in Table 3-1. They were

Table 3-1 Herbicidal activity , RMS and *logP* values of pyridone carboxanilides.

No.	Structure	RMS(Å)	*logP*	pI_{50}[a] obsd.	Eq.3-3 calcd. (△)[b]	Eq.3-4 calcd. (△)[b]
104		0.000	3.63	6.82	6.73 0.09	6.75 0.07
41		0.167	3.08	6.06	5.91 0.15	6.19 -0.13
23		0.663	2.04	3.60	3.86 -0.26	3.59 0.01
24		0.371	2.79	5.39	5.16 0.23	5.35 0.04
25		0.297	2.52	5.14	5.19 -0.05	5.13 0.01
21		0.145	2.90	4.08	— —	4.34 -0.26
66		0.106	2.52	4.74	— —	4.51 0.23

a Log of reciprocal of the concentration required for the 50% shoot growth inhibition of *Echinochloa oryzicola*

b △, the difference between observed and calculated values.

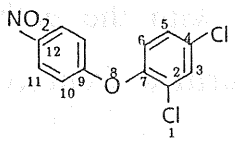
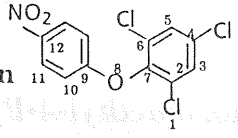
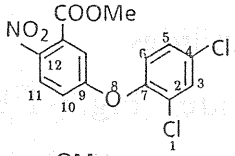
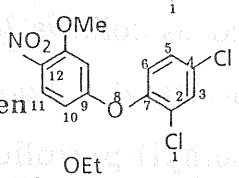
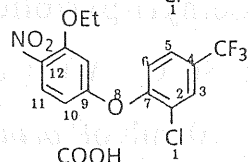
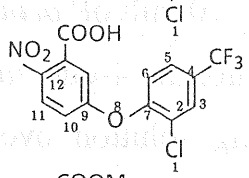
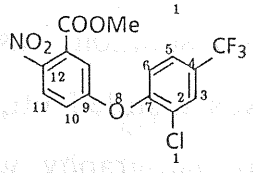
selected from the previous chapter so as to cover the potency range as widely as possible under restrictions in which the structural variations are mainly made in the substitution pattern in the anilide benzene ring and the number of compounds matches that of diphenyl ethers. Diphenyl ethers with the *ortho*-Cl substitution listed in Table 2 (**2-a** - **2-g**) were purified from commercial formulation.

3-2-2 Synthesis of 1-Butyl-2-Trifluoromethyl-4-Pyridone-3-Carboxylicacid-2,'6'-diethylanilides

The pyridone-carboxanilide (Fig.3-1:R_1=Bu, R_2=CF_3, R_5=H, 2,6-Et_2) was newly synthesized as follows (Fig.3-2).

A mixture of 4.3g of 2,6-diethyl trifluoromethyl acetoacetanilide and 2.3g of 1-(2-aminoethyl)-pyrrolidine in 20ml of toluene was stirred for 2 hours at 80°C. After distilling off the resulting water together with about 10 ml of *ortho*-xylene, a solution of 7.8g of 2,2,6-trimethyl-1,3-dioxine-4-one in 25ml of xylene was dropwise added to the remaining solution over a period of 30 minutes while refluxing. The reaction solution was further refluxed for 90 minutes. After the solvent was distilled off, the residue was purified by a silicagel column chromatography with *ortho*-xylene as the eluant, and recrystallized from *ortho*-xylene to give 2.8g of *N*-2',6'-diethyl-6-methyl-4-oxo-pyrane-2-trifluoromethyl-3-carboxanilide. To its solution in a mixture of 50ml of ethanol and 10ml of

Table 3-2 Herbicidal activity, RMS and *logP* values of *ortho*-Cl diphenyl ethers.

No.	Name	Structure	RMS(Å)	*logP*[b]	pI_{50}[a] obsd.	Eq.3-3 calcd. (Δ)		Eq.3-4 calcd. (Δ)	
2-a	nitrofen		0.358	4.17	5.91	6.10	-0.19	5.64	0.27
2-b	chlornitrofen		0.216	4.70[c]	5.94	6.84	-0.90	5.92	0.03
2-c	bifenox		0.351	3.90	5.78	5.95	0.17	6.15	-0.38
2-d	chlomethoxyfen		0.155	4.01	6.33	6.56	-0.23	6.13	0.20
2-e	oxyfluorfen		0.282	4.70[c]	7.18	6.66	0.52	7.37	-0.19
2-f	acifluorfen		0.340	3.90	5.61	5.98	-0.37	6.06	-0.45
2-g	AFM		0.352	4.10	7.25	6.08	1.17	6.71	0.54

a See footnotes to Table 3-1.
b Except for compounds 2-b and 2-e, estimated as CLOGP−1.36.
c Experimental data from Pomona Med. Chem. Data Bank. The CLOGP value of 2-b and 2-e was 5.99 and 6.13, respectively.

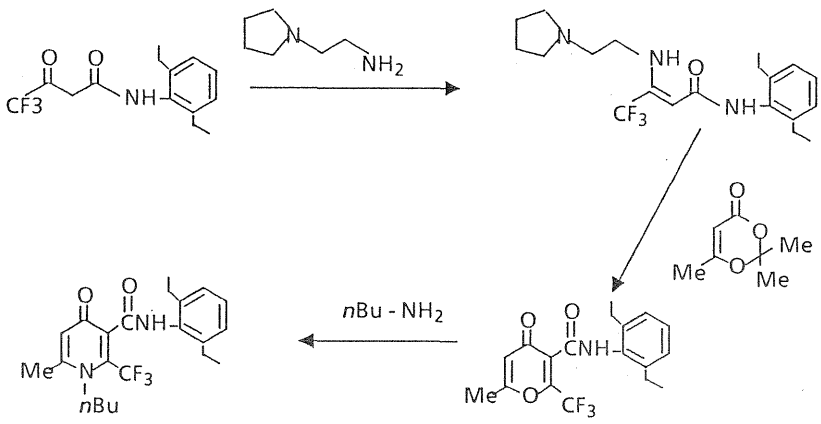


Fig.3-2 Synthetic route of 1-butyl-2-trifluoromethyl-4-pyridone-3-carboxylicacid-2',6'-diethylanilide

water was added 1.0g of butylamine and 0.7g of sodium carbonate, and the mixture was stirred for 3.5 hours at room temperature. After concentration in vacuo, the residue was dissolved in a mixture of 50ml of ethyl acetate and 50ml of methanol and the solution was washed with water, and then with saturated sodium bicarbonate solution. The organic layer was concentrated and residue was recrystallized from ethyl acetate to afford 0.8g of the 1-butyl-2',6'-diethyl-1,4-dihydro-6-methyl-4-oxo-2-trifluoromethyl-3-pyridinecarboxanilide, mp 157.4-161.2°C . ^{1}H-NMR ($CDCl_3$) δ: 0.70-2.01(7H,m), 1.18(6H,t), 2.30(3H,s) 2.72(4H,q), 3.90(2H,t), 6.31(1H,s), 8.04(1H,s).

3-2-3 Measurement of Partition Coefficient

The partition coefficient (*P*) of pyridone-carboxanilides **21**, **23-25**, **41**, **66**, and **104** with the 1-octanol-water system was experimentally measured at 25±2°C. The *logP* value was used as the parameter for the molecular hydrophobicity (Table 3-1). The experimentally measured *logP* value of diphenyl ethers, **2-b** and **2-e**, was from the data bank issued by the Pomona College Medicinal Chemistry Project.[34] The value for all the diphenyl ethers **2-a** to **2-g** was also estimated by the CLOGP3 program[34]. The CLOGP3 program is to calculate the *logP* value of the compound by summing up the component values assignable to each of the substructure fragments and structural features. The differences between observed and CLOGP-estimated values for compounds **2-b** and **2-e** were averaged and the averaged difference, -1.36, was used to correct the "CLOGP" values of other *ortho*-Cl diphenyl ethers. The values are shown in Table 3-2. The standard deviation in the experimental *logP* value was from ±0.02 to ±0.03.

3-2-4 Molecular Orbital and Molecular Mechanics Calculations

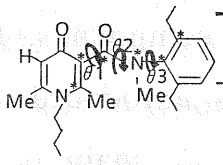
The structure of 1-*N*-unsubstituted pyridone-carboxanilides was divided into the anilide and pyridone-carboxamide moieties. The minimum-energy conformation of these moieties was first searched for by *ab initio* MO method.[35] For 2,6-diethyl acetanilide,

the most stable conformation of 2,6-diethyl part was estimated by Tripos force field[36] before the *ab initio* calculation. With these moiety structures of the minimum-energy conformation, we built the initial conformation of the 1-*N*-unsubstituted compounds. Into this initial conformation, each 1-*N*-substituent was introduced in a manner so that the plane defined by the 1-*N*-C_α-C_β chain of the substituent is perpendicular to the plane of the 4-pyridone ring with consideration of the steric repulsion from the 2,6-Me_2 substituents. The end benzene ring of the 1-*N*-benzyl substituent was fixed on the perpendicular plane, while that of 1-*N*-phenethyl substituent was estimated to be parallel to the pyridone ring plane. The full optimization of the initial conformation was made by the semi-empirical molecular orbital method PM3.[37] We regarded the fully optimized conformation as the active conformation for light-dependent herbicidal activity.

To compare the conformation of light-dependent pyridone-carboxanilides with that of the light-independent analogs, we used the light-independent *N*-methylanilide (**117**) of the compound (**66**) (Table 3-3). The stable conformations of the *N*-methyl peptide moiety was analyzed by the Tripos force field.[36] The energy difference between two most stable conformations was estimated and the full optimization for the conformation of the entire molecule was not performed.

