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Crystal and Liquid Structures of S-*n*-Butyl S′-*p*-*tert*-Butylbenzyl N-3-Pyridyldithiocarbonimidate (S-1358, Denmert®) and the S-Alkyl Analogs, Potent Fungicides†

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The structure of S-1358, a potent fungicide toward powdery mildew, has been established by X-ray crystallography as the *syn* configuration regarding the 3-pyridyl and the S-*p*-*tert*-butylbenzyl groups about the N=C bond. On the other hand it instantly gave rise to an equilibrium mixture of the *anti* and the *syn* isomers in a number of different solvents (even under deep freezing conditions). The NMR signal due to the benzylic methylene protons could be resolved into two singlets below −14°C. The isomer (topomer) ratio was dependent linearly on 1/T, and it was also affected by the bulkiness of the S-alkyl group in a series of the analogs. Fungicidal activities of S-1358 and its analogs are discussed in connection with the topomer ratios.

S-*n*-Butyl S′-*p*-*tert*-butylbenzyl N-3-pyridyldithiocarbonimidate, S-1358 or Denmert®, is a potent fungicide toward plant powdery mildews[1] but the *anti*/*syn* configuration about the N=C bond has never been studied (see Fig. 1). A NMR temperature study[2] of S-1358 and its analogs was made in order to gather detailed informations about the structures in solutions.

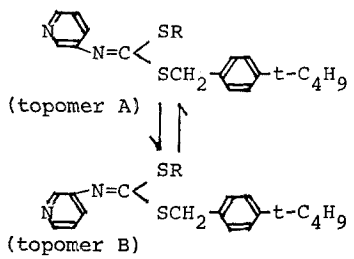


FIG. 1. Topomerization of the N-3-Pyridyldithiocarbonimidates.

(1) R=CH_3
(2) R=*i*-C_3H_7
(3) R=*n*-C_4H_9 (S-1358, Denmert®)
(4) R=*t*-C_4H_9
(5) R=*t*-C_6H_{13}
(6) R=*n*-C_6H_{17}
(7) R=CH_2-*ϕ*-*t*-C_4H_9

† Structure-Activity Study of S-*n*-Butyl S′-*p*-*tert*-Butylbenzyl N-3-Pyridyldithiocarbonimidates and Its Derivatives. Part III. See References 3, 4).

MATERIALS AND METHODS

1) Compounds. A number of the N-3-pyridyldithiocarbonimidates, (**1**) through (**7**) in Table II, and the N-3-pyridylthioformimidates, (**8**) through (**14**) in Table III, were similarly prepared by the condensation of N-3-pyridyldithiocarbamates and N-3-pyridylthioamides with *p*-*tert*-butylbenzyl bromide, respectively, in the presence of a base as previously reported.[3,4]

2) X-ray analysis. S-1358 was purified by recrystallization from *n*-hexane below −20°C (mp 33°C). The molten specimen of this pure S-1358 yielded a nice crystal which belongs to the triclinic system with space group $P\bar{1}$. The crystal data are: $a=13.657$ (3), $b=15.133$ (3) and $c=6.303$ (1) Å and $\alpha=109.12°$ (2), $\beta=100.54°$ (2) and $\gamma=60.72°$ (2). $V=1073.2$ Å^3, $Z=2$, $D_{calcd}=1.153$. Three-dimensional X-ray analysis was conducted with a Philips Pailred diffractometer. In total 2216 reflections were collected and 1854 reflections which have intensities greater than $3\sigma(I)$ were used in the least-squares refinement. Final R value was 0.095.

3) NMR spectra. NMR spectra were recorded on a R-20B NMR spectrometer 60 MHz (Hitachi) with a variable temperature equipment R-202VT (Hitachi) and a frequency counter TR-3824 (Takeda Riken).

Chemical shifts are given in δ scale and ratios of the topomers are determined from integrated peak areas as mean values from 6 through 10 times repeat of recording for each sample at 9% concentration.

4) Biological tests. The figures for the preventive effectiveness toward *S. fuliginea* and *S. sclerotiorum* at 500 ppm concentration are shown in percentages of inhibition *v.s.* controls by the method previously reported.[1)]

RESULTS AND DISCUSSION

Crystal structure of S-1358

Figure 2 shows the resulting structure of S-1358 and also its conformation in the crystal, in which the 3-pyridyl and the S-*p-tert*-butylbenzyl groups are in the *syn* configuration about the N=C bond (topomer B in Fig. 1). It is also apparent that the N=C bond is not co-planar with the 3-pyridyl group in despite of its conjugating position.

