Structure-Activity Study of S-*n*-Butyl S'-*p*-*tert*-Butylbenzyl N-3-Pyridyldithiocarbonimide (S-1358, Denmert®) and Its Derivatives

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Fungicidal activities of S-alkyl S'-*p*-substituted benzyl N-3-pyridyldithiocarbonimides toward *Coniothyrium diplodiella*, *Sclerotinia sclerotiorum* (on agar medium) and *Sphaerotheca fuliginea* (on pot test) were shown. The activities varied with the change of the S-alkyl group and were maximized at certain numbers of carbon atoms.

A different pattern was observed in the activity toward *S. fuliginea* when the carbon number was 8 or more. Bulkiness of the S-alkyl group also appeared to influence the activities. The steric factor of the *p*-alkyl substituents mainly influenced the activity toward *S. fuliginea* up to the *tert*-butyl analog. The activities toward *C. diplodiella* and *S. sclerotiorum* increased with the increase in the bulkiness and the hydrophylicity of the *p*-substituent. *R_m* values were determined on reversed phase TLC and the structure-activity correlations were analyzed against hydrophobic (*R_m*), electronic (σ) and steric (*E_s*) factors on 34 compounds.

S-*n*-Butyl S'-*p*-*tert*-butylbenzyl N-3-pyridyldithiocarbonimide [compound V (R=*n*-butyl, X=*tert*-butyl), experimental code No. S-1358* or Denmert®] in Fig. 1 showed high preventive and curative effects on powdery mildew of many agricultural and horticultural plants.¹⁾ Bioassay on agar medium showed this new fungicide had activity toward several fungi belonging to *Ascomycetes* and *fungi Imperfecti*.¹⁾ We now report structure-activity relationships of Denmert and its derivatives against three fungi; *Coniothyrium diplodiella* and *Sclerotinia sclerotiorum* on agar medium and *Sphaerotheca fuliginea* (cucumber powdery mildew) on pot test.

MATERIALS AND METHODS

Synthesis of compounds

The compounds were prepared via the routes in Fig. 1. The preparative routes of the alkyl dithiocarbamates (IV) depended on the species of the substituent R: the alkyl iodides (R-I) were treated with the triethylammonium dithiocarbamate (II)⁴⁾ for the *n*-alkyl

FIG. 1. Synthesis of the Compound V.

analogs and the alkyl mercaptans (R-SH) with the isothiocyanate (III)⁵⁾ for the *sec*- and *tert*-analogs. The dithiocarbamates (V) were obtained by the condensation of the alkyl dithiocarbamates (IV) with the substituted benzyl chlorides or bromides in the presence of a base. The structures of the compounds were confirmed by IR and NMR spectroscopy and elementary analysis for C, H, N and S. A typical procedure is shown in the following example.

1) *n*-Butyl N-3-pyridyldithiocarbamate. Triethyl-

* Mode of action²⁾ and metabolism³⁾ of Denmert were reported previously.

ammonium N-3-pyridyldithiocarbamate (27.1 g, 0.10 mole) was dissolved in 50% aq. CH_3OH (100 ml) and *n*-butyl iodide (18.4 g, 0.10 mole) was added dropwise at 20°C under cooling. After 4 hr, the resulting crystals were filtered off, washed with water (50 ml) and *n*-hexane (50 ml) and then recrystallized from iso $\text{C}_3\text{H}_7\text{OH}$ to give 14.2 g (63%) of yellow needles (mp 104~105°C).

Other *n*-alkyl N-3-pyridyldithiocarbamates were similarly prepared and are listed in Table I.

2) *tert*-Butyl N-3-pyridyldithiocarbamate. To a mixture of 2-pyridylisothiocyanate (13.6 g, 0.10 mole), benzene (50 ml) and a few drops of triethylamine was added *tert*-butyl mercaptan (10.0 g, 0.11 mole) dropwise over 15 min under stirring at 20°C. After 1 hr, the reaction mixture was heated at 35°C for 1 hr, then cooled to 10°C. The resulting crystals were filtered off, washed with benzene (100 ml) at 10°C to give 19.2 g (85%) of pale yellow needles (mp 117~119°C).

