Structure Modifications of S-*n*-Butyl S′-*p-tert*-Butylbenzyl N-3-Pyridyldithiocarbonimidate (S–1358, Denmert®) and Fungicidal Activities[†]

Shizuya Tanaka, Toshiro Kato, Shigeo Yamamoto
and Hirosuke Yoshioka

*Research Department, Pesticides Division, Sumitomo Chemical Co., Ltd.,
4–2–1 Takatsukasa, Takarazuka, Hyogo 665, Japan*
Received May 2, 1977

Since S-*n*-butyl S′-*p-tert*-butylbenzyl N-3-pyridyldithiocarbonimidate, a potent fungicide to powdery mildew, is known to inhibit ergosterol biosynthesis in *Monilinia fructigena*, the activities were assessed on 24 compounds having other substituents than the 3-pyridyl and on 24 compounds having a variety of different structures connecting the 3-pyridyl and the *p-tert*-butylphenyl group from that of the dithiocarbonimidate.

In the former group the 3-pyridyl group was essential for the activities and the substitution at the 2- or 6-position resulted, on available data, in inactive compounds. Several other β-N-heterocyclic analogs were also active. In the latter group, a number of modified compounds from the dithiocarbonimidate structure were shown to be active.

On structure modifications concerning S-*n*-butyl S′-*p-tert*-butylbenzyl N-3-pyridyldithiocarbonimidate, a potent fungicide to powdery mildew[1] and an extreme inhibitor to ergosterol biosynthesis in *Monilinia fructigena*,[2] we now report what features of the substituent Ar and the moiety B in Fig. 1 are essential for the fungicidal activity to powdery mildew on cucumber on pot test (*Sphaerotheca fuliginea*) and for the inhibition of ergosterol biosynthesis in mycelium (*M. fructigena*).

METHODS AND MATERIALS

Synthesis of the compounds. The structures of the compounds were confirmed by elementary analysis for C, H, N and S and NMR spectra (60 MHz, Hitachi R–20B NMR spectrometer). Singlet, doublet, triplet, quartet and multiplet signals are abbreviated to s, d, t, q and m respectively. Typical procedures are shown in the following examples.

1) *S-n-Butyl S′-p-tert-butylbenzyl N-5-methyl-2-thiadiazolyldithiocarbonimidate* (**23**). To a solution of 2-amino-5-methylthiadiazole (11.5 g, 0.10 mole), triethyl amine (10.1 g, 0.10 mole) and acetone (50 ml) was added carbon disulfide (7.6 g, 0.10 mole) at 15°C. After 20 hr *n*-butyl iodide (18.4 g, 0.10 mole) was

added and the mixture was kept for 5 hr at 20°C, and then diluted with water (100 ml) to form yellow precipitates, which were recrystallized from C_2H_5OH to give 7.11 g (30%) of *n*-butyl N-5-methyl-2-thiadiazolyldithiocarbamate (mp 54~56°C). *Anal.* Found: C, 38.75; H, 5.45; N, 17.11; S, 38.72. Calcd. for $C_8H_{13}N_3S_3$: C, 38.83; H, 5.31; N, 16.99; S, 38.87%.

To a solution of this dithiocarbamate (2.37 g, 0.01 mole), KOH (0.62 g, 0.011 mole) and CH_3OH (10 ml) was added *p-tert*-butylbenzyl bromide[3] (2.27 g, 0.01 mole) at 0°C and the mixture was kept for 2 hr, which was then diluted with water (100 ml), extracted with ethyl acetate (100 ml). The extract was washed with water (100 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by silicagel column chromatography with the solvent system of *n*-hexane/acetone (5/1) to give 3.24 g (81%) of white needles after tritulation in CCl_4 (mp 118~119°C). *Anal.* Found: C, 57.85; H, 7.04; N, 10.56; S, 24.38. Calcd. for $C_{19}H_{27}N_3S_3$: C, 59.96; H, 6.93; N, 10.68; S, 24.43%. NMR (CCl_4, TMS) δ: 7.25 (4H, s), 4.31 (2H, s), 3.11 (2H, t), 2.65 (3H, s), 1.30 (9H, s), 0.95 (3H, br.t).