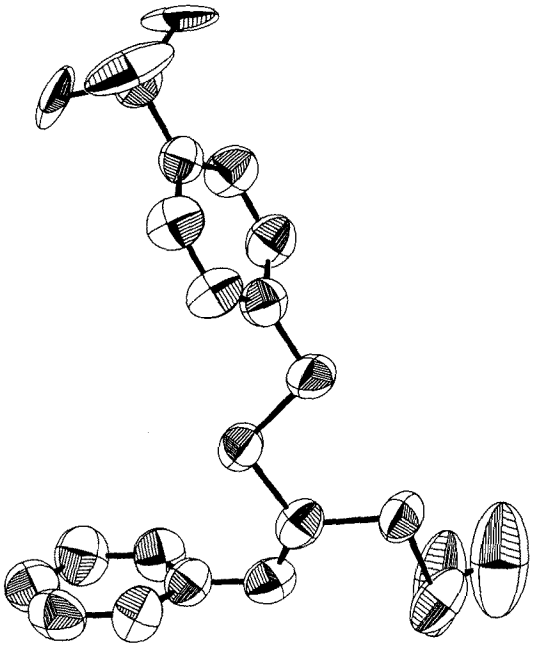


FIG. 2. Crystal Structure of S-1358.

Topomerization equilibria of the N-3-pyridyldithiocarbonimidates in solutions

Although the NMR signal for the benzylic methylene protons of S-1358 is at 4.30 ppm as a singlet at ambient temperature, it splitted into a pair of singlets at 4.22 and 4.37 ppm at −30°C (in chlorobenzene). As illustrated in Fig. 3, the coalescence temperature (Tc) for the two signals was −14°C. A similar pattern was also demonstrated for S,S′-bis(*p-tert*-butylbenzyl) N-3-pyridyldithiocarbonimidate (7) (in acetone-d_6). Because of the clear temperature dependence it is obvious that the compounds exist in a topomerization equilibrium. The topomer ratio was always 1:1 for the symmetric analog (the bis *p-tert*-butylbenzyl analog) but it was 1.63 at −30°C and 1.33 at 28°C (biological assessments were made at this temperature) for the asymmetric

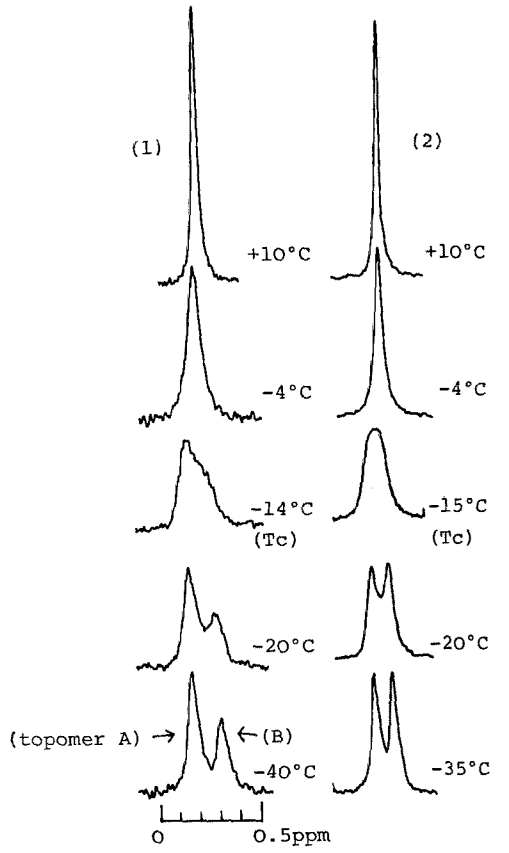


FIG. 3. NMR Signals of Benzylic Protons at Various Temperatures.

(1), S-*n*-butyl S′-*p-tert*-butylbenzyl N-3-pyridyldithiocarbonimidate (S-1358) (3) in chlorobenzene; (2), S,S′-bis(*p-tert*-butylbenzyl) N-3-pyridyldithiocarbonimidate (7) in acetone-d_6.