For the initial conformation of *ortho*-Cl diphenyl ethers,

Table 3-3. Energy-minimum conformations of compound 117



117

geometry	θ1 (degree)	θ2 (degree)	θ3 (degree)	-ΔH[a] (kcal/mol)
syn-isomer	100	65	255	20.1
trans-isomer	245	185	250	21.0

a The heat of formation calculated by the Tripos force field.

we used the coordinates of the X-ray crystal structure of AKH-7088[38] (Fig.3-3) that is also herbicidal light-dependently[39].

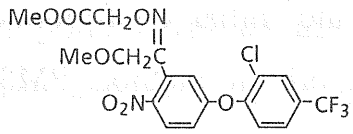


Fig.3-3 Chemical structures of AKH-7088

The initial model for the *ortho*-nitrobenzoate moiety in **2-c**, **2-f** and **2-g** was from the X-ray data of acifluorfen.[40] The initial conformation of compounds **2-a** to **2-c** was fully optimized by AM1[37] and all torsion angles of derived geometries were optimized by the *ab initio* method (STO-3G basis set). For compounds **2-d** to **2-g**, the full optimization was made by PM3.

3-2-5 Superposition of Molecules and CoMFA Analysis

All computations were performed by the molecular modeling software package SYBYL.[41] The most stable conformation of compound **104** was selected as the reference to which the similarity of the conformation of other compounds is examined. Because the anilide-benzene moiety of pyridone-carboxanilides and the chlorinated benzene moiety of diphenyl ethers are primarily to be compared, we assigned twelve atoms to be matched between the two series as indicated in Tables 3-1 and 3-2. We did not assign one of the *ortho* substituents because our quantitative structure-activity analysis for pyridone-carboxanilides indicates that the bulk of the "smaller" *ortho* substituent in the anilide-benzene ring is insignificant to govern the variations in the herbicidal potency (Chapter 2). The smaller *ortho* substituent may not exert steric interaction with the target site. The superposition of the most stable conformations was made in such a way that each of the twelve atoms assigned was situated as close as possible to each of the corresponding atoms in the reference, i.e., the root mean square (RMS) of distances of atomic positions from corresponding atomic positions of the reference is as small as possible. The Cartesian coordinates under such conditions along with the PM3 charges of the assigned atoms(1 to 12) in pyridone-carboxanilides and compounds **2-a** to **2-g** are shown in Table 3-4.

The similarity in the three-dimensional structure to the

Table 3-4. Cartesian coordinates and PM3 charges of assigned 12 atoms in pyridone carboxanilides and *o*-chlor diphenyl ethers.

Compd No.	Atom. No.	type	x	y	z	charge
104	1	C	-3.3911	2.1844	1.3674	-0.0518
	2	C	-3.3797	2.9550	0.0834	-0.0570
	3	C	-4.1329	4.1273	0.0085	-0.1071
	4	C	-4.1737	4.8681	-1.1653	-0.0970
	5	C	-3.4730	4.4354	-2.2819	-0.1073
	6	C	-2.7119	3.2643	-2.2394	-0.0649
	7	C	-2.6538	2.5292	-1.0447	-0.0362
	8	N	-1.9053	1.2892	-0.9499	-0.0050
	9	C	-0.5129	1.2298	-0.7873	0.3094
	10	C	0.1398	-0.1218	-0.8214	-0.3011
	11	C	1.4957	-0.2801	-0.6299	0.0202
	12	C	2.3951	0.8979	-0.4365	-0.1213
41	1	C	-3.2305	2.1094	1.2980	-0.0600
	2	C	-3.2974	2.9137	0.0365	-0.0640
	3	C	-4.0754	4.0738	0.0441	-0.1057
	4	C	-4.1947	4.8566	-1.0963	-0.0975
	5	C	-3.5476	4.4793	-2.2650	-0.1111
	6	C	-2.7649	3.3235	-2.3052	-0.0528
	7	C	-2.6261	2.5456	-1.1421	-0.0477
	8	N	-1.8175	1.3387	-1.2349	-0.0165
	9	C	-0.5863	1.2156	-0.5313	0.3164
	10	C	0.0657	-0.1313	-0.5859	-0.3177
	11	C	1.4332	-0.2682	-0.5703	0.0142
	12	C	2.3379	0.9220	-0.5448	-0.1116
23	1	H	-3.9611	2.2463	0.9401	0.1132
	2	C	-3.7033	2.8638	0.0706	-0.1411
	3	C	-4.5988	3.8285	-0.3727	-0.0855
	4	C	-4.2948	4.6223	-1.4739	-0.1305
	5	C	-3.0879	4.4491	-2.1430	-0.0791
	6	C	-2.1812	3.4892	-1.7158	-0.1485
	7	C	-2.4846	2.6952	-0.6027	-0.0572
	8	N	-1.5524	1.7298	-0.0887	0.0415
	9	C	-0.4651	1.2169	-0.8327	0.3206
	10	C	0.2335	0.0048	-0.3028	-0.3283
	11	C	1.5083	-0.3138	-0.7162	0.0316
	12	C	2.2836	0.5465	-1.6593	-0.1777

Compd No.	Atom. No.	type	x	y	z	charge
2-a	1	C	-3.8188	2.1670	1.5862	0.1095
	2	C	-3.5116	2.9497	0.1169	-0.1321
	3	C	-4.2366	4.1064	-0.1958	-0.0916
	4	C	-4.0064	4.7641	-1.4059	-0.1246
	5	C	-3.0521	4.2870	-2.3129	-0.0813
	6	C	-2.3249	3.1421	-2.0063	-0.1131
	7	C	-2.5571	2.4715	-0.7981	0.0464
	8	O	-1.9225	1.2607	-0.5219	-0.1238
	9	C	-0.5375	1.2566	-0.5935	0.1323
	10	C	0.0318	0.0296	-0.9799	-0.1531
	11	C	1.4140	-0.0827	-1.0514	0.0234
	12	C	2.2180	1.0265	-0.7345	-0.4596
2-b	1	Cl	-3.4537	2.1522	1.5959	0.1139
	2	C	-3.3669	2.9545	0.1065	-0.1214
	3	C	-4.0946	4.1365	-0.0607	-0.0997
	4	C	-4.0428	4.8115	-1.2832	-0.1083
	5	C	-3.2626	4.3321	-2.3392	-0.0976
	6	C	-2.5385	3.1481	-2.1771	-0.1269
	7	C	-2.5943	2.4503	-0.9562	0.0381
	8	O	-1.9784	1.2079	-0.8212	-0.1185
	9	C	-0.5972	1.2164	-0.6638	0.1321
	10	C	0.0522	0.0311	-1.0526	-0.1502
	11	C	1.4284	-0.0695	-0.8985	0.0233
	12	C	2.1447	1.0076	-0.3470	-0.4606
2-c	1	Cl	-3.8351	2.1317	1.5629	0.1134
	2	C	-3.5198	2.9382	0.1087	-0.1290
	3	C	-4.2361	4.1038	-0.1901	-0.0908
	4	C	-3.9947	4.7806	-1.3872	-0.1228
	5	C	-3.0417	4.3117	-2.3000	-0.0809
	6	C	-2.3238	3.1583	-2.0087	-0.1131
	7	C	-2.5626	2.4736	-0.8100	0.0384
	8	O	-1.9274	1.2576	-0.5489	-0.1176
	9	C	-0.5440	1.2584	-0.6292	0.1351
	10	C	0.0403	0.0036	-0.8766	-0.1426
	11	C	1.4220	-0.0946	-0.9795	0.0241
	12	C	2.2191	1.0557	-0.8386	-0.4280

24

1	Cl	-3.8683	2.1139	1.4907	0.0738
2	C	-3.5962	2.9802	0.0669	-0.1530
3	C	-4.4365	4.0479	-0.2320	-0.0910
4	C	-4.2422	4.7723	-1.4016	-0.1121
5	C	-3.2177	4.4107	-2.2735	-0.0875
6	C	-2.3787	3.3480	-1.9861	-0.1045
7	C	-2.5502	2.6219	-0.8013	-0.0400
8	N	-1.7283	1.5088	-0.4073	0.0227
9	C	-0.4235	1.2535	-0.8865	0.3233
10	C	0.1488	-0.1130	-0.6732	-0.3268
11	C	1.5046	-0.3359	-0.7702	0.0319
12	C	2.4842	0.7623	-1.0230	-0.1789

25

1	C	-3.7294	2.0987	1.3018	-0.0797
2	C	-3.5396	2.9058	0.0673	-0.0920
3	C	-4.2787	4.0782	-0.0971	-0.0981
4	C	-4.1245	4.8630	-1.2328	-0.1093
5	C	-3.2297	4.4799	-2.2255	-0.1031
6	C	-2.4860	3.3145	-2.0848	-0.0786
7	C	-2.6317	2.5258	-0.9375	-0.0565
8	N	-1.9028	1.2790	-0.8351	0.0003
9	C	-0.4850	1.2591	-0.7511	0.3209
10	C	0.1739	-0.0294	-0.3732	-0.3216
11	C	1.5169	-0.2334	-0.6020	0.0274
12	C	2.4129	0.8376	-1.1272	-0.1732

21

1	C	-3.2948	2.2520	1.4177	-0.0499
2	C	-3.3310	2.9828	0.1108	-0.0533
3	C	-4.0936	4.1484	0.0284	-0.1097
4	C	-4.1917	4.8462	-1.1682	-0.0966
5	C	-3.5354	4.3773	-2.2967	-0.1073
6	C	-2.7610	3.2153	-2.2463	-0.0645
7	C	-2.6508	2.5201	-1.0312	-0.0467
8	N	-1.8948	1.2835	-0.9012	-0.0022
9	C	-0.4843	1.2546	-0.9874	0.3180
10	C	0.1674	-0.0917	-1.0541	-0.3219
11	C	1.4707	-0.2664	-0.6521	0.0234
12	C	2.2954	0.8566	-0.1170	-0.1777