The dithiocarbonimidates (**1**)–(**3**), (**5**)–(**15**), (**17**)–(**19**) and (**25**) and the monothiocarbonimidates (**26**) and (**27**) were similarly prepared and are listed in Tables I, II and III.

2) *1-(3-Pyridyl)-2-p-tert-butylbenzyl-3-ethylisothiourea* (**4**). To a mixture of 70% ethylamine (3.22 g, 0.05 mole) and benzene (30 ml) was added 3-pyridylisothiocyanate[4] (6.81 g, 0.05 mole) at 15°C and then benzene and water were evaporated *in vacuo*. The oily residue was tritulated in CCl_4 to give 7.24 g (80%)

[†] Structure-Activity Study of S–1358 and Its Derivatives. Part II.

Moiety B
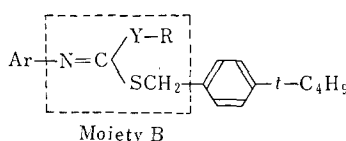
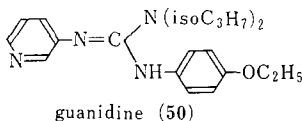Denmert (1) : Ar=3-pyridyl,   Y—R=S—n—C$_4$H$_9$

guanidine (50)

Fig. 1.

of white crystals of 1-ethyl-3-(3-pyridyl)thiourea after recrystallization from CCl$_4$/CHCl$_3$ (4/1) (mp 116~117°C). *Anal.* Found: C, 52.85; H, 6.22; N, 23.28; S, 17.53. Calcd. for C$_8$H$_{11}$N$_3$S: C, 53.00; H, 6.13; N, 23.19; S, 17.69%.

To a solution of this thiourea (3.62 g, 0.02 mole), KOH (1.23 g, 0.022 mole) and CH$_3$OH (20 ml) was added p-tert-butylbenzyl bromide (5.00 g, 0.022 mole) at 5°C, and the mixture was kept for 1 hr. After working up as described in example 1, 3.20 g (81%) of the isothiourea (4) was obtained as white amorphous crystals (mp 89.5~90.5°C). *Anal.* Found: C, 69.63; H, 7.74; N, 12.73; S, 9.66. Calcd. for C$_{19}$H$_{25}$N$_3$S: C, 69.67; H, 7.71; N, 12.83; S, 9.79%. NMR (CCl$_4$, TMS) δ: 8.15 (2H, m), 7.35~7.04 (2H, m), 7.20 (4H, q), 4.56 (1H, br.s), 3.90 (2H, s), 3.29 (2H, br.q), 1.30 (9H, s), 1.08 (3H, t).

The isothioureas (16), (20)–(22), (24) and (28) were similarly prepared and are listed in Tables I, II and III.

3) *1-(3-Pyridyl)-2-p-ethoxyphenyl-3,3-diisopropylguanidine* (50) in Fig. I.   1-p-Ethoxyphenyl-3-(3-pyridyl)-thiourea was prepared in 85% yield as described in example 2 (mp 126.5~127°C from C$_2$H$_5$OH). To a solution of this thiourea (8.20 g, 0.03 mole), KOH (1.68 g, 0.03 mole) and C$_2$H$_5$OH (50 ml) was added ethyl iodide (5.15 g, 0.033 mole) at 20°C and the mixture was kept for 6 hr, diluted with water (150 ml) and extracted with ethyl acetate (100 ml). The extract was washed with water (100 ml), dried (Na$_2$SO$_4$) and evaporated *in vacuo*. The residue was purified by silicagel column chromatography with the solvent system of n-hexane/acetone (10/1) to give 5.61 g (62%) of 1-(3-pyridyl)-2-ethyl-3-p-ethoxyphenylisothiourea after tritulation in CCl$_4$ (mp 88~89°C). *Anal.* Found: C, 63.65; H, 6.28; N, 14.08; S, 10.63. Calcd. for C$_{16}$H$_{19}$N$_3$SO: C, 63.75; H, 6.37; N, 13.94; S, 10.64%.

