6-アルキルチオ-2-ピリジル アルカンスルホナート類の化学構造と殺虫,殺ダニ活性

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Original Article

Chemical Structures and Insecticidal, Acaricidal Activities of 6-Alkylthio-2-pyridyl Alkanesulfonates*

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6-Alkylthio-2-pyridyl alkanesulfonates, and their sulfoxides and sulfones were synthesized, and their lethal activity was tested to five species of insects and mites. Methanesulfonates, with 6-alkyl-thio, -sulfinyl and -sulfonyl substituents having one to six carbon atoms, showed remarkable insecticidal activity to *Nephotettix cincticeps, Nilaparvata lugens* and *Culex pipiens*. Insecticidal activity of 6-alkylthio-2-pyridyl methanesulfonates to strains of *Nephotettix cincticeps* susceptible and resistant to organophosphates and carbamates was related parabolically to the hydrophobicity of the molecule, the optimum alkyl-thio substituents being C_3–C_4 alkyl groups. In a series of 6-*iso*-butylthio-2-pyridyl alkanesulfonates and their sulfoxides and sulfones, the methane-, ethane- and chloromethane-sulfonates showed stronger insecticidal activity than higher alkanesulfonates. The 6-*n*-propyl-sulfinyl-, -sulfonyl-, 6-*iso*-butyl-sulfinyl- and -sulfonyl-2-pyridyl methanesulfonates and the 6-*iso*-butylsulfonyl-substituted ethanesulfonate showed strong inhibitory activity against acetylcholinesterase preparations from the susceptible and resistant strains of *Nephotettix cincticeps*.

INTRODUCTION

We have found that 3-alkylthiophenyl methanesulfonates and their derivatives are insecticidal, and examined relationships between chemical structure and insecticidal activity of a number of analogs,[1] and in our continuing effort to develop novel sulfonate insecticides, we have synthesized analogous pyridine derivatives. In this paper, we report structure-activity relationships of 6-alkylthio-2-pyridyl methanesulfonates and the related compounds, and their sulfoxides and sulfones.

MATERIALS AND METHODS

1. *Synthesis of Compounds*

The general synthesis method is shown in Fig. 1. We prepared alkanesulfonates (**VI**), (**VII**), (**VIII**) by a method similar to the one previously reported[1]: First, 6-alkylthio-2-pyridinols (**V**) were prepared by reacting 6-halogeno-2-pyridinols with alkyl mercaptans or dialkyl disulfides (Route A).[2] This method needed cuprous oxide or metallic copper, high reaction temperature (>150°C) and long reaction time, however, and the isolation of a desired product was often very complicated. Therefore, we developed a new method (Route B) to synthesize 6-alkylthio-2-pyridinols (**V**) under mild reaction conditions, which were derived from 6-alkylthio-2-chloropyridines[3] (**III**) *via* the corresponding 6-alkylthio-2-methoxypyridines[3] (**IV**). The structure of compounds was confirmed by ^{1}H NMR, IR and mass spectrometries. Some typical preparations by Route B are as below.

1.1 *2-Chloro-6-n-propylthiopyridine* (**III**: $R^1 = n\text{-}C_3H_7$)

To a solution of *n*-propyl mercaptan (26.9 g, 0.35 mol), 2,6-dichloropyridine (52.4 g, 0.35 mol), tetra-*n*-butylammonium bromide (6 g,

* Structure-Activity Studies of Methanesulfonate Insecticides (Part 2). See Ref. 1).