Other *sec*- and *tert*-alkyl N-3-pyridyldithiocarba-

mates were similarly prepared and are listed in Table I.

3) *S*-*tert*-Butyl *S'*-*p*-*tert*-butylbenzyl N-3-pyridyldithiocarbonimidate (5). *tert*-Butyl N-3-pyridyldithiocarbamate (2.26 g, 0.01 mole) was dissolved in a NaOCH_3 solution at below 10°C prepared from Na (0.23 g, 0.01 mole) and CH_3OH (50 ml). Then *p*-*tert*-butylbenzyl bromide^{b)} (2.27 g, 0.011 mole) was added dropwise to the cold solution and the mixture was allowed to stand for 1 hr, poured into cold water (300 ml) and extracted with ethyl acetate (100 ml). The extract was washed with water (100 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The oily residue was purified by silicagel column chromatography with the solvent system of *n*-hexane/acetone (50/1) to give 3.00 (81%) of oil which then crystallized to give white needles (mp 91~92°C).

Other S-alkyl *S'*-*p*-substituted benzyl N-3-pyridyldithiocarbonimidates were similarly prepared and are listed in Tables II and III.

TABLE I. LIST OF S-ALKYL N-3-PYRIDYLDITHIOCARBAMATES (IV)

No.	Alkyl ^{a)}	mp(°C) ^{b)}	Elementary analysis (%)				
				C	H	N	S
1	CH ₃	133~134	f ^{c)}	44.96	4.68	14.66	34.58
			c ^{d)}	45.62	4.38	15.20	34.79
2	C ₂ H ₅	116~118	f	48.21	5.12	13.96	32.63
			c	48.45	5.09	14.13	32.33
3	<i>i</i> -C ₃ H ₇	124~125	f	51.12	5.61	13.01	29.92
			c	50.90	5.71	13.20	30.20
4	<i>n</i> -C ₃ H ₇	88~ 89	f	50.82	5.68	13.01	29.86
5	<i>t</i> -C ₄ H ₉	117~119	f	52.93	6.21	12.22	28.15
			c	53.05	6.25	12.38	28.32
6	<i>i</i> -C ₄ H ₉	89~ 91	f	53.11	6.28	12.15	28.21
7	<i>s</i> -C ₄ H ₉	94.5~ 96	f	53.38	6.37	12.54	28.43
8	<i>n</i> -C ₄ H ₉	104~105	f	53.09	6.10	12.34	28.25
9	<i>t</i> -C ₅ H ₁₁	120~121	f	55.11	6.53	11.48	26.60
			c	54.95	6.72	11.66	26.67
10	<i>s</i> -C ₅ H ₁₁	60~ 62	f	55.01	6.71	11.92	25.51
11	<i>n</i> -C ₅ H ₁₁	90~ 91	f	54.87	6.69	11.72	26.57
12	<i>t</i> -C ₆ H ₁₃	135~136	f	56.38	7.38	11.28	25.55
			c	56.64	7.15	11.01	25.20
13	<i>n</i> -C ₆ H ₁₃	85~ 86	f	56.53	7.22	10.88	25.39
14	<i>n</i> -C ₇ H ₁₅	81~ 82	f	58.06	7.61	10.38	23.90
			c	58.16	7.52	10.44	23.88
15	<i>n</i> -C ₈ H ₁₇	86.5~87.5	f	60.01	7.88	9.70	22.61
			c	59.52	7.87	9.92	22.70
16	<i>n</i> -C ₉ H ₁₉	87.5~88.5	f	60.80	8.23	9.30	21.92
			c	60.75	8.17	9.45	21.62
17	<i>n</i> -C ₁₀ H ₂₁	91.5~ 93	f	62.10	8.45	9.01	20.42
			c	61.88	8.46	9.02	20.65
18	<i>n</i> -C ₁₂ H ₂₅	95~ 96	f	63.80	8.94	8.13	18.75
			c	63.84	8.95	8.27	18.94

^{a)} *n*, *i*, *s* and *t* are abbreviations of normal, iso, secondary and tertiary respectively.