A mixture of this isothiourea (3.01 g, 0.01 mole) and diisopropyl amine (30 ml) was refluxed for 5 hr, during which ethyl mercaptan was evolved and led to aq.NaOH solution through the top of the reflux condenser. Then excess of diisopropyl amine was evaporated *in vacuo* and the residue was purified by the

similar chromatography to that of the above isothiourea to give 2.45 g (71%) of white amorphous crystals after tritulation in CCl$_4$ (mp 88~90°C). *Anal.* Found: C, 70.34; H, 8.52; N, 16.51. Calcd. for C$_{20}$H$_{28}$N$_4$O: C, 70.54; H, 8.30; N, 16.46%. NMR (CDCl$_3$. TMS) δ: 8.17 (1H, d-d), 7.92 (1H, d-d), 6.97 (2H, m), 6.68 (4H, s), 5.50 (1H, br.s), 3.85 (4H, m), 1.38 (3H, t), 1.27 (12H, d).

The guanidine (31) was similarly prepared (Table III).

4) *S-n-Butyl N-3-pyridyl-β-(p-tert-butylphenyl)ethylthioformimidate* (30).   An ethereal Grignard solution prepared from Mg metal (1.2 g, 0.05 mole), p-tert-butylphenethyl bromide (12.1 g, 0.05 mole) and ether (100 ml) was added to a mixture of 3-pyridylisothiocyanate (6.6 g, 0.05 mole) and ether (100 ml) at 15°C and kept for 0.5 hr. The resulting slurry was decomposed with saturated aq. NH$_4$Cl (100 ml) and the ether layer was washed with water (100 ml), dried (Na$_2$SO$_4$) and evaporated *in vacuo*. The residue was purified by silicagel column chromatography with the solvent system of n-hexane/acetone (5/1) to give 8.5 g (57%) of N-3-pyridyl-β-(p-tert-butylphenyl)thiopropionamide (41) after tritulation in benzene (mp 118~120°C). *Anal.* Found: C, 72.68; H, 7.53; N, 9.28; S, 10.82. Calcd. for C$_{18}$H$_{22}$N$_2$S: C, 72.43; H, 7.44; N, 9.39; S, 10.74%. NMR (CDCl$_3$, TMS) δ: 9.35 (1H, br.s), 8.25 (3H, m), 7.35 (1H, m), 7.22 (4H, q), 3.13 (4H, s), 1.30 (9H, s).

Equal moles of this thioamide and p-tert-butylbenzyl bromide were reacted as described in example 1 in the presence of KOH in CH$_3$OH to give the thioformimidate (30) in 60% yield (n_D^{24} 1.5600). *Anal.* Found: C, 74.63; H, 8.52; N, 8.03; S, 9.11. Calcd. for C$_{22}$H$_{30}$N$_2$S: C, 74.51; H, 8.54; N, 7.90; S, 9.04%. NMR (CCl$_4$, TMS) δ: 8.12 (1H, d-d), 7.85 (1H, d), 6.99 (4H, q), 6.95 (1H, d-d), 6.57 (1H, d-t), 2.80 (6H m), 1.60 (4H, m), 1.28 (9H, s), 0.94 (3H, br.t).

The thioformimidate (29) was similarly prepared (Table III).

5) *1-(3-Pyridyl)-4-(p-tert-butylphenyl)-1,3-butadiene* (32).   To a solution of β-3-pyridyl-trans-acrylaldehyde[5] (2.66 g, 0.02 mole), triphenyl-p-tert-butylbenzylphosphonium bromide[*1] (9.78 g, 0.02 mole) and CH$_3$OH (30 ml) was dropwise added a NaOCH$_3$ solution prepared from Na metal (0.46 g, 0.02 mole) and CH$_3$OH (10 ml) at 15°C and the mixture was kept for 1 hr, diluted with water (100 ml) and extracted with ether (100 ml). The extract was washed with water (100 ml), dried (Na$_2$SO$_4$) and evaporated *in vacuo* and the residue was purified by silicagel column chromatography with the solvent system of n-hexane/acetone (20/1) to give 2.21 g (42%) of yellow oil. This com-

---

[*1] Prepared quantitatively by refluxing a benzene solution of triphenylphosphine and p-tert-butylbenzyl bromide (mp 227~229°C).

pound consists of the cis and trans isomers in a 1:1 ratio and submitted to bioassy test. They could be separated*[2] by the chromatography with the solvent system of n-hexane/acetone (100/1), but were easily equilibrated with light since each isomers spotted on TLC plate (10 μl of 10 ^{wt}% acetone solution) were placed in the sun light for 10 min and then chromatographed to give again two spots of the trans and cis isomers in a ratio of 5:1.