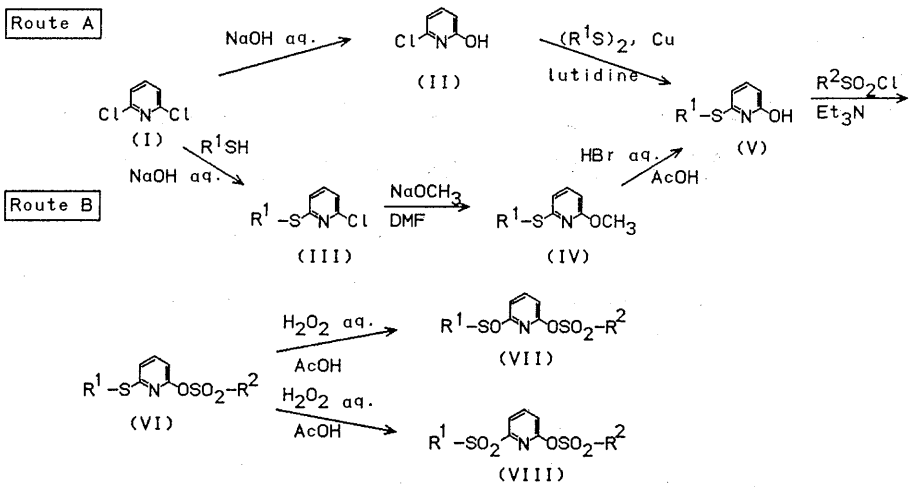


Fig. 1 Synthetic routes of 6-R^1-$S(O)_x$-substituted 2-pyridyl alkanesulfonates.

0.019 mol) and benzene (70 ml) was added 10% aq. NaOH (350 ml) at room temperature. The mixture was stirred at 80°C for 8 hr, cooled, poured into water (200 ml) and extracted with benzene (300 ml). The organic layer was washed with water (200 ml) and dried over sodium sulfate. After the solvent was removed, the residue was distilled under reduced pressure to yield 56.2 g (84.6%) of the desired 2-chloro-6-*n*-propylthiopyridine as a colorless oil, bp 78°C/2 mmHg. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.04 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2S$), 1.74 (2H, m, J=7 Hz, $CH_3C\underline{H}_2CH_2S$), 3.14 (2H, t, J=7 Hz, $CH_3CH_2C\underline{H}_2S$), 6.96 (1H, d, J=8 Hz, aromatic), 7.05 (1H, d, J=7 Hz, aromatic), 7.40 (1H, t, J=8 Hz, aromatic).

1.2 2-Methoxy-6-n-propylthiopyridine (**IV**: R^1=*n*-C_3H_7)

Sodium methoxide (16.2 g, 0.3 mol) was slowly added to a mixture of 2-chloro-6-*n*-propylthiopyridine (18.8 g, 0.1 mol) and *N*,*N*-dimethylformamide (100 ml) at 20–30°C. The solution was stirred at 80–90°C for 3 hr, cooled, poured into ice water (300 ml) and extracted with toluene (200 ml×2 times). The combined organic phase was washed with water and dried over sodium sulfate. After the solvent was removed, the residue was distilled under reduced pressure to yield 15.6 g (85.1%) of 2-methoxy-6-*n*-propylthiopyridine as a colorless oil, bp 131–133°C/18 mmHg. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.03 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2S$), 1.75 (2H, m, J=7 Hz, $CH_3C\underline{H}_2CH_2S$), 3.13 (2H, t, J=7 Hz, $CH_3CH_2C\underline{H}_2S$), 3.92 (3H, s, $C\underline{H}_3O$), 6.39 (1H, d, J=8 Hz, aromatic), 6.75 (1H, d, J=8 Hz, aromatic), 7.35 (1H, t, J=8 Hz, aromatic).

1.3 6-n-Propylthio-2-pyridinol (**V**: R^1=*n*-C_3H_7)

To a solution of 2-methoxy-6-*n*-propylthiopyridine (14 g, 0.076 mol) in acetic acid (40 ml) was added 47% aq. HBr (26.4 g, 0.15 mol) at 10–20°C. The mixture was heated at 80–90°C for 2 hr and evaporated to dryness. The residue was dissolved by adding 10% aq. NaOH, and then the solution was acidified with 10% aq. HCl and cooled to 10–15°C. The precipitated material was collected by filtration and dried to give 12.4 g (96.4%) of 6-*n*-propylthio-2-pyridinol as colorless crystals, which were recrystallized from 2-propanol, mp 120–121°C. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.07 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2S$), 1.75 (2H, m, J=7 Hz, $CH_3C\underline{H}_2CH_2S$), 3.17 (2H, t, J=7 Hz, $CH_3CH_2C\underline{H}_2S$), 6.61 (1H, d, J=8 Hz, aromatic), 6.65 (1H, d, J=8 Hz, aromatic), 7.61 (1H, d-d, J=8 Hz, aromatic), 7.85 (1H, bs, OH).