^{b)} All melting points are uncorrected.

^{c)} Found.

^{d)} Calculated.

TABLE II. FUNGICIDAL ACTIVITIES AND PHYSICAL PROPERTIES OF S-ALKYL S'-p-tert-BUTYPBENZYL

No.	R(Alkyl)	N-3-Pyridylidithiocarbonimidates				Activity (ED ₅₀ μM)		
		mp ^{a)} or n _D ²²	R _M	Es ^{a)}	σ ^{e)}	C. d. ^{d)}	S. s. ^{e)}	S. f. ^{f)}
1	CH ₃	56~57	-0.78	0.00	0.00	1.00	1.50	550
2	C ₂ H ₅	56.5~58.5	-0.62	-0.38	-0.10	0.34	0.96	140
3	i-C ₃ H ₇ ^{g)}	69~70.5	-0.55	-1.08	-0.19	0.29	0.95	13.0
4	n-C ₃ H ₇	35.5~37	-0.48	-0.67	-0.12	0.29	1.20	36.0
5	t-C ₄ H ₉	91~92	-0.48	-2.46	-0.30	0.21	3.40	2.70
6	i-C ₄ H ₉	1.5935	-0.42 ^{h)}	-1.24	-0.13	0.32	5.00	9.00
7	s-C ₄ H ₉	1.5966	-0.42 ^{h)}	-1.74	-0.21	0.27	1.30	7.40
8	n-C ₄ H ₉	31~33	-0.38	-0.70	-0.13	0.30	3.20	5.00
9	t-C ₅ H ₁₁	39~41	-0.34 ^{h)}	-2.71	-0.31	0.12	5.80	2.50
10	s-C ₅ H ₁₁	1.5860	-0.32	-2.59	-0.23	0.10	3.50	2.10
11	n-C ₅ H ₁₁	1.5910	-0.25 ^{h)}	-0.71	-0.13	0.22	4.80	4.40
12	t-C ₆ H ₁₃	1.5900	-0.23	-3.39	-0.34	0.20	24.0	2.40
13	n-C ₆ H ₁₃	1.5830	-0.11	-0.64	-0.13	0.31	20.0	5.20
14	n-C ₇ H ₁₅	1.5695	-0.01	-0.64	-0.13	0.96	>100 ⁱ⁾	7.50
15	n-C ₈ H ₁₇	1.5762	0.17	-0.64	-0.13	7.20	>100 ⁱ⁾	4.70
16	n-C ₉ H ₁₉	1.5730	0.30 ^{h)}	-0.64	-0.13	10.0	>100 ⁱ⁾	3.00
17	n-C ₁₀ H ₂₁	1.5640	0.46	-0.64	-0.13	>100 ⁱ⁾	>100 ⁱ⁾	2.30
18	n-C ₁₁ H ₂₃	1.5592	0.78	-0.64	-0.13	>100 ⁱ⁾	>100 ⁱ⁾	2.50

^{a)} Uncorrected. ^{b)} Hancock's steric constant, see Ref. 14. ^{c)} Taft's electronic constant, see Refs. 12 and 13. ^{d)} *C. diplodiella*. ^{e)} *S. sclerotiorum*. ^{f)} *S. fuliginea*. ^{g)} *n*, *i*, *s* and *t* are abbreviations of normal, iso, secondary and tertiary. ^{h)} Obtained by Eq. 1 in the footnote. ⁱ⁾ Omitted from the regression analysis.