66

1	C	-3.3345	2.2288	1.4050	-0.0496
2	C	-3.3499	2.9708	0.1038	-0.0533
3	C	-4.0912	4.1502	0.0239	-0.1090
4	C	-4.1626	4.8613	-1.1666	-0.0970
5	C	-3.5029	4.3923	-2.2927	-0.1076
6	C	-2.7464	3.2184	-2.2439	-0.0644
7	C	-2.6604	2.5117	-1.0335	-0.0458
8	N	-1.9129	1.2707	-0.9010	-0.0012
9	C	-0.5028	1.2387	-0.9427	0.3176
10	C	0.1559	-0.1057	-0.9920	-0.3215
11	C	1.4810	-0.2539	-0.6515	0.0266
12	C	2.3229	0.8953	-0.2062	-0.1789

2-d

1	Cl	-3.4375	2.0771	1.5252	0.1166
2	C	-3.3717	2.9373	0.0862	-0.1300
3	C	-4.1532	4.0814	-0.0599	-0.0989
4	C	-4.1109	4.7900	-1.2569	-0.1203
5	C	-3.2975	4.3768	-2.3114	-0.0939
6	C	-2.5169	3.2368	-2.1728	-0.0937
7	C	-2.5576	2.5159	-0.9747	0.0309
8	O	-1.9251	1.2812	-0.8615	-0.1168
9	C	-0.5511	1.2775	-0.7694	0.1742
10	C	0.0152	-0.0105	-0.8158	-0.1879
11	C	1.3852	-0.1532	-0.7091	0.0397
12	C	2.2173	0.9682	-0.5770	-0.4693

2-e

1	Cl	-3.6570	2.1109	1.5363	0.1295
2	C	-3.4707	2.9482	0.0946	-0.1601
3	C	-4.3035	4.0301	-0.1771	-0.0340
4	C	-4.1702	4.7221	-1.3783	-0.1815
5	C	-3.1882	4.3653	-2.3007	-0.0231
6	C	-2.3527	3.2830	-2.0435	-0.1367
7	C	-2.5066	2.5641	-0.8529	0.0834
8	O	-1.8563	1.3665	-0.5994	-0.1176
9	C	-0.4842	1.3070	-0.7304	0.1632
10	C	0.0209	-0.0046	-0.7964	-0.1793
11	C	1.3905	-0.2007	-0.8317	0.0392
12	C	2.2745	0.8868	-0.8175	-0.4600

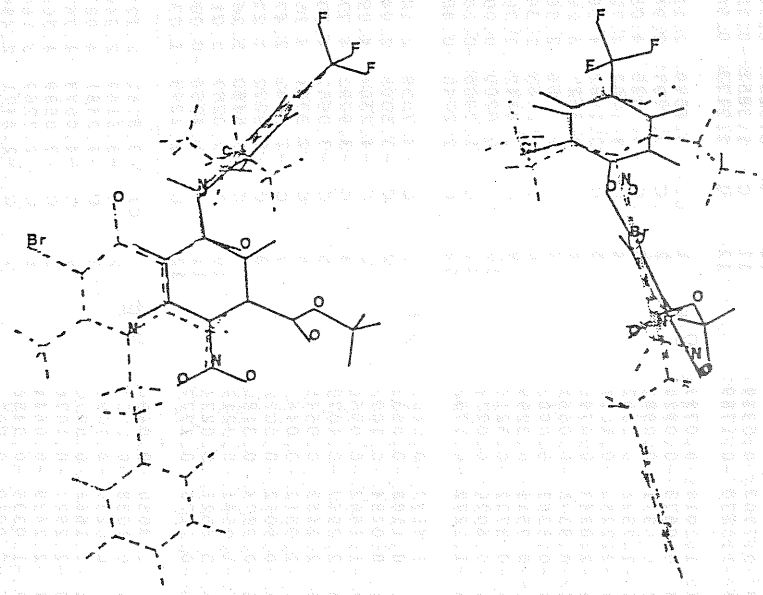
2-f

1	C	-3.7938	2.1298	1.5431	0.1308
2	C	-3.5068	2.9411	0.1035	-0.1566
3	C	-4.2304	4.0964	-0.1867	-0.0330
4	C	-3.9993	4.7745	-1.3810	-0.1770
5	C	-3.0652	4.3046	-2.3025	-0.0240
6	C	-2.3394	3.1531	-2.0235	-0.1289
7	C	-2.5542	2.4791	-0.8161	0.0721
8	O	-1.9272	1.2716	-0.5258	-0.1170
9	C	-0.5480	1.2635	-0.6208	0.1287
10	C	0.0257	0.0186	-0.9103	-0.1362
11	C	1.4056	-0.0862	-0.9884	0.0127
12	C	2.2293	1.0325	-0.7886	-0.3978

2-g

1	Cl	-3.8151	2.1294	1.5405	0.1302
2	C	-3.5169	2.9404	0.1024	-0.1574
3	C	-4.2481	4.0879	-0.2000	-0.0322
4	C	-4.0073	4.7675	-1.3911	-0.1788
5	C	-3.0589	4.3045	-2.3016	-0.0229
6	C	-2.3269	3.1602	-2.0105	-0.1320
7	C	-2.5471	2.4865	-0.8034	0.0751
8	O	-1.9126	1.2877	-0.4989	-0.1167
9	C	-0.5355	1.2737	-0.6203	0.1271
10	C	0.0243	0.0202	-0.9004	-0.1368
11	C	1.4022	-0.0968	-0.9941	0.0105
12	C	2.2380	1.0175	-0.8196	-0.3975

reference compound was estimated by the minimum RMS value which is listed in Tables 3-1 and 3-2. An example of the superposition was shown in Fig.3-4 for the compound **2-g** and the reference **104**.



Front view Side view

Fig.3-4 Orthogonal Superposition views between compound 104(dashed lines) and 2-g(AFM, solid lines)

The CoMFA analysis was carried out by using the QSAR option of SYBYL version 5.41. We placed the active conformers on a lattice of 20 x 20 x 20 $Å^3$ with 2.0Å spacing where they are superposed under conditions as mentioned above. Then, the potential energy fields of each active conformer were calculated at lat-

tice points surrounding the entire molecule. For the calculation of the Coulombic electrostatic potential at each of the lattice points, the H^+ ion as a probe and the atomic charges in each of the entire molecules derived from the PM3 calculation were used. Dielectric constant of the medium was taken to be 1.0. The steric interaction (Lenard-Jones) potential at the lattice points was calculated by using the sp^3-carbon atom as a probe. The *logP* value was introduced as an additional variable in the analyses.

Because the number of energy indices at every lattice points is enormous, the data matrix is analyzed with a statistical procedure named PLS (partial least squares)[42] in the CoMFA analysis. In this procedure, the enormous number of "original" independent lattice variables are linearly combined so that each of the transformed variables are orthogonal, and to reduce the standard deviation of the estimates as far as possible while making the cross-validation tests. The transformed variables are usually so complex in their composition that they are dealt with as latent variables. The results of the analysis are expressed as correlation equations including latent variable terms and displayed as contour diagrams of coefficients of field descriptor terms showing favorable and unfavorable potential regions.

We first selected the number of compounds in the set as the number of the cross-validation and then performed the analysis using the optimum number of variables deduced from the

cross-validation tests without cross-validation. The auto-scaling of variables was done by SYBYL STD command.[41]

3-3 Results

3-3-1 Conformational Analysis of Pyridone-Carboxanilides

The bond connecting the NH with the benzene ring in unsubstituted acetanilide was rotated from 0° with every 10° intervals and the energy of each conformation was calculated with the use of the 3-21G basis set. The conformation with the minimum-energy was that in which the amide side chain is coplanar with the benzene ring. This was taken as the initial conformation of the unsubstituted anilide moiety. For *ortho*-Me acetanilide, a similar calculation showed that there are two minimum-energy conformations as shown in Fig.3-5. The energy of the conformation B in which *ortho*-Me is located at the *anti*-position to the amide carbonyl was more stable than the conformation A. Although the energy difference between conformations A and B was not substantial in this molecule, the *ortho*-Cl analog showed only a single minimum-energy conformation corresponding to the conformation B of the *ortho*-Me compound. From these results, we assumed that the *ortho* substituents in mono-substituted anilide-benzene take the *anti*-conformation with regard to the NHAc-carbonyl. For the 2,6-Et_2 acetanilide examined with the STO-3G basis set, the minimum-