1.4 6-n-Propylthio-2-pyridyl methanesulfonate (**VI**: R^1=*n*-C_3H_7, R^2=CH_3) (**3**)

Methanesulfonyl chloride (8.2 g, 0.072 mol) was added dropwise to a mixture of 6-*n*-

propylthio-2-pyridinol (10.2 g, 0.06 mol), triethylamine (9.1 g, 0.09 mol) and methylene chloride (60 ml) at 20–30°C and poured into water (100 ml). The organic phase was successively washed with water, 5% aq. HCl and water, and dried over sodium sulfate. After the solvent was removed, the residue was purified by column chromatography on silica gel, eluted with *n*-hexane–toluene (20: 1) to give 12.1 g (81.5%) of 6-*n*-propylthio-2-pyridyl methanesulfonate as a colorless oil. n_D^{25} 1.5465. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.00 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2S$), 1.78 (2H, m, J=7 Hz, $CH_3C\underline{H}_2CH_2S$), 3.07 (2H, t, J=7 Hz, $CH_3CH_2C\underline{H}_2S$), 3.34 (3H, s, $C\underline{H}_3SO_2O$), 6.73 (1H, d, J=8 Hz, aromatic), 7.09 (1H, d, J=8 Hz, aromatic), 7.58 (1H, t, J=8 Hz, aromatic).

1.5 6-n-Propylsulfinyl-2-pyridyl methanesulfonate (**VII**: R^1=*n*-C_3H_7, R^2=CH_3) (**4**)

To a solution of 6-*n*-propylthio-2-pyridyl methanesulfonate (2.8 g, 0.013 mol) in acetic acid (20 ml) was added dropwise 35% aq. H_2O_2 (2.7 g, 0.028 mol) at 10–15°C. After stirring at room temperature for 7 hr, the reaction mixture was poured into water (50 ml) and extracted twice with methylene chloride (50 ml). The combined organic layers were successively washed with water, 5% aq. NaOH and water, and dried over sodium sulfate. Evaporation of the solvent left 2.6 g (86.5%) of 6-*n*-propylsulfinyl-2-pyridyl methanesulfonate as colorless crystals, which were recrystallized from a mixture of *n*-hexane and toluene, mp 52–53°C. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.06 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2SO$), 1.75 (2H, m, $CH_3C\underline{H}_2CH_2SO$), 2.94 (2H, m, $CH_3CH_2C\underline{H}_2SO$), 3.47 (3H, s, $C\underline{H}_3SO_2O$), 7.19 (1H, t, J=8 Hz, aromatic), 7.88–8.15 (2H, m, aromatic).

1.6 6-n-Propylsulfonyl-2-pyridyl methanesulfonate (**VIII**: R^1=*n*-C_3H_7, R^2=CH_3) (**5**)

6-*n*-Propylthio-2-pyridyl methanesulfonate (2.8 g, 0.013 mol) was oxidized in acetic acid (20 ml) by adding 35% aq. H_2O_2 (5.1 g, 0.052 mol) dropwise at 10–15°C and stirring at 80–90°C for 10 hr. The reaction mixture was poured into cold water (50 ml) and extracted with methylene chloride (50 ml×2). Usual treatment of the methylene chloride layer afforded 2.7 g (84.0%) of 6-*n*-propylsulfonyl-2-pyridyl methanesulfonate as colorless crystals, which were recrystallized from a mixture of *n*-hexane and toluene, mp 44–44.5°C. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 1.03 (3H, t, J=7 Hz, $C\underline{H}_3CH_2CH_2SO_2$), 1.77 (2H, m, $CH_3C\underline{H}_2CH_2SO_2$), 3.33 (2H, m, $CH_3CH_2C\underline{H}_2SO_2$), 3.58 (3H, s, $C\underline{H}_3SO_2O$), 7.46 (1H, d, J=8 Hz, aromatic), 8.06–8.34 (2H, m, aromatic).