TABLE III. FUNGICIDAL ACTIVITIES AND PHYSICAL PROPERTIES OF S-n-BUTYL S'-p-SUBSTITUTED BENZYL N-3-PYRIDYLDITHIOCARBONIMIDATES (group B)

No.	X	mp ^{a)} or n _D ²²	R _M	Es ^{b)}	σ ^{c)}	Activity (ED ₅₀ μM) to		
						S. f. ^{d)}	C. d. ^{e)}	S. s. ^{f)}
19	NO ₂	50~51.5	-0.76	0.28	0.778	1660	2.50 ⁱ⁾	2.70
20	Cl	1.6225	-0.62 ^{h)}	0.27	0.227	660	1.30	1.60
21	H	1.6190	-0.81 ^{h)}	1.24	0.000	>10000 ⁱ⁾	0.21	9.50
22	OCH ₃	1.6160	-0.85	0.69	-0.268	1120	0.65	2.10
23	CH ₃	1.6060	-0.61	0.00	-0.170	2200	0.70	2.90
24	C ₂ H ₅	1.6108	-0.54	-0.07	-0.151	880	0.75	3.90
25	i-C ₃ H ₇ ^{g)}	1.6008	-0.48	-0.47	-0.151	525	0.64	8.80
26	n-C ₄ H ₉	1.5945	-0.30	-0.39	-0.161	350	10.0	>100 ⁱ⁾
27	i-C ₄ H ₉	1.5940	-0.32	-0.93	-0.115	140	5.00	70.0
28	s-C ₄ H ₉	1.5957	-0.28	-1.13	-0.123	60	2.40	>100 ⁱ⁾
29	n-C ₅ H ₁₁	1.5887	-0.14	-0.40	-0.161	65	>100 ⁱ⁾	100
30	s-C ₅ H ₁₁	1.6103	-0.19	-1.13	-0.123	85	>100 ⁱ⁾	95.0
31	c-C ₆ H ₁₁	1.6053	-0.13	-0.79	-0.200	100	62.0	99.0
32	n-C ₆ H ₁₃	1.5785	-0.01	-0.33	-0.161	400	>100 ⁱ⁾	>100 ⁱ⁾
33	n-C ₇ H ₁₅	1.5790	0.14 ^{h)}	-0.33	-0.161	500	>100 ⁱ⁾	>100 ⁱ⁾
34	n-C ₈ H ₁₇	1.5750	0.29	-0.33	-0.161	230	>100 ⁱ⁾	>100 ⁱ⁾
8	t-C ₄ H ₉	31~33	-0.38	-1.54	-0.197	5	0.30	3.20

^{a)} Uncorrected. ^{b)} Taft's steric constant, see Ref. 13. ^{c)} Hammett's electronic constant. ^{d)} *S. fuliginea*. ^{e)} *C. diplodiella*. ^{f)} *S. sclerotiorum*. ^{g)} *n*, *i*, *s*, *t* and *c* are abbreviations of normal, iso, secondary, tertiary and cyclo. ^{h)} Calculated by the Eq. 1 in the footnote. ⁱ⁾ Omitted from the regression analysis.

Biological tests

ED₅₀ (μ M) on agar medium for *C. diplodiella* and *S. sclerotiorum* and ED₅₀ (μ M) of preventive effects on cucumber powdery mildew of *S. fuliginea* were obtained by the methods previously reported¹¹ and are listed in Tables II and III.

R_M from reversed phase thin-layer chromatography

In the course of screening study for a potential fungicide, it was confirmed that the hydrophobicity of substituents was an important factor for activity. The π constant is a well-known parameter of the hydrophobicity of a substituent and because of its additive and constitutive character,⁷⁾ the π constant was used for the new compounds under consideration. But intramolecular interactions among individual substituents⁸⁾ often reduce the reliability of the conventional π constants and it seemed very unreliable to use π constants by checking our compounds only by the distribution methods⁷⁾ in the range of substituent change from methyl through dodecyl, since solubility of the Denmert-type compounds was in the order of only a few ppm.⁹⁾ Boyce and Milborrow¹⁰⁾ have demonstrated that R_M values from reversed phase TLC system correlate well with π constants. So R_M values were adopted as a parameter of hydrophobicity and are listed in Tables II and III, which show mean R_M values of five observations. Standard errors of the mean were below 0.05.