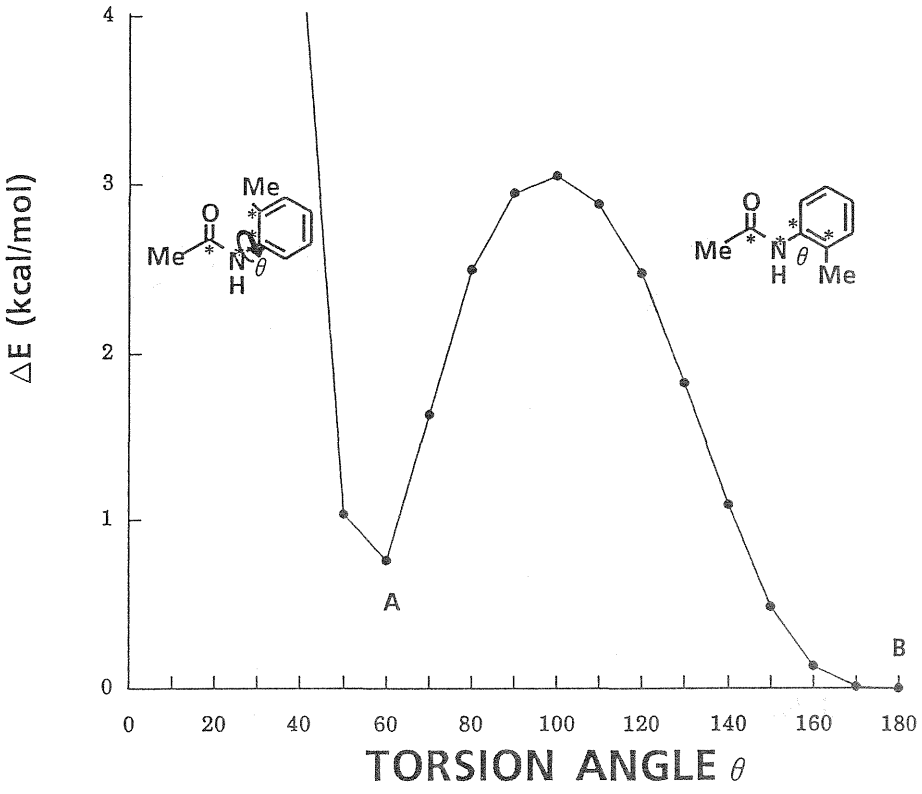


Fig.3-5 Energy-plot of *ortho*-methyl-acetanilide (3-21G)

energy torsion angle was estimated as 250° as shown in Fig.3-6. The minimum-energy conformation of 1,4-dihydro-4-oxo-nicotin-*N*-methylamide was estimated by the 3-21G basis set showing that the plane of the side chain amide NH is almost "*syn*" to the pyridone-4-carbonyl (Fig.3-7). This almost coplanar geometry was in accord to our previous NMR experiment indicating an internal hydrogen-bond formation between the amide NH and the pyridone-carbonyl in 4-pyridone-3-carboxanilides.[43]

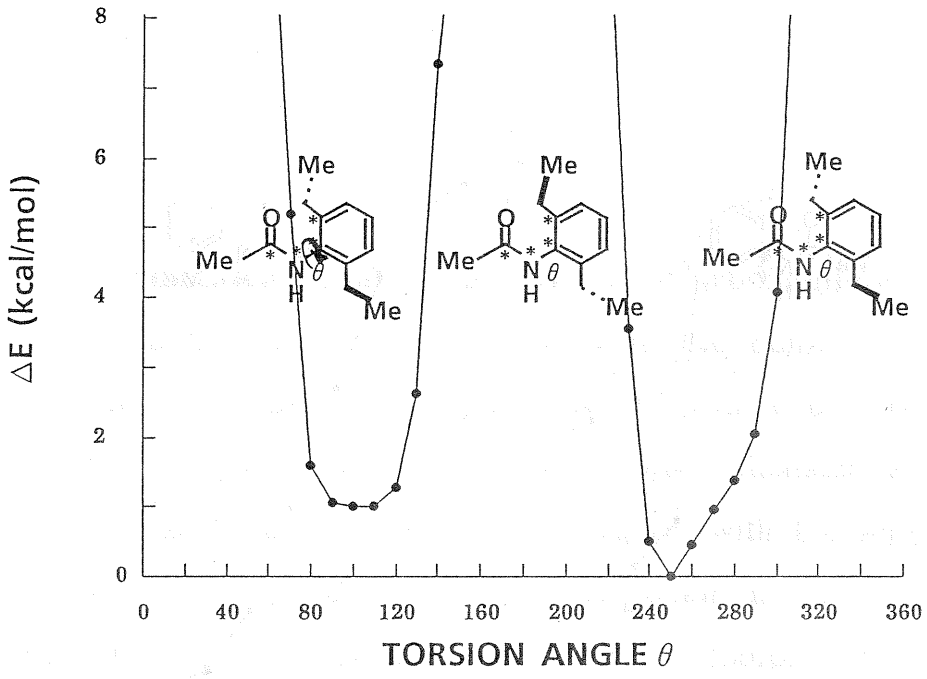


Fig.3-6 Energy-plot of 2,6-diethyl-acetanilide (STO-3G)

Each of the minimum-energy conformation of the above model compounds was combined to construct the initial geometry of the 4-pyridone-3-carboxanilides into which the phenethyl(**104**, **41**, **23** - **25**), benzyl(**21**), and *n*-butyl(**66**) were introduced to the 1-*N* position in the manner described in the method section. The most stable initial conformation of the 1-*N* phenethyl group in compound **104** was searched for by rotating the end benzene ring around the C(aromatic)-C_α bond with the AM1 single-point calculation. The conformation corresponded with that in which the benzene ring is parallel to the pyridone ring (Fig.3-8).

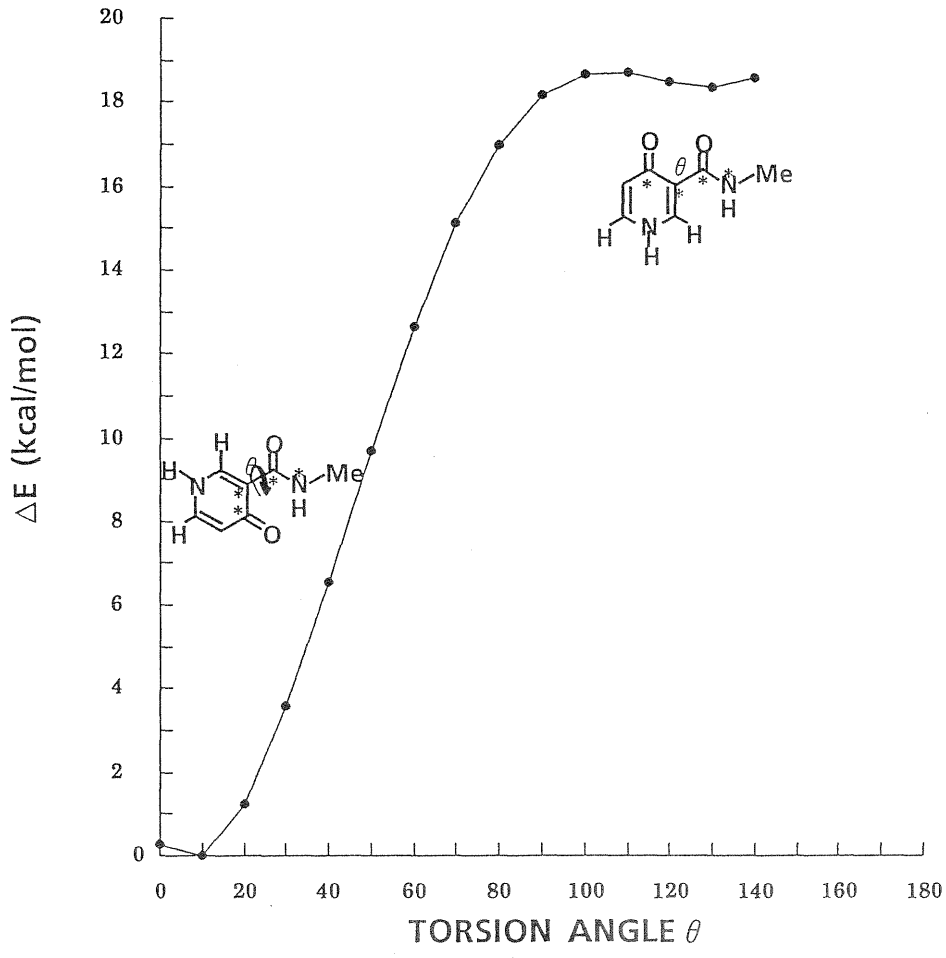


Fig.3-7 Energy-plot of 1,4-dihydro-4-oxo-nicotin-*N*-methyl-amide (3-21G)

The conformational analysis of compound **117** around the *N*-methylated amide bond was done by rotating three torsion angles(θ_1, θ_2, θ_3) whose increment was 5 degrees. Two conformations were picked out as the most stable ones (Table 3-3). In one of which, the *N*-Me and carbonyl were located on the same side