2. *Biological Activity*

2.1 Test species

We used two strains of green rice leafhopper, *Nephotettix cincticeps*, the Ageo strain (S) susceptible to organophosphates and carbamates collected in Ageo City, Saitama Prefecture in 1968, and the Izumi strain (R) resistant to organophosphates and carbamates collected in Izumi City, Kagoshima Prefecture in 1980, and one strain of rice brown planthopper, *Nilaparvata lugens*, the Kaseda strain collected in Kaseda City, Kagoshima Prefecture in 1976. The hoppers had been reared with rice seedlings through generations. The Ageo strain of diamondback moth, *Plutella xylostella*, collected in Ageo City, Saitama Prefecture in 1973 had been reared with cabbage leaves, while the Kawasaki strain of house mosquito, *Culex pipiens*, collected in Kawasaki City, Kanagawa Prefecture in 1962 with rabbit blood. The Nagano strain of two-spotted spider mite, *Tetranychus urticae*, collected in Suzaka City, Nagano Prefecture in 1983 had been reared with leaves of kidney bean, *Phaseolus vulgaris*.

2.2 Insecticidal and acaricidal test methods

Foliar-spray method to green rice leafhoppers (Ageo strain) and rice brown hoppers: Ten heads of adult females of each hopper 3–5 days after emergence were inoculated on rice seedlings (5 in a bundle) of tetrafoliate stage grown in a pot (1/10,000 a) covered with wire mesh. The plants grown in the pot had been previously sprayed with test chemical solution (50 ml) with a compressor spray gun (1.5 kg/cm^2) and air-dried. The test solution was prepared by diluting an emulsifiable mixture containing 20% of each compound (prepared by mixing a test compound, xylene, isopropyl alcohol and polyoxyethylenealkylphenol at a ratio of 20: 35: 35: 10, w/w) to the 200 ppm emulsion with water. After 48

hr at 25°C, the numbers of alive and dead insects were counted to calculate the mortality.

Foliar-spray method to diamondback moths: Ten heads of third instar larva were transferred to a potted cabbage of penta- to hexa-foliate stage in a wire mesh cage. The potted cabbage had been previously sprayed with a test chemical solution in a procedure similar to the treatment of hoppers. The mortality was recorded at 48 hr.

Immersion method to house mosquitoes: Ten heads of third instar larva were placed in a plastic tumbler (ϕ 9 cm) containing 1 ppm test solution (200 ml) which had been prepared by diluting 20% emulsifiable solution with water. After 48 hr the mortality was determined.

Leaf-dipping method to two-spotted spider mites: About 30 heads of adult females were infested on the first two leaves of dwarf kidney bean (*Phaseolus vulgaris*) grown in a porous pot. The leaves were cut into squares (3 cm×3 cm), and dipped into 200 ppm emulsion of each test compound. The mites on the cut leaves were then raised in a greenhouse at 25°C. After 48 hr the numbers of alive and dead mites were counted through a binocular microscope for determination of the mortality.

The topical application was used to determine the LD_{50} value of methanesulfonates against two strains of green rice leafhoppers, the susceptible Ageo strain (S) and the resistant Izumi strain (R). The 24-hr-percent mortality was calculated for various concentrations of methanesulfonates by applying 0.5 μl acetone solution onto the ventral abdomen of carbon dioxide-anesthetized adult females 3–5 days after emergence. Each treatment was repeated twice. Before and during the experiments, the insects were kept at 25–27°C. The LD_{50} value was calculated by probit analysis.[4]

2.3 Acetylcholinesterase inhibition

Inhibitory activity of 6-alkylthio-2-pyridyl alkanesulfonates, their sulfoxides and sulfone, and propoxur (2-isopropoxyphenyl *N*-methylcarbamate) against acetylcholinesterase preparations obtained by homogenizing the Ageo (S) and Izumi (R) strains of green rice leafhoppers and the Kaseda strain of rice brown planthoppers was measured by the method reported previously.[1]

3. Hydrophobicity of Compounds

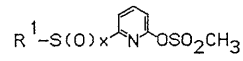
Hydrophobicity of compounds (**1–3**, **6–9**, **12–14**, **17** and **22–28**) was estimated by reversed phase HPLC analysis at 25°C with a Cosmosil $5C^{18}$-packed column (4.6×150 mm) (Nakarai Chemicals Ltd.) [head pressure: 113 kg/cm^2, analytical wavelength: 254 nm, mobile phase: H_2O/MeOH (3/7, v/v), flow rate: 1 ml/min, nonretained substance: MeOH] on a HITACHI L-6000 liquid chromatograph equipped with a L-6000 pump, a L-4000 UV detector, a 655A-52 Column oven and a D-2000 Chromato-integrator. The capacity factor (k') was evaluated from the retention time of a test compound (t_R) and MeOH (t_0) by the following equation: $k'=(t_R-t_0)/t_0$. The log k' value was used as the index of hydrophobicity in quantitative structure-activity analysis.