RESULTS AND DISCUSSION

In order to learn what features of each substituent R or aromatic substituent X are essential for fungicidal activities, the compounds V are classified into two groups. One group contains the S-alkyl S'-*p*-*tert*-butylbenzyl N-3-pyridyldithiocarbonimidates (group A) listed in Table II, and the other the S-*n*-butyl S'-*p*-substituted benzyl N-3-pyridyldithiocarbonimidates (group B) in Table III.

Structure-activity correlations in the group A

The fungicidal activities (log 1/ED₅₀) seem to be parabolically dependent on the carbon numbers of the *n*-alkyl substituents (an increasing hydrophobicity) (see Fig. 2). The activities of *sec*- and *tert*-alkyl analogs toward *C. diplodiella* and *S. fuliginea* are higher than those of *n*-alkyl analogs except the activity toward *S. sclerotiorum*. The amyl analogs have the highest activity toward *C. diplodiella* and *S. fuliginea* and the ethyl

FIG. 2. Correlation of Fungicidal Activity with Carbon Numbers of *n*-Alkyl Substituents of S-Alkyl S'-*p*-*tert*-Butylbenzyl N-3-Pyridyldithiocarbonimidates.

●—●, *S. fuliginea*; ○—○, *C. diplodiella* (carbon numbers ≥ 10 , activity < 4.0); △—△, *S. sclerotiorum* (carbon numbers ≥ 7 , activity < 4.0).

FIG. 3. Linear Correlation of R_M values with ($\pi_R + \pi_X$) values of S-Alkyl S'-*p*-Substituted Benzyl N-3-Pyridyldithiocarbonimidates.

●, group A (X = *tert*-butyl in the compound V); ○, group B (R = *n*-butyl in the compound V); π_R , π values of the substituent R (alkyl); π_X , π values of the *p*-substituent X.

analog is the most active toward *S. sclerotiorum*.

The analogs having 8 or more carbon atoms in the S-alkyl group show a quite different activity pattern toward *S. fuliginea* than toward the other two fungi. This may originate from the different methods of assessing ac-

TABLE IV. CORRELATIONS OF THE FUNGICIDAL ACTIVITY ($\log 1/ED_{50}$) IN S-ALKYL S'-p-tert-BUTYLBENZYL N-3-PYRIDYLDITHIOCARBONIMIDATES (group A)

Fungus	Equation ^{a)}	n ^{b)}	r ^{c)}	s ^{d)}	Eq. No.
<i>C. d.</i> ^{e)}	$6.08 - 0.11Es^c - 2.64RM - 3.67RM^2$ (± 0.15) (± 0.08) (± 0.43) (± 0.80)	16 ⁱ⁾	0.980	0.12	2
<i>S. s.</i> ^{f)}	$4.13 + 0.16Es^c - 6.31RM - 5.17RM^2$ (± 0.68) (± 0.15) (± 3.23) (± 3.66)	13 ^{j)}	0.920	0.21	3
<i>S. f.</i> ^{g)}	$4.96 - 0.23Es^c - 1.98RM^{h)} - 5.54RM^2$ (± 0.44) (± 0.17) (± 2.43) (± 3.66)	14 ^{k)}	0.955	0.24	4
	$5.09 + 1.90RM - 1.58RM^2$ (± 0.12) (± 0.72) (± 0.86)	5 ^{l)}	0.996	0.03	4'

^{a)} The figures in parentheses are the 95% confidence intervals. ^{b)} Numbers of the compounds included in the correlation. ^{c)} Correlation coefficient. ^{d)} Standard deviation. ^{e)} *C. diploidiella*. ^{f)} *S. sclerotiorum*. ^{g)} *S. fuliginea*. ^{h)} More than 90% confidence level. ⁱ⁾ Analogs (1)–(16) were included. ^{j)} Analogs (1)–(13) were included. ^{k)} Analogs (1)–(14) were included. ^{l)} Analogs (14)–(18) were included.

tivity (agar medium test and pot test). There are no intramolecular interactions among individual substituent in the compounds V, since high linear correlation*¹ is found between *RM* values and additive and constitutive π constants (see Fig. 3).