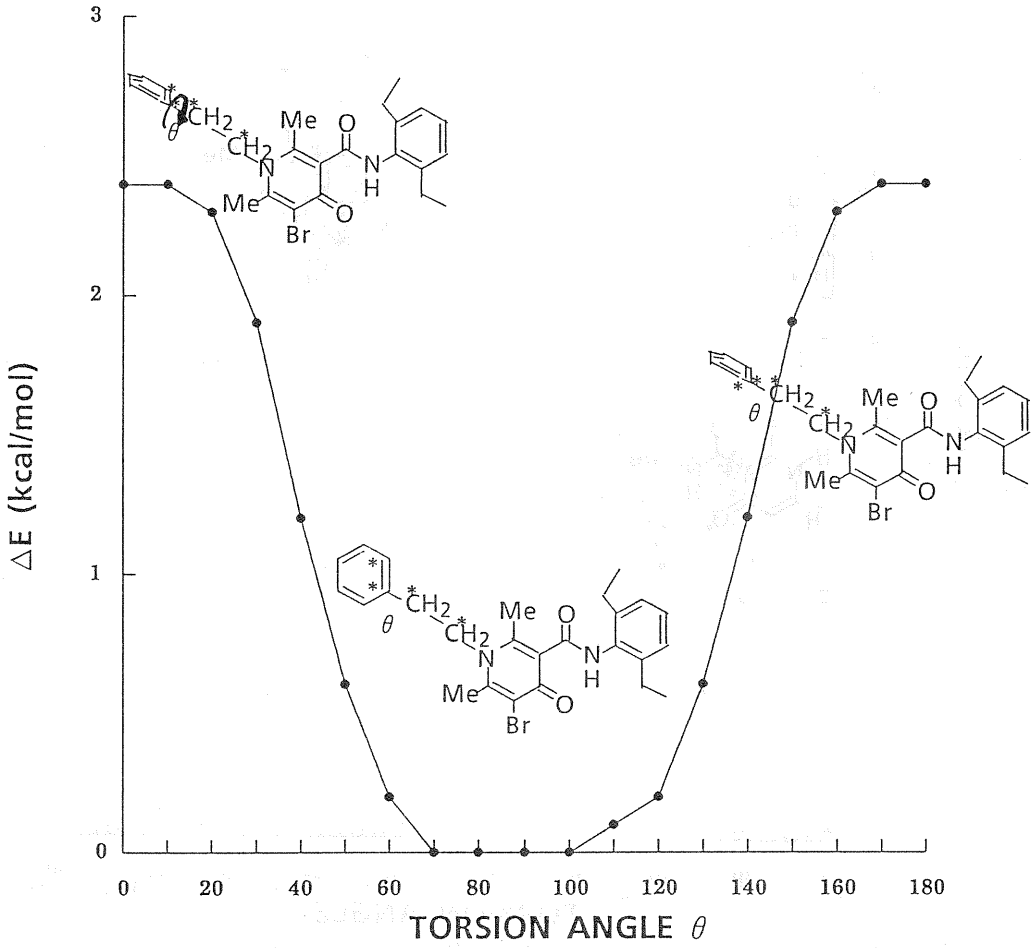
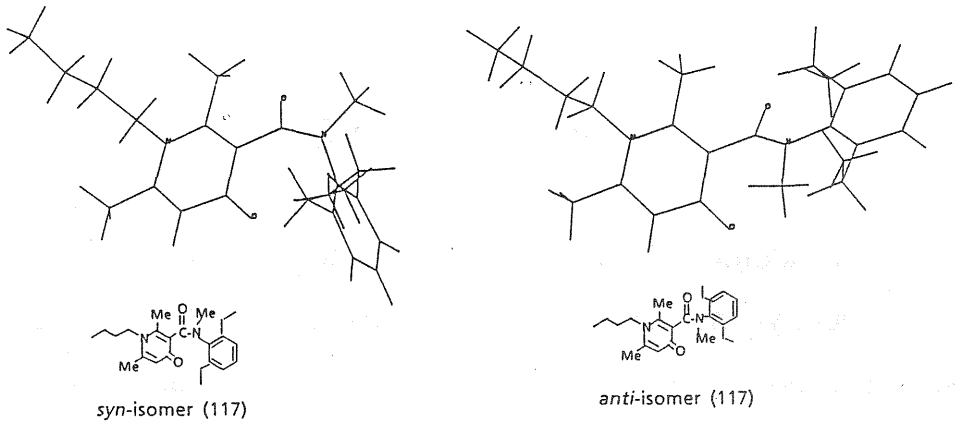


Fig.3-8 Energy-plot of compound 104 (AM1)

of the C-N bond (*syn*), while, in the other, on the opposite sides (*anti*). There was no significant difference in the heat of formation of *syn* and *anti* isomers. The skeleton models of these conformations are shown in Fig.3-9.



syn-isomer (117) *anti*-isomer (117)

Fig.3-9 Conformations of compound 117 (*syn*- and *anti*-isomers)

3-3-2 Structure-Activity Analysis with Superpositional Steric Parameter for Pyridone-Carboxanilides and *ortho*-Cl Diphenyl Ethers

We examined first how far the three-dimensional similarity in terms of the minimized RMS value based on the superposed structures defined by the twelve atoms could rationalize the variations in the activity. The RMS value of the reference compound **104** is zero by definition. With the RMS value only, no acceptable correlation equation was formulated. Attempting to consider other variables, we found that the molecular hydrophobicity is significant as a single parameter although the correlation quality is not satisfactory as shown in Eq.3-1.

$$pI_{50} = 0.98\ logP + 2.27 \qquad [3\text{-}1]$$
$$(0.50) \qquad (1.78)$$
$$n=14,\ s=0.70,\ r=0.78,\ F_{1,12}=18.51.$$

The addition of the RMS term into Eq.3-1 was not significant. Evidently, the RMS value representing a dissimilarity of the substructure only was not the parameter to rationalize the potency variations which are regulated by the characteristics of the entire molecule. We thought, however, if we could select subsets of compounds in which the skeletal substructure defined by twelve atoms is indeed a dominant feature and the contribution from substructures other than the skeleton is identical to or canceled out each other, we would at least be able to ascertain the importance of the hypothetical "common" substructure. We examined to use indicator variables differentiating pyridone-carboxanilides (**104**, **41**, **23** - **25**, **21**, **66**) from diphenyl ethers (**2-a** to **-g**), 1-*N*-phenethyl-pyridone-carboxanilides (**104**, **41**, **23** - **25**) from others (**21** and **66**), and 4-trifluoromethylated diphenyl ethers (**2-e** to **-g**) from other ethers (**2-a** to **-d**). We found that the addition of the indicator variable term differentiating compounds (**104**, **41**, **23** - **25**) from (**21** and **66**) leads to an acceptable correlation Eq.3-2.

$$pI_{50} = 0.63\ logP - 2.87\ RMS - 1.42\ I(1\text{-}N) + 4.48 \qquad [3\text{-}2]$$

(0.49) (2.61) (1.22) (2.26)

n=14, s=0.50, r=0.89 $F_{3,10}$=18.21

The I(1-N) takes the value of unity when the 1-*N* substituent is either benzyl or butyl in pyridone-carboxanilides. Omitting these two compounds, Eq.3-3 of a similar quality was obtained.

$$pI_{50} = 0.66\ logP - 2.75\ RMS + 4.34 \qquad [3\text{-}3]$$

(0.51) (2.66) (0.32)

n=12, s=0.56, r=0.86, $F_{2,9}$=12.35.

The pI_{50} value calculated with Eq.3-3 was shown in Tables 3-1 and 3-2. Eqs.3-2 and 3-3 indicate that the lower the dissimilarity of the substructural skeleton defined by twelve atoms as well as the higher the hydrophobicity, the higher the activity. The butyl and benzyl groups as the 1-*N*-substituent on the pyridone ring are inferior to the phenethyl substituent. The requirement, in which the 1-*N*-substituent should be kept unchanged for the RMS value to work in Eqs.3-2 and 3-3, is understandable, because our earlier quantitative-structure-activity analysis for a set of pyridone-carboxanilides in which the 1-*N* substituent was varied from lower alkyls, alkoxys, benzyl and phenethyl to chain struc-

tures being combined with the 2-position, indicates that the stereo-electronic nature of the 1-*N*-substituent is very important in regulating the herbicidal potency (Chapter 2). Eqs.3-2 and 3-3 requiring no significant contribution from the factor differentiating between pyridone-carboxanilides and diphenyl ethers should be considered to mean that the effect of substructural moieties other than the twelve atomic skeleton is fortuitously nearly equivalent. The effects of a part of the pyridone ring plus 1-*N*-phenethyl of the pyridone-carboxanilides and a part of the nitrated benzene ring bearing alkoxy or carb(alk)oxy groups plus the 4-substituent such as Cl and CF_3 are not significantly different from each other in the contribution to the herbicidal potency. The *logP* value is the parameter for the entire molecule, but, for twelve compounds included in Eq.3-3, it may be roughly collinear with the substructural hydrophobicity of the anilide benzene and *ortho*-chlorinated benzene rings of respective series of compounds. The addition of the term defining electronic structure was examined by using similarity indices for the electrostatic potential field as proposed by Carbo[44] and Hodgkin[45] and their respective coworkers, but neither of these indices improved the correlation. Apparently, the pattern of the electrostatic potential field is governed by the entire molecular structure.

In spite of these drawbacks, Eqs.3-2 and 3-3 were considered to support the procedure in which fourteen members of

pyridone-carboxanilides and diphenyl ethers were superposed on each other according to the assigned twelve atoms whenever above mentioned conditions for contributions from other parts of the molecule are satisfied.

3-3-3 The CoMFA Analysis for Pyridone-Carboxanilides and *ortho*-Cl Diphenyl Ethers

Because the procedure to superpose fourteen active conformations of pyridone-carboxanilides and diphenyl ethers seemed relevant in spite of certain restrictions, we proceeded to the CoMFA analysis to examine our hypothesis.

The CoMFA-PLS analysis was performed under conditions in which cross-validation = 14 for the same compounds as used to derive Eq.3-2, to indicate that the optimum number of latent variables was four (cross-validated r = 0.80). Then, the PLS analysis was repeated without cross-validation, under conditions in which the number of latent variables is four, leading to Eq.3-4. The press is the standard deviation from the leave-one-out cross-validation.

pI_{50}=0.77*logP*+[steric & electrostatic field descriptor terms]+1.58 [3-4]

n=14, r=0.97, s=0.27, press=0.77, $F_{4,9}$=33.55.

The *logP* and CoMFA field descriptors performed very

well to correlate the pI_{50} values, accounting for 94% of their variance. The relative contributions of *logP* and steric and electrostatic field descriptors were 0.275, 0.330 and 0.396, respectively. The calculated pI_{50} value from Eq.3-4 are shown in Tables 3-1 and 3-2. Eq.3-4 indicates that the three-dimensional steric and electrostatic factors of entire molecule are indeed significant in addition to the whole molecular hydrophobicity. It also shows an essential role of the alignment of the twelve atoms common between two series of compounds in the interaction with the hypothetical receptor site.