RESULTS

Table 1 shows the lethal activity of 6-R^1-S(O)$_x$-substituted 2-pyridyl methanesulfonates to five species of insects and mites. At 200 ppm by the foliar-spray method, compounds with alkyl- or cycloalkyl-thio, -sulfinyl or -sulfonyl substituent having one to six carbon atoms (**1–17**, **23–25** and **28**), and the benzylthio (**22**), phenylthio (**26**) and 2-methylthioethyl (**27**) derivatives recorded 100% mortality to the hoppers. The *n*-octylthio derivative (**18**), and its sulfoxide (**19**) and sulfone (**20**), and the *n*-laurylthio derivative (**21**) showed little or no activity. The activity of methanesulfonates was largely lower against the backmoths than against the hoppers. Only the *t*-butylthio derivative (**12**) showed 100% mortality, while the isoamylsulfonyl (**16**) and cyclopropylmethylthio (**24**) derivatives exhibited moderate activity at 200 ppm. The activity to the mosquitoes at 1 ppm varied almost in parallel to that to the hoppers except for the methylthio derivative (**1**). To the two-spotted spider mites the isobutylthio (**9**) and 2-methylthioethylthio (**27**) derivatives exhibited high activity but the others were weakly active (**2**, **10**, **11**, **14–16** and **24**) or almost inactive.

The insecticidal activity of 6-R^1-S-substituted 2-pyridyl methanesulfonates varied with substituent R^1. We examined quantita-

Table 1 Insecticidal and acaricidal activities of 6-R^1-$S(O)_x$-substituted 2-pyridyl methanesulfonates.

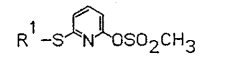


No.	R^1	x	mp (°C) / n_D^{25}	Mortality (%)[a]				
				N. c.[b]	*N. l.*[c]	*P. x.*[d]	*C. p.*[e]	*T. u.*[f]
				200	200	200	1	200 ppm
1	CH_3	0	1.5633	100	100	20	0	−
2	C_2H_5	0	1.5476	100	100	0	100	+
3	*n*-C_3H_7	0	1.5465	100	100	0	100	−
4	*n*-C_3H_7	1	52–53	100	100	0	100	−
5	*n*-C_3H_7	2	44–44.5	100	100	0	100	−
6	*i*-C_3H_7	0	1.5444	100	100	0	100	−
7	*n*-C_4H_9	0	1.5320	100	100	0	100	−
8	*s*-C_4H_9	0	1.5420	100	100	0	100	−
9	*i*-C_4H_9	0	40–40.5	100	100	0	100	++
10	*i*-C_4H_9	1	87.5–88.5	100	100	0	100	+
11	*i*-C_4H_9	2	1.5156	100	100	0	100	+
12	*t*-C_4H_9	0	1.5480	100	100	100	100	−
13	*n*-C_5H_{11}	0	1.5362	100	100	30	100	−
14	*i*-C_5H_{11}	0	1.5356	100	100	10	100	+
15	*i*-C_5H_{11}	1	1.5281	100	100	30	100	+
16	*i*-C_5H_{11}	2	1.5145	100	100	60	100	+
17	*n*-$C_3H_7(CH_3)CH$	0	1.5371	100	100	20	100	−
18	*n*-C_8H_{17}	0	1.5228	0	0	30	0	−
19	*n*-C_8H_{17}	1	49–50.5	0	0	30	0	−
20	*n*-C_8H_{17}	2	58–59.5	10	0	30	20	−
21	*n*-$C_{12}H_{25}$	0	46–46.5	0	10	10	0	−
22	$C_6H_5CH_2$	0	71–72	100	100	0	100	−
23	*c*-C_5H_9	0	1.5620	100	100	20	100	−
24	*c*-$C_3H_5CH_2$	0	1.5635	100	100	80	100	+
25	*c*-C_6H_{11}	0	79–80	100	100	0	100	−
26	C_6H_5	0	59.5–60.5	100	100	10	100	−
27	$CH_3SCH_2CH_2$	0	1.6028	100	100	0	100	++
28	*t*-$C_4H_9CH_2$	0	1.5360	100	100	0	100	−