The butadienes (33) and (34) were similarly prepared (Table IV).

6) β-(3-Pyridyl)vinyl p-tert-butylbenzyl sulfone (38). A mixture of p-tert-butylbenzylsulfonylacetic acid*[3] (5.4 g, 0.02 mole), nicotinaldehyde (2.2 g, 0.02 mole), pyridine (30 ml) and piperidine (0.5 ml) was heated at 80°C for 1 hr and the mixture was then poured into cold water (200 ml) and extracted with ethyl acetate (100 ml). The extract was washed with 3% aq. NaHCO$_3$, dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was purified by silicagel column chromatography with the solvent system of n-hexane/acetone (10/1) to give 0.33 g (5.2%) of crystals after recrystallization from CCl$_4$ (mp 149.5~150°C). The main product was p-tert-butylbenzyl methyl sulfone. Anal. Found: C, 68.43; H, 6.75; N, 4.32; S, 10.02. Calcd. for C$_{18}$H$_{21}$NSO$_2$: C, 68.53; H, 6.72; N, 4.44; S, 10.16%. NMR (CCl$_4$, TMS) δ: 8.65 (2H, m), 7.45 (1H, d, J=15), 7.35 (4H, q), 7.80~7.20 (2H, m), 6.68 (1H, d, J=15), 4.30 (2H, s), 1.32 (9H, s).

The sulfones (39) and (40) were similarly prepared by the Cope's condensation from the corresponding ester or amide[7] (Table IV).

7) 1-(p-tert-Butylphenoxy)-2-(3-pyridyloxy) ethane (42). A mixture of p-tert-butylphenol (15.0 g, 0.1 mole), ethylene bromide (37.6 g, 0.2 mole), NaOH (4.0 g, 0.1 mole) and water (50 ml) was refluxed for 5 hr, and then cooled and extracted with ether (100 ml). The extract was washed with 5% aq. NaOH (50 ml), dried (Na$_2$SO$_4$) and evaporated in vacuo and the residue was distilled to give 4.2 g (16.3 %) of β-p-tert-butylphenoxyethyl bromide (bp 93~96°C at 0.3 mm Hg). Anal. Found: C, 56.11; H, 6.56; Br, 31.01.

Calcd. for C$_{12}$H$_{17}$BrO: C, 56.05; H, 6.68; Br, 31.05%.

A mixture of this bromide (3.86 g, 0.015 mole), 3-hydroxypyridine (1.43 g, 0.015 mole), NaOH (0.60 g, 0.015 mole) and water (15 ml) was refluxed for 2 hr. After working up as described above, the residue was purified by the silicagel column chromatography with the solvent system of n-hexane/acetone (3/1) to give 0.50 g (12.3%) of plates after recrystallization from n-hexane (mp 67~68°C). Anal. Found: C, 75.21; H, 7.85; N, 5.20. Calcd. for C$_{17}$H$_{21}$NO$_2$: C, 75.23; H, 7.82; N, 5.16%. NMR (CCl$_4$, TMS) δ: 8.12 (2H, m), 7.08 (2H, m), 6.90 (4H, q), 4.22 (4H, s), 1.28 (9H s).

The oxime ethers (35)–(37) were similarly prepared from the corresponding aldoxime[8] and ketoximes[9] and p-tert-butylbenzyl bromide (Table IV).