Structure-activity correlations were analyzed by the regression analysis¹¹⁾ against the physicochemical parameters; *RM* (hydrophobic), σ^* (electronic)¹²⁾ and *Es*^{c)} (steric).¹³⁾ The most important equations (from the statistical point of view)¹⁴⁾ were selected and are listed in Table IV (see Eqs. 2, 3, 4 and 4'). The activity toward *S. fuliginea* can be expressed by two equations: one contains the analogs (1)–(14) and the other the analogs (14)–(18). It is confirmed from these equations that the activities toward any of the three fungi are correlated with the hydrophobic (*RM* and *RM*²) and steric parameters of the substituents and seem to be maximized when *RM* is -0.36 ($\pi_R = 2.07$) for *C. diploidiella*,

-0.61 ($\pi_R = 1.17$) for *S. sclerotiorum*, -0.20 ($\pi_R = 2.27$)¹⁵⁾ and 0.60 ($\pi_R = 5.43$) for *S. fuliginea* if the steric factors are the same. As shown by Pennistone,¹⁵⁾ the structural changes of the S-alkyl group may effect the permeation of the compound V through a number of lipoidal-aqueous interfaces to reach to a critical receptor site.

Structure-activity correlations in the group B

The activity toward *S. fuliginea* is highly position-specific, since the *p*-tert-butyl analog (8) was 100 times more active than the *m*-tert-butyl analog.¹⁶⁾ Structure-activity correlations were similarly analyzed and listed in Table V. The effects of the substituent X on the activities toward the three fungi differ from those of the substituent R. Linear correlation was found between the steric parameter (*Es*) and the activity toward *S. fuliginea*, which indicated that the bulkier the substituent, the higher the activity (see Eq. 5). However this correlation was not observed in the analogs carrying bulkier groups than *tert*-butyl, since the *tert*-amyl analog (37) was still active at 500 ppm concentration, but inactive at lower concentration and the analogs (35), (36) and (38) were inactive (see Table VI). The substituent X seems to have an optimum *Es* value for the activity toward *S. fuliginea*.

*¹ Expressed as Eq. 1; $RM = 0.279 (\pm 0.011)$ ($\pi_R + \pi_X$) $- 1.389 (\pm 0.047)$ where π_R and π_X are π values of the substituents R and X, and the figures in parenthesis are 95% confidence intervals. $n = 26$, $r = 0.995$ and $s = 0.037$.

² Taft's σ^ constant.^{12,13)} *³ Hancock's *Es*^{c)} constant.¹⁴⁾ *⁴ With a confidence level better than 95% by *F* and Student's *t* test. *⁵ Denmert is one of these analogs.

TABLE V. CORRELATIONS OF THE FUNGICIDAL ACTIVITY ($\log 1/ED_{50}$) in *S-n*-BUTYL *S'*-*p*-SUBSTITUTED BENZYL N-3-PYRIDYLDITHIOCARBONIMIDATES (group B)

Fungus	Equation ^{a)}	n ^{b)}	r ^{c)}	s ^{d)}	Eq. No.
<i>S. f.</i> ^{e)}	3.22-0.97Es (±0.24) (±0.34)	16 ⁱ⁾	0.849	0.37	5
<i>C. d.</i> ^{f)}	3.17-0.83Es-4.98RM (±1.19) (±0.59) (±2.12)	11 ^{j)}	0.905	0.35	6
<i>S. s.</i> ^{g)}	3.08-0.52Es ^{h)} -3.66RM (±0.97) (±0.55) (±1.72)	12 ^{h)}	0.887	0.37	7

a) The figures in parentheses are the 95% confidence intervals.

b) Numbers of the compounds included in the correlation.

c) Correlation coefficient.

d) Standard deviation.

e) *S. fuliginea*.

f) *C. diplodiella*.

g) *S. sclerotiorum*.

h) More than 90% confidence level.

i) Analog (21) was not included.

j) Analogs with activity over 100 μ M were not included.