[a] See text.
[b] *Nephotettix cincticeps* (Ageo strain).
[c] *Nilaparvata lugens*.
[d] *Plutella xylostella*.
[e] *Culex pipiens*.
[f] *Tetranychus urticae*. Mortality was shown by rating scores: (+++) 100% mortality; (++) 51–99%; (+) 11–50%; (−) 0–10%.

tive relationships between the activity index against the green rice leafhoppers and physicochemical parameters of these methanesulfonates. The compounds and their insecticidal activity index in terms of log $(1/LD_{50})$ determined by topical application against the Ageo and Izumi strains are shown in Table 2. Among physicochemical parameters, hydrophobicity in terms of log k' seems to correlate best to activity variations when used singly as shown in Figs. 2 and 3, for which Eqs. (1) and (2) were derived.

Table 2 Insecticidal activity of 6-R[1]-S-substituted 2-pyridyl methanesulfonates against *Nephotettix cincticeps*.



No.	R[1]	Substituents and structural parameters						log 1/LD$_{50}$ (M)[a]			
								Ageo		Izumi	
		π[b]	B_1[c]	B_5[c]	E_s[d]	I[e]	log k'	Obsd.	Calcd.[f]	Obsd.	Calcd.[g]
1	CH_3	0.54	1.52	2.04	0.00	0.0	−0.259	6.71	6.95	5.74	5.98
2	C_2H_5	1.08	1.52	3.17	−0.07	0.0	−0.034	8.14	8.06	7.33	6.99
3	*n*-C_3H_7	1.62	1.52	3.49	−0.36	0.0	0.196	8.57	8.52	7.65	7.44
6	*i*-C_3H_7	1.40	1.90	3.17	−0.47	0.0	0.163	8.43	8.50	7.39	7.41
7	*n*-C_4H_9	2.16	1.52	4.54	−0.39	0.0	0.425	8.30	8.32	7.41	7.29
8	*s*-C_4H_9	1.94	1.90	3.49	−1.13	1.0	0.370	8.24	8.43	7.68	7.92
9	*i*-C_4H_9	2.03	1.52	4.45	−0.93	1.0	0.399	8.16	8.38	7.95	7.87
12	*t*-C_4H_9	1.72	2.60	3.17	−1.54	0.0	0.277	7.82[j]	8.53	6.87[j]	7.45
13	*n*-C_5H_{11}	2.70	1.52	4.94	−0.40	0.0	0.649	7.43	7.47	6.74	6.57
14	*i*-C_5H_{11}	2.57	1.52	4.54	−0.35	0.0	0.614	7.24	7.64	6.44	6.72
17	*n*-$C_3H_7(CH_3)CH$	2.48	1.90	4.54	−1.02	1.0	0.590	7.65	7.75	7.41	7.35
22	$C_6H_5CH_2$	2.22	1.52	6.02	−0.38	0.0	0.330	7.91[j]	8.49	6.97[j]	7.42
23	*c*-C_5H_9	2.33	1.90	4.09	−0.51	1.0	0.447	8.39	8.26	7.82	7.78
24	*c*-$C_3H_5CH_2$	1.68	1.70	4.53	−0.93[h]	1.0	0.192	8.64	8.52	7.80	7.97
25	*c*-C_6H_{11}	2.76	1.91	3.49	−0.79	1.0	0.664	7.69	7.39	7.28	7.04
26	C_6H_5	1.68	1.71	3.11	0.23	0.0	0.268	8.53	8.53	7.30	7.45
27	$CH_3SCH_2CH_2$	0.71	1.52	4.80	−0.39[i]	0.0	−0.174	7.70	7.45	6.54	6.43
28	*t*-$C_4H_9CH_2$	2.41	1.52	4.45	−1.74	0.0	0.558	8.26	7.89	6.69	6.93

a) By topical application.
b) Cited from Ref. 5) or calculated from π values based on log P for aliphatic substituents by means of the additivity principle in Ref. 5).
c) STERIMOL width parameter taken from Refs. 6) and 7).
d) Taft's steric constant taken from Refs. 8) and 9).
e) Indicator variable for compounds with alkyl substituents whose E_s value is between −1.02 and −0.51.
f) By Eq. (3).
g) By Eq. (5).
h) Taken as that of *i*-C_4H_9.
i) Taken as that of *n*-C_4H_9.
j) Not included in the deviation of Eqs. (3) and (5).