8) p-tert-Butylphenyl β-3-pyridylacrylate (43). A solution of β-3-pyridylacrylic acid[5] (3.0 g, 0.02 mole), p-tert-butylphenol (3.0 g, 0.02 mole), dicyclohexyl carbodiimide (4.1 g, 0.02 mole) and benzene (30 ml) was heated at 60°C for 1.5 hr, then cooled to 10°C and filtered off. The filterate was washed with 1% aq. NaOH (10 ml), dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was purified by silicagel column chromatography with the solvent system of n-hexane/acetone (10/1) to give 4.6 g (81%) of white needles after recrystallization from CCl$_4$ (mp 104~106°C). Anal. Found: C, 76.74; H, 6.81; N, 5.07. Calcd. for C$_{18}$H$_{19}$NO$_2$: C, 76.83; H, 6.82; N, 4.98%. NMR (CDCl$_3$, TMS) δ: 8.73 (1H, m), 8.53 (1H, m), 7.75 (1H, d, J=16), 7.70 (1H, m), 7.24 (1H, m), 7.17 (4H q), 6.16 (1H, d, J=16), 1.34 (9H, s).

The ester (44) was similarly prepared (Table V).

The carbamates (45)–(47) were similarly prepared as previously reported[10] and the hydrazones (48) and (49) were prepared from the corresponding acid hydrazides and aldehydes (Table V).

Biological tests. The preventive effectiveness on powdery mildew on cucumber (S. fulginea) at 500 ppm concentration and the inhibition of ergosterol biosynthesis (M. fructigena) at 50 ppm were expressed by the percentages of inhibition v.s. untreated by the methods previously reported.[1,2]

RESULTS AND DISCUSSION

The effects of the substituent Ar on the fungicidal activity

Denmert (1) and 1-(3-pyridyl)-2-p-tert-butylbenzyl-3-ethylisothiourea (4) have the highest activity to S. fuliginea and M. fructigena (see Table I). Among the unsubstituted pyridyl derivatives, the 2- and 4-analogs (2) and (3) were inactive and only the 3-pyridyl analogs (1) and (4) were active. The N atom of the β-position from the imidate or the ureido

---

*[2] 1-(3-Pyridyl)-4-(p-tert-butylphenyl)-trans, trans-1,3-butadiene, mp 119~121°C from CH$_3$OH. NMR (CCl$_4$, TMS) δ: 8.55 (1H, d, J=2), 8.35 (1H, d-d, J=5 and 2), 7.58 (1H, d-t, J=8 and 2), 7.07 (1H, d-d, J=8 and 5), 7.26 (4H, s), 6.83~6.50 (4H, m), 1.30 (9H, s).

1-(3-Pyridyl)-4-(p-tert-butylphenyl)-trans, cis-1, 3-butadiene, n_D^{24} 1.6410. NMR (CCl$_4$, TMS) δ: 8.53 (1H d, J=2), 8.35 (1H, d-d, J=5.4 and 2), 7.62 (1H, d-t, J=8 and 2), 7.13 (1H, d-d, J=8 and 4.5), 7.28 (4H, q, J=15.5), 6.80~7.08 (4H, m), 1.35 (9H, s).

*[3] Prepared by the oxidation of the corresponding glycolic acid thioether as previously reported[6] (mp 173~175°C from CH$_3$COOH).

Table I.   The Fungicidal Activity of the Pyridyl and the Phenyl Derivatives

$$Ar-N=C \overset{Y-R}{\underset{SCH-\langle\;\rangle-t-C_4H_9}{}}$$
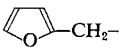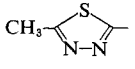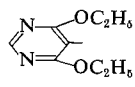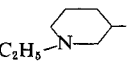
No.	Ar[a]	Y-R	mp[d] or n_D^{24}	S.f.[b] 500 ppm	M.f.[c] 50 ppm
1	3-Py	S-n-C$_4$H$_9$	31～33	100	95
2	4-Py	S-n-C$_4$H$_9$	1.5920	0	0
3	2-Py	S-n-C$_4$H$_9$	1.6055	0	0
4	3-Py	NHC$_2$H$_5$	89.5～90.5	100	94
5	5-CH$_3$-3-Py	S-n-C$_4$H$_9$	1.5850	100	86
6	6-OCH$_3$-3-Py	S-n-C$_4$H$_9$	1.5872	5	0
7	6-N(CH$_3$)$_2$-3-Py	S-n-C$_4$H$_9$	78～79	7	0
8	2-N(CH$_3$)$_2$-3-Py	S-n-C$_4$H$_9$	1.5980	1	0
9	ϕ	S-n-C$_4$H$_9$	33～35	0	0
10	2-OCH$_3$-ϕ	S-n-C$_4$H$_9$	68～71	0	0
11	3-OCH$_3$-ϕ	S-n-C$_4$H$_9$	1.5909	0	0
12	4-OCH$_3$-ϕ	S-n-C$_4$H$_9$	1.5849	0	0
13	4-OH-ϕ	S-n-C$_4$H$_9$	92～94	9	0
14	3-OH-ϕ	S-n-C$_4$H$_9$	1.5996	7	0
15	3-NO$_2$-ϕ	S-n-C$_4$H$_9$	1.5985	0	0
16	3-NO$_2$-ϕ	NHC$_2$H$_5$	91～92	0	0