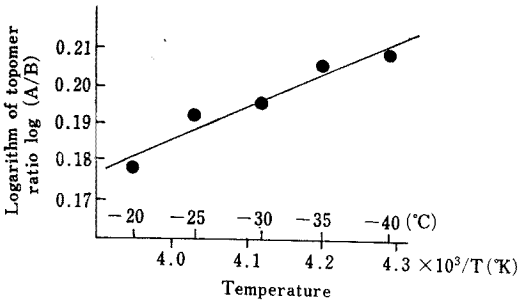


FIG. 4. Temperature Dependence of the Topomer Ratio (A/B) of S-*n*-Butyl S'-*p*-*tert*-Butylbenzyl N-3-Pyridyldithiocarbonimidate (S-1358) in Chlorobenzene.

analog (S-1358), since it was linearly dependent on 1/T as shown in Fig. 4.

Similar equilibria were also demonstrated in a number of different solvents and are summarized in Table I, in which the topomerization rate did not appear to be much influenced by the polarity of the solvents, as reported by Kessler *et al.*[5] for the N-phenyldithiocarbonimidates. S-1358 may be also in equilibrium in more polar solvent, for example in water (dielectric constant: 78.4). Hence it appears that S-1358 can exist in an almost constant topomerization equilibrium in aqueous or lipoidal system where biological interactions between the compound and any of transportation or receptor cites are critically involved.

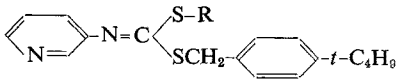
The topomerization equilibria were also revealed for the various S-alkyl analogs in Fig. 1 and are summarized in Table II, in which

TABLE I. TOPOMERIZATION OF S-*n*-BUTYL S'-*p*-*tert*-BUTYLBENZYL N-3-PYRIDYLDITHIOCARBONIMIDATE (S-1358) IN VARIOUS SOLVENTS AT −30°C

Solvent	Dielectric constant[a]	Tc[b]	Chemical shift[c] benzylic	protons
CD_3OD	32.7	−27	4.32	4.28
$(CD_3)_2CO$	20.7	*ca.*−30	4.40[d]	4.38[d]
ϕ-Cl	5.6	−14	4.37	4.22
$CDCl_3$	4.8	−22	4.35	4.30
CS_2	2.6	−23	4.20	4.15

a) Taken from Ref. 6).
b) Coalescence temperature (°C).
c) 9% concentration, δ scale.
d) at −40°C.

TABLE II. TOPOMERIZATION OF THE N-3-PYRIDYLDITHIOCARBONIMIDATES IN CHLOROBENZENE CHEMICAL SHIFTS OF BENZYLIC PROTONS AND TOPOMER RATIO (A/B)



No.	R[a]	Tc[b]	A (at −30°C)	B[c] (at −30°C)	A/B (at −30°C)	A/B (at 35°C)[d]
1	CH_3	−9	4.32	4.17	1.38	4.25
2	*i*-C_3H_7	−8	4.38	4.18	1.45	4.28
3	*n*-C_4H_9	−14	4.37	4.22	1.67	4.30
4	*t*-C_4H_9	−22	4.33	4.15	0.52	4.20
5	*t*-C_8H_{13}	−23	4.32	4.18	0.55	4.22
6	*n*-C_8H_{17}	−13	4.38	4.25	1.85	4.30
7	CH_2-ϕ-*t*-C_4H_9	−15	4.43	4.35	1.00	4.39

a) *i*, *n*, *t* and ϕ are abbreviations of iso, normal, tertiary and phenyl respectively.
b) Coalescence temperature (°C).
c) 9% concentration, δ scale.
d) One sharp singlet signal.

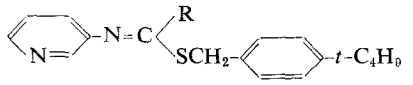
it is most noteworthy that the topomer ratios (A/B) of the *tert*-butyl and the *tert*-hexyl analogs, (**4**) and (**5**), were reversed from those of the other analogs. This appears to be due to a peculiar steric effect associated with the bulky *tert*-alkyl groups that tend to increase the ratio of the *syn* topomer (regarding the 3-pyridyl and the S-*p*-*tert*-butylbenzyl groups) in comparison with the *anti* topomer. Therefore, the topomer A may be deduced to be the *anti* and B to the *syn* form.*1

The topomer ratios and the fungicidal activities of the S-alkyl analogs of S-1358 and the N-3-pyridylthioformimidates

Walter *et al.*[7] reported the topomerization of the N-phenylthioformimidates(Ph-N=CR_1-SR_2),*2 among which the R_1 *tert*-butyl analog exist only in the *syn*(Z) form regarding the phenyl and the SR_2 groups, while the other analogs were in the topomerization equilibria with the *anti* (E) dominant ratios. Thermo-

*1 In attempts to obtain a NMR spectrum of the pure *syn* topomer in a freezing condition, S-1358 crystals were added to a precooled solvent (−60°C) and the NMR spectrum was recorded immediately. An equilibrated NMR spectrum was always found.