To the *Ageo strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(1.946)}{-5.511}(\log k')^2 + \underset{(1.060)}{2.669}\log k' + \underset{(0.236)}{8.077} \quad (1)$$

$n=18$, $s=0.296$, $r=0.842$, $F_{2,15}=18.33$

To the *Izumi strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(2.644)}{-5.153}(\log k')^2 + \underset{(1.441)}{2.970}\log k' + \underset{(0.321)}{7.099} \quad (2)$$

$n=18$, $s=0.402$, $r=0.756$, $F_{2,15}=9.98$

In these and following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, and F_{ν_1,ν_2} is the F value of correlation when $\nu_1=m$ and $\nu_2=n-m-1$: m is the number of independent variables used in correlation. The figures in parentheses are 95% confidence intervals of the corresponding constant.

In trying to improve the correlation of Eqs. (1) and (2), we noticed that the activity of the *t*-butyl-thio (**12**) and benzyl-thio (**22**) derivatives deviated more than any others toward

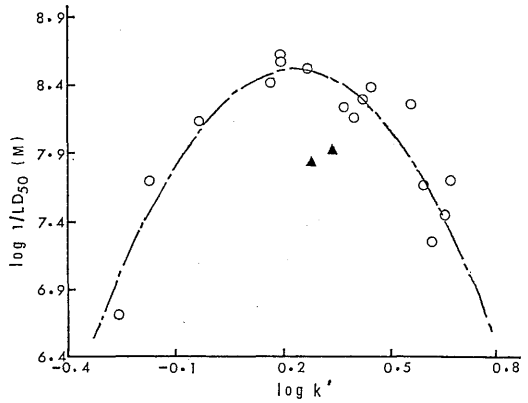


Fig. 2 Plot of insecticidal activity to the susceptible Ageo strain of *N. cincticeps* against hydrophobicity of compounds.

▲: Compounds **12** and **22** not included in the derivation of Eq. (3) for which the parabola is drawn by broken line.

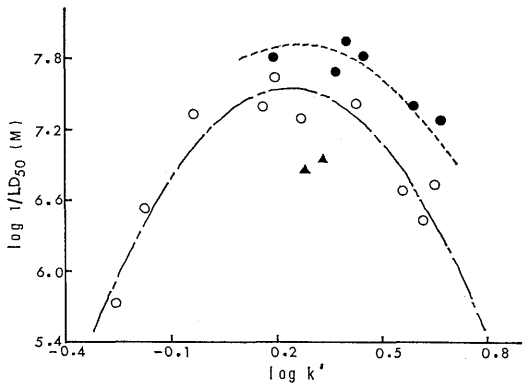


Fig. 3 Plot of insecticidal activity to the resistant Izumi strain of *N. cincticeps* against hydrophobicity of compounds.

▲: Compounds **12** and **22** not included in Eqs. (4) and (5). ●: Compounds **8**, **9**, **17**, **23**, **24** and **25**.

the lower direction than the calculated value. These deviations are probably attributable to steric effects of alkyl groups. *t*-Butyl has the largest B_1 value while benzyl shows the largest B_5 value among substituents in the compounds tested here. B_1 and B_5 are the STERIMOL steric parameters developed by Verloop and coworkers,[6] B_1 being the smallest and B_5 being the largest width perpendicular to the axis connecting the α-atom of the substituent with the rest of the molecule. There seem to be limiting steric conditions for substituent R^1 in insecticidal activity. By deleting these two compounds from the analyses, Eqs. (3) and (4) were obtained.