[a] Py=pyridyl, ϕ=phenyl.   [b] Percentage of preventive value to S. fuliginea v.s. untreated.
[c] Percentage inhibition of ergosterol biosynthesis to M. fructigena v.s. untreated.   [d] Uncorrected.

Table II.   The Fungicidal Activity of the Heterocyclic Derivatives

$$Ar-N=C \overset{Y-R}{\underset{SCH_2-\langle\;\rangle-t-C_4H_9}{}}$$

No.	Ar	Y-R	mp[a] or n_D^2	S.f.[b] 500 ppm	M.f.[c] 50 ppm
17	⟨furanyl⟩-CH$_2$-	S-n-C$_4$H$_9$	1.5863	0	0
18	⟨SO$_2$⟩	S-n-C$_4$H$_9$	1.5696	5	0
19	⟨triazole, H-N, N-N⟩	S-n-C$_4$H$_9$	1.5791	32	90
20	⟨triazine, N-N⟩	NHC$_2$H$_5$	173～176	95	88
21	⟨pyrazine, N, N⟩	NHC$_2$H$_5$	83～84	100	96
22	⟨pyrazine, N, N-Cl⟩	NHC$_2$H$_5$	73～76	5	64
23	CH$_3$-⟨thiadiazole, S, N-N⟩	S-n-C$_4$H$_9$	118～120	1	0
24	⟨pyrimidine, N, N, OC$_2$H$_5$, OC$_2$H$_5$⟩	NHC$_2$H$_5$	1.5612	5	0
25	C$_2$H$_5$-N⟨piperidine⟩	S-n-C$_4$H$_9$	1.5500	0	0

[a] Uncorrected.   [b] Percentage of preventive value to S. fuliginea v.s. untreated.
[c] Percentage inhibition of ergosterol biosynthesis to M. fructigena v.s. untreated.

group appears to be important for the activity. Moreover the α-position of this N atom seems critical for the activity, since introduction of a dimethylamino group at either the 2- or the 6-position as well as a methoxy group at 6-position resulted in the inactive compounds (6), (7) and (8) while the 5-methyl analog (5) was still active.

Concerning the other substituents Ar, all of the phenyl analogs (9) through (16), the furfuryl analog (17) and the tetramethyl-enesulfonyl analog (18) were inactive (see Tables I and II). On the other hand, the triazolyl analogs (19) and (20), the pyrazyl analog (21) and the pyrimidyl analog (22), all of which contain N atom at the β-position, were active to one or both of the fungi (see Table II). But the methylthiadiazolyl analog (23) and the ethoxypyrimidyl analog (24) were inactive, that is similar to the case of the 3-pyridyl analogs. The N-ethylpiperidyl analog (25) was also inactive. The presence of the β-N-heteroaromatic structure may be essential for the fungicidal activity and the specific geometry requirement for the N atom appears to suggest that coordination of the N atom to a cationic receptor site may be important for the activity.

The effects of the partial structure (moiety B) connecting the Ar and the p-tert-butylphenyl group

Regarding the dithiocarbonimidate (Denmert-type) analogs, S,S'-bis(p-tert-butylbenzyl) and S,S'-bis(p-isopropylbenzyl) N-3-pyridyldithiocarbonimidate were active to S. fuliginea, but S,S'-bis(n-butyl) and S,S'-bis(n-heptyl) N-3-pyridyldithiocarbonimidate were inactive.[11] The phenyl group in the carbonimidates appears to be indispensable for the activity. Among the Denmert-type analogs, the compounds having the p-tert-butylphenyl group showed the highest activity to S. fuliginea as previously reported,[10] therefore structure modifications were studied on the partial structure connecting the 3-pyridyl and the p-tert-butylphenyl group.