TABLE VI. ACTIVITY TOWARD *S. fuliginea* ON THE COMPOUNDS WITH BULKY SUBSTITUENT X

No.	X	mp ^{a)} or n _D ²⁰	Es ^{b)}	Activity (ppm) ^{c)}		
				500	50	5
35	-CH ₂ -C ₆ H ₅ ^{d)}	1.6140	-1.50	C	C	C
36	-CH ₂ -C ₆ H ₅	1.6233	-1.76	C	C	C
37	- <i>t</i> -C ₄ H ₉	1.5920	-1.79	A	C	C
38	- <i>t</i> -C ₆ H ₁₃	1.5805	-2.47	C	C	C
8	- <i>t</i> -C ₄ H ₉	31 ~ 33	-1.54	A	A	A

a) Uncorrected.

b) Taken from Ref. 14.

c) A; preventive value above 95%; C; preventive value below 60%.

d) Phenyl group.

The antihistamine activity of diphenhydramines¹⁷⁾ and the insecticidal activity^v of DDT analogs¹⁸⁾ are known to be maximized at certain Es values of their *p*-substituents and the substituents of the latter were explained to have an optimum size to fit the flexible pouch-like receptor site for the activity.¹⁸⁾ This suggests that there may be a similar step to reach to a receptor site for the activity of the compound V.

The structure-activity correlations* against *C. diplodiella* and *S. sclerotiorum* are quite

similar and the hydrophobicity and the steric factors of the substituent X are important for the activities. The less hydrophobic and the bulkier substituents appear to increase the activity (see Eqs. 6 and 7), but the activity of the analogs (19) and (30) toward *C. diplodiella* and that of the analogs (26) and (28) toward *S. sclerotiorum* are lower than expected from these equations. When the activity correlates

* The analogs with the activity (ED_{50}) over 100 μ M were omitted from the regression analysis because accurate values could not be obtained experimentally.

linearly with the π term, Hansch *et al.*⁸⁾ pointed out that the compound plays an important role in the perturbation of the cell envelope if the coefficient of the π term is 1.07 ± 0.14 , while the adsorption on enzyme or protein systems is critical for the activity if the coefficient of the π term is 0.74 ± 0.09 . The coefficients of the R_M term of Eqs. 6 and 7, which correspond to 1.39 and 1.02 as the coefficients of the π term calculated by Eq. 1, suggest that the perturbation of the cell envelope is a critical step for the fungicidal activity in these compounds. Kato *et al.*²⁾ reported that Denmert inhibited biosynthesis of ergosterol, a known constituent of the cell membrane of many fungi, in *Monilinia fructigena*.

We synthesized and tested other compounds, such as S-alkyl N-3-pyridyldithiocarbamates (IV), S-*p*-substituted benzyl N-3-pyridyldithiocarbamates, S-alkyl N-3-pyridylthiolcarbama-tes, S-*p*-substituted benzyl N-3-pyridylthiolcarbama-tes, 3-pyridylisothiocyanate (III), 3-aminopyridine (I), di-*n*-butyl disulfide, di-*p*-substituted benzyl disulfides and S-oxides of Denmert-type compounds.¹⁶⁾ These compounds were inactive toward the three fungi, although Denmert and its S-oxides showed antifungal activity toward *M. fructigena* in liquid cultures.³⁾ The electronic factors of the substituent X or R are thought to influence such reactions as bond-scission between C-S-benzyl or C-S-alkyl, addition to the carbon atom of an $-N=C\langle$ double bond and oxidation of sulfur atoms. If these reactions or the compounds resulting from them are critical for the fungicidal activity, the activity may be influenced by the electronic factors of the substituent R or X. The structure-activity correlations reveal that only the hydrophobic and/or the steric factors of the substituent R and X in the compound V influence the activities toward any of the three fungi but electronic factors do not.

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