TABLE III. NMR CHEMICAL SHIFT OF BENZYLIC PROTONS AND FUNGICIDAL ACTIVITIES OF THE S-*p*-*tert*-BUTYLBENZYL N-3-PYRIDYL-THIOFORMIMIDATES

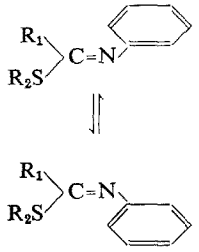


No.	R[a]	mp[b] or n_D^{24}	Chemical shift[c]	Activity[d] *S.f.* 500 ppm	Activity[d] *S.s.* 500 ppm
8	Methyl	1.5875	4.17	99	100
9	*n*-Propyl	1.5754	4.13	97	100
10	*i*-Propyl	1.5735	4.05	100	100
11	*t*-Butyl	87–80	3.37	65	61
12	*i*-Butyl	1.5700	4.13	100	100
13	*s*-Butyl	1.5675	4.08	100	100
14	*o*-Tolyl	1.6045	4.35	100	100

[a] *n, i, t, s* and *o* are abbreviations of normal, iso, tertiary, secondary and ortho respectively.
[b] Uncorrected.
[c] 9% concentration in CCl_4, δ scale (35°C).
[d] Preventive effectiveness *v.s.* controls toward *S. fuliginea* and *S. sclerotiorum*.

dynamic similarity between the pyridyl and the phenyl groups reported by Lepoivre *et al.*[8] and Riddell *et al.*[9] suggests the analogy between N-3-pyridylthioformimidates (Py–N=CR_1–SR_2) and N-phenyl analogs(Ph–N=CR_1–SR_2). In this connection, a number of N-3-pyridyl-thioformimidates which have similar fungicidal activities[4] to those of S-1358 analogs were prepared as closer references and assessed fungicidally (toward *S. fuliginea* and *S. sclerotiorum*). The results are compiled in Table III, in which the *tert*-butyl analog (**11**) appears to be distinguished from the others in the NMR chemical shift of the benzylic methylene protons (at 35°C) as well as its low fungicidal activities. The NMR data suggest that the benzylic protons of the *tert*-butyl analog (**11**) are under a spatial diamagnetic effect possibly resulting from the 3-pyridyl group in the *syn* configuration to the S-benzyl group.*3 In contrast, the fungicidal activities of S-1358 and the S-alkyl analogs toward *S. fuliginea, S. sclerotiorum* and *C. diplodiella* were mainly dependent on the hydrophobicity of the alkyl group and there was no striking defference in the fungicidal activities between the S-*n*-alkyl and the S-*tert*-alkyl analogs.*4 The difference in the fungicidal activities appears to result, in parts, from the difference between the N-3-pyridyldithiocarbonimidates and the N-3-pyridylthioformimidates in the topomerization equilibrium.

*2 R_1	R_2	Solvent	E/Z
CH_3	C_2H_5	C_6D_6	95/5
i-C_3H_7	CH_3	$CDCl_3$	82/12
t-C_4H_9	CH_3	$CDCl_3$	0/100
CH_3	Benzyl	C_6D_6	94/6
o-Tolyl	CH_3	$CDCl_3$	78/22



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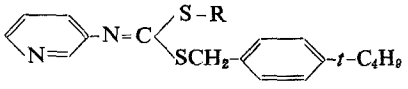
*3 The benzylic protons did not split even at −60°C and higher structural strain was observed in the Stuart model of the *anti* form of this compound.

*4 R	Activity (ED_{50} μM) *S.f.*	*S.s.*	*C.d.*
n-C_4H_9	5.00	3.20	0.30
t-C_4H_9	2.70	3.40	0.21
n-C_6H_{13}	5.20	20.0	0.31
t-C_6H_{13}	2.40	24.0	0.20

Detailed data are shown in Ref. 3).

Activities of the *n*- and the *tert*-alkyl N-3-pyridyl-dithiocarbonimidates



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