Figs.3-10 and 3-11 are the contour maps drawn according to Eq.3-4 showing regions in which steric and electrostatic potential fields, respectively, are either favorable or unfavorable to potentiating the light-dependent activity with the use of compounds **104** and **2-g** (**AFM**) as examples. Fig.3-10 shows that the smaller one of *ortho*-substituents in the anilide moiety in pyridone-carboxanilides and *ortho*-chlorinated benzene ring in diphenyl ethers, being surrounded by unfavorable region, is not needed to potentiate the light-dependent herbicidal activity. It also shows that the region at the vicinity of the 1-*N*-position of the pyridone ring is sterically unfavorable to the activity. The sterically unfavorable region is extended along the direction in which the 1-*N* substituent is lengthened. On the other hand, the regions accommodating the 3'-substituent in diphenyl ethers as well as the 2-substituent on the

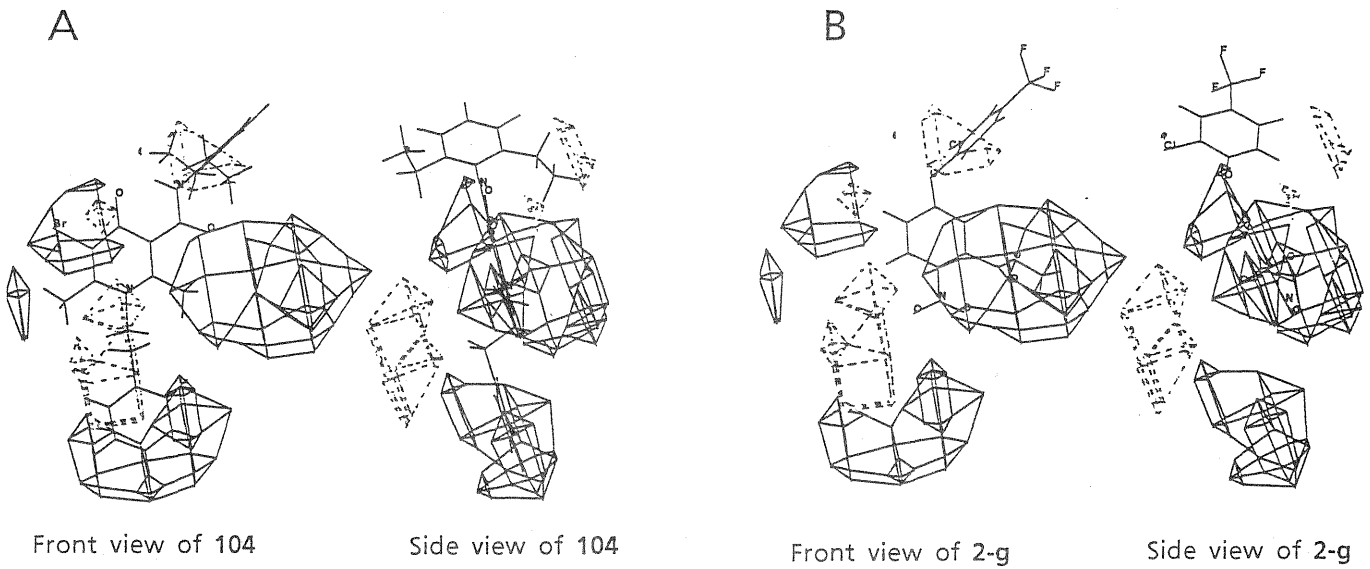


Fig.3-10 Orthogonal Views of Steric field map of Compounds 104 (A) and 2-g (B). The contours(solid lines) surround regions where a higher steric interaction increase light-dependent activity at the 0.01 coefficient level.The contours(dashed lines) surround regions where a lower steric interaction increase the activity at the -0.01 coefficient level.

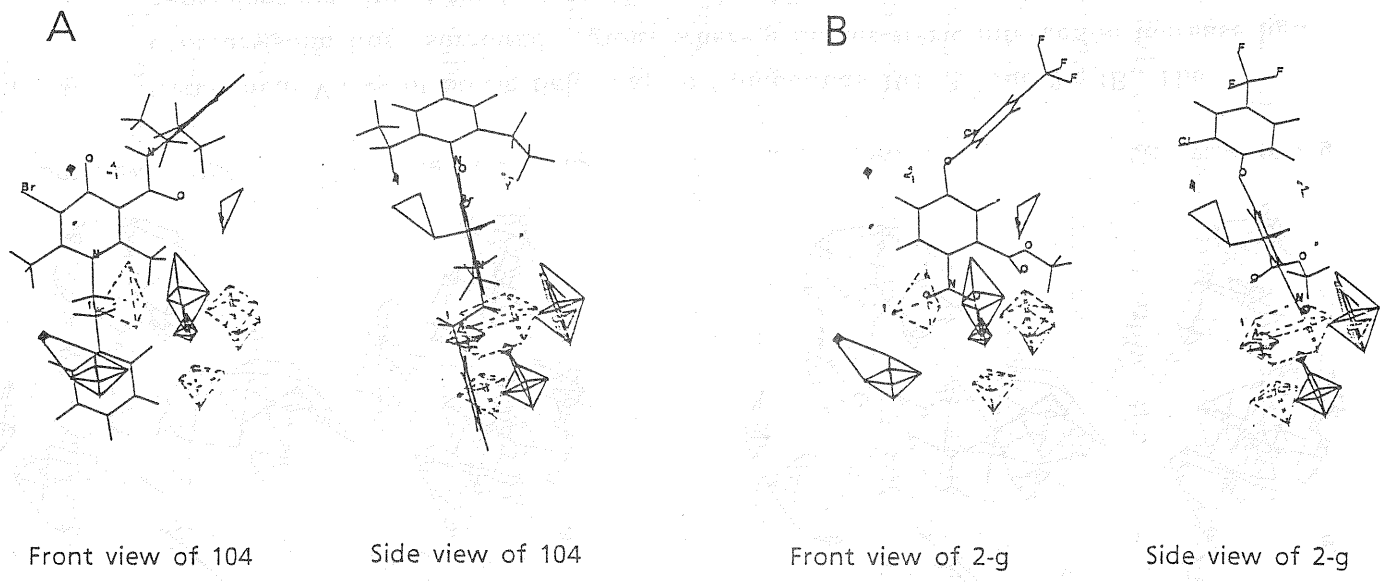


Fig.3-11 Orthogonal Views of Electrostatic field map of Compounds 104 (A) and 2-g (B). The contours(solid lines) surround regions where a more negative electrostatic interaction increase the light-dependent activity at the -0.015 coefficient level. The contours(dashed lines) surround regions where a more positive electrostatic interaction increase the activity at the 0.015 coefficient level.

pyridone ring, and the end benzene ring of the 1-*N*-phenethyl group and the 5-substituent in the pyridone ring in the pyridone-carboxanilides are sterically favorable to the activity.

Fig.3-10 indicates that the pattern of the electrostatic field in regions surrounding the pyridone moiety and the non-chlorinated benzene ring is of primary importance in governing the variations in the activity. The region surrounding a part of the 4'-NO_2 group in diphenyl ethers as well as the 2-substituent in the pyridone ring is electronegative. The region nearby the 3'-position in diphenyl ethers as well as the carbonyl oxygen of the amide linkage in pyridone-carboxanilides are also electronegative. The higher the electron density of atomic positions surrounded by the electronegative regions, the higher is the activity. Fig.3-11 also indicates an electro-negative contour in the region corresponding to the end benzene ring of the 1-*N* phenethyl substituent and a positive contour in the region of the alkyl chain of the 1-*N* substituents in pyridone-carboxanilides.

3-4 Discussion

The CoMFA results were in accord with our previous QSAR analysis with the use of free-energy-related substituent parameters and the traditional regression analysis. According to the previous analysis, the bulk of the larger one of two *ortho*-substitu-

ents in the anilide moiety and that of the 5-substituent in the pyridone ring are favorable to the activity with their respective optimum. The lengthy but slim substituents at the 1-*N* position are also advantageous. The inductively electron- donating property of the 1-*N* substituent works to potentiate the activity. These features in stereo-electronic effects of substituents at respective positions were nicely reproduced by the CoMFA analysis in terms of the contour maps for coefficients of steric and electronic descriptors at the lattice points.

The fact that the *logP* value of the entire molecule is significant in Eq.3-4 is somewhat inconsistent with the earlier QSAR in which the hydrophobicity of the anilide benzene ring was only significant in governing the potency variations of pyridone-carboxanilides. For pyridone-carboxanilides, the hydrophobicity of the entire molecule could be one of the significant factors in such processes as transport, but the anilide moiety may be given the critical role for the overall potency variations. Another possibility is that, as briefly mentioned before, the molecular *logP* may be collinear with the hydrophobicity of anilide-benzene and *ortho*-chlorinated benzene moieties as far as two types of compounds included in the present analysis are concerned.

The effect of the electron withdrawing characters of the 4'-NO_2 group and such 3'-substituents as carb(alk)oxy groups in diphenyl ethers could be rationalized by the electronegative regions

close to these groups as shown in Fig.3-11. The electro-positive region appearing also near the 3'-substituent could accommodate a partial positive charge of alkoxy-oxygen brought about by delocalization of lone pair electrons in compounds **2-d** and **-e**. A part of the 4'-NO_2 group is, however, surrounded by the positive region, so the overall electrostatic potential field at the vicinity of the 4'-substituent would be nearly neutral. The fact that a diphenyl ether coded as MC10878 (Fig.3-1: Y_n=4-CF_3, R'_3=COOMe, 4'=H in place of NO_2) is reported to exhibit a potent light-dependent herbicidal activity[46] is not inconsistent with the present CoMFA result. It should be mentioned that this type of the 4'- substituent effect as discussed above was revealed only with the analysis combined with pyridone-carboxanilides. With the subset of seven diphenyl ethers in which the 4'-NO_2 group is invariably substituted, no information for the 4'-substituent effect is extracted.

There was another support to the present analysis covering the two different series of compounds. In the subset of seven pyridone-carboxanilides, the 2-substituent is always Me. Because the electronegative region close to the 4'-NO_2 group in diphenyl ethers also covers the 2-substituent position of the pyridone ring in Fig.3-11, and also because the region accommodating this substituent position is not sterically forbidden in Fig.3-10, the introduction of an electron-withdrawing substituent into this position of the pyridone ring was expected to give a highly potent compound. We

synthesized the 2-CF_3 analog (Fig.3-1:R_1=n-Bu, R_2=CF_3, R_5=H), which actually showed a very potent light-dependent activity of at least 25 times more active than compound **66**. The fact that the DLH-1777 with the propyl group at this position, that was not included in the analysis, is highly active, was regarded as a further support to the analysis.