The monothiocarbonimidates (26) and (27),

TABLE III. THE EFFECTS OF THE PARTIAL STRUCTURE (MOIETY B) CONNECTING THE 3-PYRIDYL GROUP AND THE p-tert-BUTYLPHENYL GROUP ON THE FUNGICIDAL ACTIVITY (I)

$$\left\langle\!\!\!\begin{array}{c}\\N\end{array}\!\!\!\right\rangle\text{-(Moiety B)-}\left\langle\!\!\!\begin{array}{c}\\ \end{array}\!\!\!\right\rangle\text{-t-C}_4\text{H}_9$$

No.	Moiety B[a]	$mp^{b)}$ or n_D^{24}	S.f.[c] 500 ppm	M.f.[d] 50 ppm
26	$-N=C\begin{smallmatrix}O-n-C_4H_9\\SCH_2-\end{smallmatrix}$	50~51	100	91
27	$-N=C\begin{smallmatrix}S-n-C_4H_9\\OCH_2-\end{smallmatrix}$	1.5530	100	90
28	$-N=C\begin{smallmatrix}NH-n-C_4H_9\\SCH_2-\end{smallmatrix}$	84.5~85.5	100	94
29	$-N=C\begin{smallmatrix}CH_2-i-C_3H_7\\SCH_2-\end{smallmatrix}$	1.5700	100	90
30	$-N=C\begin{smallmatrix}S-n-C_4H_9\\CH_2CH_2-\end{smallmatrix}$	1.5600	100	90
31	$-N=C\begin{smallmatrix}NH-n-C_4H_9\\NHCH_2-\end{smallmatrix}$	80~82	0	0

[a] n and i are abbreviations of normal and iso.
[b] Uncorrected.
[c] Percentage of preventive value to S. fuliginea v.s. untreated.
[d] Percentage inhibition of ergosterol biosynthesis to M. fructigena v.s. untreated.

the isothiourea (28) and the thioformimidates (29) and (30) were active to both of the fungi (see Table III). The S atom of the Y–R or S-benzyl group is not essential for the activity since either of the two S atoms can be replaced by the O, C and/or N atom. Moreover the oxidation products of Denmert (S-n-butyl S'-p-tert-butylbenzyl N-3-pyridyldithiocarbonimidate S-oxide or S'-oxide)[12] were also active to M. fructigena. Structure-activity correlations of Denmert-type compounds showed[10] that the electronic factors of the substituents of the n-butyl moiety (R moiety in Fig. 1) or those of the p-tert-butyl moiety did not influenced the activities to S. fuliginea, C. diplodiella and S. sclerotiorum and suggested the dithiocarbonimidate structure not to be essential for the activity. Such other modified compounds as the 1,3-butadienes (32) through (34) and the oxime ethers (35) through (37) were also active (see Table

Table IV. The Effects of the Partial Structure (Moiety B) Connecting the 3-Pyridyl Group and the p-tert-Butylphenyl Group on the Fungicidal Activity (II)

$$\langle \overset{\hspace{2mm}}{\underset{N}{}}\rangle-(\text{Moiety B})-\langle \hspace{4mm}\rangle-t\text{-}C_4H_9$$

No.	Moiety B[a]	mp[b] or n_D^{24}	S.f.[c] 500 ppm	M.f.[d] 50 ppm
	–CH=C(R)–CH=CH–			
32	R: H	119~121	100	90
33	: C_2H_5	1.6158	90	90
34	: n-C_3H_7	1.6066	92	91
	–C(R)=N–OCH$_2$–			
35	R: H	1.5625	100	89
36	: CH_3	1.5600	70	91
37	: n-C_4H_9	1.5442	60	90
	–CH=C(R)–SO$_2$CH$_2$–			
38	R: H	149.5~150	8	91
39	: $CO_2C_2H_5$	80~81	0	0
40	: CONH-i-C_3H_7	172~173	0	0

a)   Normal and iso are abbreviated to n and i.
b)   Uncorrected.
c)   Percentage of preventive value to S. fuliginea v.s. untreated.
d)   Percentage inhibition of ergosterol biosynthesis to M. fructigena v.s. untreated.