As described in Chapter 1, some pyridone-carboxanilides in which R_1=benzyl, R_2=Me and R_5=H are fixed but X_n is varied within combinations of small substituents show the herbicidal activity under the light as well as dark conditions. These compounds may be able to take the active conformation essential to the light-dependent activity. The *N*-methylated-anilide compound (**117**) is light-independent the potency of which is very low, the I_{50} value being close to 2×10^{-3}M. This compound was selected because its light-dependent activity is almost lost and also because the modification of the structure from the light-dependent parent compound (**66**) is only slight. As shown in Fig.3-9 and Table 3-3, the light-independent **117** has two stable conformations. The *syn*-type conformation that differs more drastically than the *anti*-type from the stable conformations of light-dependent pyridone-carboxanilides could be the active conformation for the light-independent activity.

In summary, the CoMFA procedure for light-dependent herbicides was able to reproduce our earlier QSAR results. Furthermore, from the analysis in which two structurally different

series of compounds were dealt with as a single set, additional structure-activity information was extracted that was able not only to rationalize the experimental results beyond those for the series of compounds included in the analysis but also to predict new analogs of higher potency. One of the difficulties in the CoMFA procedure is, however, to find out how to superpose the molecules, in particular, when the set of structurally different types of compounds is to be analyzed. Some extent of arbitrariness seems to be inevitable and the results should be examined by comparing with those from the traditional QSAR analyses. Another is that, even though it is the quantitative procedure, the results are interpreted rather qualitatively than the traditional quantitative procedure. The merit of visualization of the results may also be compensated by the use of latent variables the meaning of which are not straightforward. We believe that the CoMFA approach can be used for more complicated structure-activity problems but complemental supports are necessary from the traditional QSAR procedures.

Chapter 4 Preparation of Compounds

Various types of 4-pyridone-3-carboxanilides were synthesized, mainly by the following methods.

1-Benzyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide(21)

N-(2,6-diethylphenyl)-3-oxobutanamide (2.66, 11.4mmol) was allowed to react with benzylamine (1.22g, 11.4mmol) in toluene (5ml) solution of diketene (1.34g, 15.9mmol), and after stirring for 4hr, by treatment with 1N methanolic NaOH solution (5ml). After stirring for 3hr at 0°C, toluene (30ml) was added and the solution was washed with brine, dried over $MgSO_4$ and evaporated. The residue was crystallized from toluene-Et_2O to afford 3.40g (77%) of 1-benzyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide having mp 142-146.5°C . ^{1}H-NMR ($CDCl_3$) δ: 1.18(6H,t), 2.28(3H,s), 2.66(4H,q), 2.78(3H,s), 5.20(2H,s), 6.48(1H,s), 6.75-7.60(8H,m), 11.64(1H,br).

1-Butyl-1,4-dihydro-2,6-dimethyl-2'-methoxy-4-oxo-3-pyridinecarboxanilide:(49)

A solution of 4.21 g (20.3 mmol) of *N*-(2-methoxyphenyl)-3-oxo-butaneamide, 2.08 g (28.4 mmol) of butylamine, and three drops of acetic acid in 25 ml of toluene was refluxed for 1.5 hr.

The water generated by the reaction and the excess of butylamine were removed through Dean-Stark's water separator together with about 12 ml of toluene. While refluxing, a toluene solution of 2,2,6-trimethyl-4*H*-1,3-dioxine-4-one (2M, 21.7 ml) was added dropwise to the mixture in a 30 min period. After the reaction mixture was refluxed further for 45 min, it was cooled to room temperature. The crystals precipitated were separated by filtration and dried under reduced pressure to afford 3.47 g of 1-butyl-1,4-dihydro-2,6-dimethyl-2'-methoxy-4-oxo-3-pyridinecarboxanilide having mp 158-160°C . ^{1}H- NMR ($CDCl_3$) δ: 0.93(3H,t), 1.13-1.93(4H,m), 2.33(3H,s), 2.86(3H,s), 3.60-4.00(5H,m), 6.35(1H,s), 6.60-7.24(3H,m), 8.10-8.60(1H,m), 10.90(1H,br).

2',6'-Diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-1-(2-propinyl)-3-pyridinecarboxanilide (82):

A solution of 4.05 g (17.4 mmol) of *N*-(2,6-diethylphenyl)-3-oxo-butaneamide, 1.34 g (24.3 mmol) of propargylamine and one drop of acetic acid in 25 ml of toluene was refluxed for 1.5 hr. The water generated by the reaction and excess of propargylamine were removed through Dean-Stark's water separator together with about 12 ml of toluene. While heating, a toluene solution of 2,2,6-trimethyl-4*H*-1,3-dioxine-4-one (2M, 21.7 ml) was added dropwise to the mixture in a 30 min period. After the reaction mixture was refluxed further for 1.5 hr, it was cooled to room temperature. The

crystals precipitated were separated by filtration and dried under reduced pressure to afford 3.47g of 2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-1-(2-propinyl)-3-pyridinecarboxanilide having mp 259-261°C. ^{1}H- NMR ($CDCl_3$) δ :1.20(6H,t), 2.49-2.86(8H,m), 3.02(3H,s), 4.65(2H,d), 6.39(1H,s), 7.2(3H,s), 10.86(1H,br).

2',6'-Diethyl-6,7,8,9,-tetrahydro-4-methyl-2-oxo-2*H*-quinolizine-1-carboxanilide (87):

A solution of 3.10 g of methyl (hexahydro-2-pyridinylidene)acetate in 10 ml of xylene was gently refluxed, and a solution of 7.81 g of 2-ethyl-2,6-dimethyl-4*H*-1,3-dioxine-4-one in 10 ml of xylene was added dropwise in a period of 20 min. The mixture was further refluxed for 2 hr, removing the by-product, methyl ethyl ketone, with the Dean-Stark's apparatus. The reaction mixture was cooled to room temperature. The resulted crystals were filtered to obtain 4.11 g of 6,7,8,9-tetrahydro-4-methyl-2-oxo-2*H*-quinolizine-1-carboxylate. A mixture of 3.50 g of this compound and 126 g of 5% aqueous sodium hydroxide solution was stirred for 2 hr at 70°C. To the reaction mixture 13.9 ml of concentrated hydrochloric acid was added under ice-cooling. The mixture was extracted with $CHCl_3$, and the extract was dried and concentrated. The residue was recrystallized from a mixture of toluene and $CHCl_3$ to afford 1.89 g of 6,7,8,9-tetrahydro-4-methyl-2-oxo-2*H*-quinolizine-1-carboxylic acid. To a solution of 1.0 g of

this acid in 15 ml of CH_2Cl_2 a solution of 0.37 ml of $SOCl_2$ in 5 ml of CH_2Cl_2 was added dropwise under ice-cooling. Then, a solution of 0.79 g of 2,6-diethylaniline and 1.34 ml of triethylamine in 5 ml of CH_2Cl_2 was added to the above reaction mixture and stirred for 1 hr under ice-cooling. After allowing to stand overnight at room temperature, the reaction mixture was washed with water and saturated NaCl solution, dried and concentrated. The crystalline residue was recrystallized from ethyl acetate to afford 0.80 g of 2',6'-diethylphenyl)-6,7,8,9-tetrahydro-4-methyl-2-oxo-2*H*-quinolizine-1-carboxanilide having mp 134.5-137°C. ^{1}H-NMR ($CDCl_3$) δ: 1.16(6H,t), 1.60-2.04(4H,m), 2.28(3H,s), 2.58(4H,q), 3.56(2H,t), 3.84(2H,t), 6.36(1H,s), 7.04(3H,s), 11.65(1H,br).

1-Butyl-5-chloro-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide:(89)

A mixture of 500mg (1.41 mmol, m.p. 110°-112°C.) of 1-butyl-*N*-(2,6-diethylphenyl)-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridine carboxanilide and 188mg (1.41mmol) of *N*-chlorosuccinimide was dissolved in 15ml of chloroform and refluxed with stirring. To the reaction mixture, 190mg of *N*-chloro-succinimide was added in twice, and refluxed for 15.2 hr.

The reaction mixture, transferred to a separately funnel, was washed with water, saturated sodium bicarbonate and water. The

organic layer was dried and concentrated in a usual manner to give a yellow oil, which was purified by column chromatography (Wacogel C-200) with a mixture of ethyl acetate and hexane, affording 300mg of 1-Butyl-5-chloro-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide having m.p. 125.5°-126.5°C. ^{1}H-NMR($CDCl_3$) δ:1.18(6H,t), 0.8-2.0(7H,m), 2.62(3H,s), 2.66(4H,q), 2.83(3H,s), 4.02(2H,s), 7.07(3H,s), 10.88(1H,br)

5-Bromo-1-butyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide (90):

To a mixture of 658 mg (1.85 mmol) of 1-butyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxanilide, 14 ml of CH_2Cl_2 and 1.18 g (11.10 mmol) of sodium carbonate, a solution of 297 mg (1.86 mmol) of bromine in 6 ml of CH_2Cl_2 was added under vigorous stirring for 8 hr. The insoluble product in CH_2Cl_2 was filtered off and the filtrate was concentrated under reduced pressure to give a crystalline residue. The residue was recrystallized from ethyl acetate and hexane to afford 669 mg of 5-bromo-1-butyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-3-pyridinecarboxainilide having mp 161-162.5°C. ^{1}H- NMR($CDCl_3$) δ: 1.17(6H,t), 0.7-2.0(7H,m), 2.65(4H,q), 2.71(3H,s), 2.83(3H,s), 4.04(2H,t), 7.07(3H,t), 10.86(1H,br).

1-Butyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-5-phenylmethyl-3-pyridinecarboxanilide:(93)

A mixture of 1.00g (2.57mmol,m.p.95°-96°C.) of 2',6'-diethyl-2,6-dimethyl-4-oxo-5-phenylmethyl-4*H*-pyrane-3-carboxanilide and 0.28g (3.85mmol) of butyl amine was dissolved in 5ml of toluene and 1*N* hydroxysodium methanol solution and refluxed with stirring for 48hr at room temperature. The reaction mixture was transferred to a separately funnel, was washed with water. The organic layer was dried and concentrated in a usual manner to give a oil, affording 0.75g of 1-Butyl-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-5-phenylmethyl-3-pyridinecarboxanilide. ^{1}H-NMR($CDCl_3$) δ: 0.60-2.00(7H,m), 1.17(6H,t), 2.32(3H,s), 2.66(4H,q), 2.86(3H,s), 3.93(2H,t), 4.06(2H,s), 6.90-7.25(8H,m), 11.77(1H,br)

3-Bromo-2'-chloro-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxanilide: (104)

A solution of 20.0 g of methyl (hexahydro-2-azepinylidene)acetate in 77 ml of xylene was gently refluxed, and a solution of 41.9 g of 2,2,6-trimethyl-4*H*-1,3-dioxine-4-one in 41 ml of xylene was added dropwise in 45 min and the whole was refluxed for 2 hr. The by-product and acetone were removed with the Dean-Stark apparatus. The reaction mixture was cooled to room temperature. The resulting crystals were filtered, washed by

cold xylene and dried to afford 21.4 g of methyl-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxylate having m.p.174-176°C. To a solution of 14.1 g of the resulted compound and 38.2 g of sodium carbonate in 178 ml of CH_2Cl_2, a solution of 3.69 ml of bromine in 89 ml of CH_2Cl_2 was added dropwise at room temperature in 30 min, followed by stirring for 80 min at room temperature. The reaction mixture was washed with 10% aqueous sodium bisulfite, saturated sodium bicarbonate and water, consecutively, dried and concentrated. The crystalline residue was recrystallized from a mixture of ethyl acetate and methanol to afford 15.7 g of methyl 3-bromo-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxylate. A mixture of this compound and 10% aqueous sodium hydroxide solution was stirred for 3 hours at 100°C and cooled to room temperature. The precipitated crystals were filtered, washed and dried under reduced pressure to obtain 14.2 g of 3-bromo-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxylic acid. To a solution of 0.90 g of this acid in 11 ml of CH_2Cl_2 a solution of 0.23 ml of $SOCl_2$ in 4 ml of CH_2Cl_2 was added dropwise under ice-cooling. Then, a solution of 0.79g of 2-chloroaniline and 1.34 ml triethylamine in 5 ml of CH_2Cl_2 was added to the above reaction mixture and stirred for 100 min under ice-cooling. After allowing to stand overnight at room temperature, the reaction mixture was washed with 10% aqueous sodium hydroxide solution and water, dried and concen-

trated. The crystalline residue was recrystallized from CH_2Cl_2 to afford 0.80 g of 3-bromo-2'-chloro-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine]-1-carboxanilide having mp 252.0-255.0°C. ^{1}H-NMR (DMSO-d6) δ: 1.43-1.97(6H,m), 2.67(3H,s), 3.03-3.41(2H,m), 4.11-4.45(2H,m), 6.94-7.67(3H,m), 7.95-8.32(1H,m), 10.70(1H,br).

3-Bromo-2',6'-diethyl-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxanilide (107):

A solution of 20.0 g of methyl (hexahydro-2-azepinylidene)acetate in 77 ml of xylene was gently refluxed, and a solution of 41.9 g of 2,2,6-trimethyl-4*H*-1,3-dioxine-4-one in 41 ml of xylene was added dropwise in 45 min and refluxed for 2 hr. The by-product and acetone was removed with the Dean-Stark apparatus. The reaction mixture was cooled to room temperature. The resulting crystals were filtered, washed by cold xylene and dried to afford 21.4 g of methyl-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxylate having m.p.174-176°C. To a solution of 14.1 g of the resulted compound and 38.2 g of sodium carbonate in 178 ml of CH_2Cl_2, a solution of 3.69 ml of bromine in 89 ml of CH_2Cl_2 was added dropwise at room temperature in 30 min, followed by stirring for 80 min at room temperature. The reaction mixture was washed with 10% aqueous sodium bisulfite, saturated sodium bicarbonate and water, consecutively, dried and

concentrated. The crystalline residue was recrystallized from a mixture of ethyl acetate and methanol to afford 15.7 g of methyl 3-bromo-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a] azepine-1-carboxylate. This compound was converted into 3-bromo-2',6'-diethyl-2,6,7,8,9,10-hexahydro-4-methyl-2-oxo-pyrido[1,2-a]azepine-1-carboxanilide, having mp 178-179.5°C, by hydrolysis and amidation in a manner similar as to afford (**87**). ^{1}H-NMR($CDCl_3$) δ: 1.18(6H,t), 1.75-2.10(6H,m), 2.67(4H,q), 2.70(3H,s), 3.30-3.70(2H,m), 4.00-4.20(2H,m), 7.08(3H,s), 10.58(1h,br).

General Conclusion

In this thesis, potent light-dependent herbicidal pyridone-carboxanilides were selected and physicochemical bases for the selection of candidate light-dependent herbicides for developmental studies were analyzed by use of traditional regression analysis and comparative molecular field analysis.

In Chapter 1, novel 4-pyridone-3-carboxanilide derivatives containing various substituents on the anilide benzene and 4-pyridone rings were synthesized, and their herbicidal activity against *Echinochloa oryzicola* was evaluated. These compounds exhibited light-dependent herbicidal activity, except for some 1-*N*-benzyl analogs substituted on the anilide moiety which was light-independent. Among compounds synthesized, 5-bromo-2',6'-diethyl-1,4-dihydro-2,6-dimethyl-4-oxo-1-phenethyl-3-pyridinecarboxanilide was found to possess the highest light-dependent herbicidal activity, being almost equivalent with that of oxyfluorfen. The effect of substituents of the anilide benzene and 4-pyridone rings on the activity was discussed.

In Chapter 2, the variations in the light-dependent herbicidal activity to *Echinochloa oryzicola* of a number of 4-pyridone-3-carboxanilides substituted by various substituents on the anilide-benzene and pyridone rings were examined by use of physicochemical substituent parameters and the regression analysis.

The effects of substituents on the anilide ring were such that the activity was related parabolically not only with the substituent hydrophobicity (π) but also with the steric bulk parameter ($-E_s$) of the bulkier ortho substituent. The effect of substituents at the 1-*N* position was analyzed steric(STERIMOL L and B_5) and electronic(σ_I) parameters. That of the 5-position substituents of the pyridone ring was explained by a parabolic function of a steric (MR) parameter. The analyses for the activity of 105 analogs in total confirmed that our previous selection of a candidate compound in this series for field trials was indeed appropriate in terms of physicochemical substituent effects.

In Chapter 3, using a set of representative members selected from 4-pyridone-3-carboxanilides and *ortho*-chlorinated diphenyl ethers exhibiting light-dependent herbicidal activity, we examined the three-dimensional structure-activity relationships quantitatively. The most stable conformation of each compound regarded as the "active conformation" was determined by either semi-empirical or *ab initio* molecular orbital calculations. With a hypothesis defining a common substructural skeleton between the two different compound series, each molecule was superposed. We first analyzed the structure-activity relationship using an index for the substructure shape similarity according to the superposed conformations. After finding a relevance of the hypothesis, we examined the three-dimensional structure-activity relationship using

the comparative molecular field analysis procedure. The result suggested that the two different series of compounds share a common region of the receptor site. The variations in the light-dependent herbicidal potency were governed by hydrophobicity and three-dimensional steric and electronic field parameters of molecules participating in the transport process and the interaction with the receptor site. The result was consistent with that derived from our previous quantitative analysis with the use of free-energy-related substituent parameters and the traditional regression procedure for a large number of pyridone-carboxanilides.

The present approach would substantiate not only the selection of potent light-dependent pyridone-carboxanilides but also discovery of novel types of light-dependent herbicides. It is hoped that the procedures used here could be extended to other related fields such as insecticides, fungicides, and plant growth regulators as well as various types of medicines in rationally designing novel compounds.

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H. Osabe, Y. Morishima, Y. Goto, K. Masamoto, H. Yagihara and T. Fujita, "Light-dependent herbicidal activity of 4-pyridone-3-carboxanilide derivatives against *Echinochloa oryzicola*", *Pestic. Sci.*, **32**, (1991) 73-84.

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Acknowledgements

The author would like to his sincere gratitude to Professor Toshio Fujita for his supervision and stimulating discussions. He also wishes to express his acknowledgement to Professor Shooichi Matsunaka of Kobe University for his leading me the herbicide study. The author thanks Messrs. Manabu Kai, Tatsuo Goto and Hiroshi Yagihara of Daicel Chemical Industries, LTD. for their unfailing interest and encouragement. He is deeply indebted to Dr. Yoshiaki Nakagawa, Dr. Miki Akamatsu and Mr. Nobuhiro Oikawa, Department of Agricultural Chemistry, Kyoto University for their expert advises. Grateful acknowledgement is made to Dr. Yoichiro Ueda and Messrs. Yukihisa Goto and Kazuhisa Masamoto for synthesizing pyridone-carboxanilide derivatives. He thanks Dr. Yasuo Morishima for his guidance of the mode of action study of light-dependent herbicides. He also appreciates the help of Mr. Hiroshi Itoh in the computational assistance.

Finally, the author sincerely thanks to all my colleagues in Research Center, Daicel Chemical Industries, LTD. for their help.