Table V. The Effects of the Partial Structure (Moiety B) Connecting the 3-Pyridyl Group and the p-tert-Butylphenyl Group on the Fungicidal Activity (III)

$$\langle \overset{\hspace{2mm}}{\underset{N}{}}\rangle-(\text{Moiety B})-\langle \hspace{4mm}\rangle-t\text{-}C_4H_9$$

No.	Moiety B	mp[a] or n_D^{24}	S.f.[b] 500 ppm	M.f.[c] 50 ppm
41	–NH–CS–CH$_2$CH$_2$–	118~120	8	0
42	–O–CH$_2$CH$_2$–O–	67~68	0	6
43	–CH=CH–CO–O–	104~106	0	0
44	–O–CO–CH=CH–	1.5975	0	0
45	–NH–CS–SCH$_2$–	144~145	9	0
46	–NH–CS–OCH$_2$–	124~125	5	0
47	–NH–CO–SCH$_2$–	177~179	3	0
48	–CH=NNH–CO–	124~125	0	0
49	–CO–NHN=CH–	204~205.5	0	0

a)   Uncorrected.
b)   Percentage of preventive value to S. fuliginea v.s. untreated.
c)   Percentage inhibition of ergosterol biosynthesis to M. fructigena v.s. untreated.

IV). But the ester or the amide structure appear to be unfavorable to the activity, since

the vinyl sulfonylmethyl derivative (38) was still active to M. fructigena, but introduction of the ester or the amide group resulted in the inactive compounds (39) and (40) and the thioamide (41), the acrylates (43) and (44), the carbamates (45) through (47) and the acid hydrazides (48) and (49) were inactive (see Table V). The diether derivative (42) was also inactive.

1-(3-Pyridyl)-2-p-ethoxyphenyl-3,3-diisopropylguanidine (50) in Fig. 1 and its analogs[13] were found to be highly active to powdery mildew, but these compounds did not inhibited the ergosterol biosynthesis. They may have a different interaction to the fungi from that of the Denmert-type compounds. The guanidine (31) was inactive to S. fuliginea and did not inhibit the ergosterol biosynthesis (see Table III).

As far as the present data indicate, a number of the modified compounds from Denmert, which contain different moities connecting the β-N-heterocyclic nucleus and the substituted phenyl group, were fungicidally active. Beside the dithiocarbonimidate moiety in Denmert, the examples which were incorporated with the certain partial structures, the 4-membered chain structures, can still be active but with a certain limitation. Incorporation of either of the amide, the ester, the diether and the guanidine group failed, in spite of the 4-membered chain structures, to give any of active compounds.

REFERENCES

1)   T. Kato, S. Tanaka, S. Yamamoto, Y. Kawase and M. Ueda, *Ann. Phytopath. Soc. Jap.*, **41**, 1 (1975).
2)   T. Kato, S. Tanaka, M. Ueda and Y. Kawase, *Agric. Biol. Chem.*, **39**, 169 (1975).
3)   J. B. Shoesmith and A. Makie, *J. Chem. Soc.*, **1936**, 300.

4) J. C. Jochim, *Chem. Ber.*, **101**, 1746 (1968).

5) C. S. Marvel, L. E. Collman, Jr. and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

6) S. Schodroff and W. F. Whitmore, *J. Am. Chem. Soc.*, **72**, 1073 (1950).

7) H. J. Backer, *Recl. Trav. Chim.*, **72**, 119 (1953).

8) A. Steinhards and W. Mathes, U. S. Patent, 2924604 (1958) [*C.A.*, **56**, 736d (1962)].

9) CIBA Ltd., Neth. appl., 6600834 (1966) [*C.A.*, **66**, 28501a (1967)].

10) S. Tanaka, T. Kato, S. Yamamoto and H. Yoshioka, submitted to *Agric. Biol. Chem.*

11) S. Tanaka *et al.*, unpublished data.

12) H. Ohkawa, Y. Okihara and J. Miyamoto, *Agric. Biol. Chem.*, **40**, 1175 (1976).

13) S. Tanaka *et al.*, unpublished data.