To the *Ageo strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(1.576)}{-6.374}(\log k')^2 + \underset{(0.844)}{3.052}\log k' + \underset{(0.190)}{8.173} \quad (3)$$

$n=16$, $s=0.244$, $r=0.925$, $F_{2,13}=38.34$

To the *Izumi strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(2.399)}{-6.170}(\log k')^2 + \underset{(1.285)}{3.422}\log k' + \underset{(0.289)}{7.212} \quad (4)$$

$n=16$, $s=0.341$, $r=0.852$, $F_{2,13}=17.27$

The correlation for the Ageo strain is much improved in Eq. (3). In closer examinations of Fig. 3 for the Izumi strain, we noticed that the log $(1/LD_{50})$ values of *sec*-butyl-thio (**8**), isobutyl-thio (**9**), 1-methyl-*n*-butyl-thio (**17**), cyclopentyl-thio (**23**), cyclopropylmethyl-thio (**24**) and cyclohexyl-thio (**25**) derivatives are almost uniformly higher than a parabola sensibly defined by the log $(1/LD_{50})$ values of the other compounds. In other words, when *t*-butyl- and benzyl-thio compounds are omitted, the activity index to the resistant strain is approximately expressible with two "parallel" parabolas with respect to the log k'. The alkyl group in compounds included in the upper parabola has an E_S value between -1.13 and -0.51, while that in the lower parabola has an E_S value below and above this range. Since the deviation of the activity for each compound from each of the parabolas does not seem to relate much to the E_S and other steric parameters of the alkyl groups, an indicator variable (I) assigned to be 1 for the compounds aligned on the upper parabola was used to differentiate the two groups of compounds to give Eq. (5).

$$\log(1/LD_{50}) = \underset{(1.596)}{-5.622}(\log k')^2 + \underset{(0.891)}{2.841} \cdot \log k' + \underset{(0.270)}{0.538}I + \underset{(0.198)}{7.097} \quad (5)$$

$n=16$, $s=0.221$, $r=0.945$, $F_{3,12}=33.60$

The correlation is much improved in Eq. (5). The steric effects exerted by *t*-butyl and benzyl

groups, are such that the minimum as well as the maximum width of substituents should not be too large for high activity. In addition, there is another type of steric effect by the alkyl group in terms of E_S. The alkyl groups, the E_S value of which is outside a certain range, were unfavorable to the insecticidal activity of this series of compounds against the resistant green rice leafhoppers. Insecticidal activity to the resistant strain seemed to be governed by steric effects of the alkyl group in alkylthio substituents more complex than those to the susceptible strain. The log $(1/LD_{50})$ values calculated by using Eqs. (3) and (5) are summarized in Table 2, together with the observed values. From Eqs. (3) and (5), the optimum hydrophobicity in terms of log k' was estimated 0.24–0.25 irrespective of the difference in strains, corresponding to that of C_3–C_4 alkylthio and phenylthio compounds.

Without omitting the *t*-butyl and benzyl groups as outliers, and instead of using the indicator variable for the alkyl groups, the E_S value of which is located in the above-mentioned region, we examined the steric effects of alkyl groups in appropriate "continuous" steric parameter terms. The STERIMOL B_5 parameter works best for the activity to the Ageo strain, while the E_S value is most legitimate for that to the Izumi strain.

To the *Ageo strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(1.748)}{-4.939}(\log k')^2 \underset{(1.095)}{+2.029}\log k' \underset{(0.132)}{-0.169}(B_5)^2 \underset{(1.113)}{+1.397}B_5 \underset{(2.178)}{+5.434} \quad (6)$$

$n=18$, $s=0.252$, $r=0.904$, $F_{4,13}=14.50$

To the *Izumi strain* of *N. cincticeps*

$$\log(1/LD_{50}) = \underset{(2.396)}{-4.324}(\log k')^2 \underset{(1.506)}{+2.170}\log k' \underset{(0.830)}{-1.115}(E_S)^2 \underset{(1.572)}{-1.939}E_S \underset{(0.479)}{+6.669} \quad (7)$$

$n=18$, $s=0.335$, $r=0.862$, $F_{4,13}=9.38$

An advantage of Eqs. (6) and (7) is that they include all of the compounds in a set. As mentioned above, however, the deviations of the activity of each compound from the parabolas defined by Eqs. (1) and (2) are not necessarily related linearly or parabolically to any steric parameter. Therefore, the correlation of Eqs. (6) and (7) in terms of s and r is poorer in quality than that of Eqs. (3) and (5) respectively. Since the effect of *t*-butyl- and benzyl-thio substituents in lowering the activity in parabolic relationships is very similar in both susceptible and resistant strains as shown in Figs. 2 and 3, it should be unreasonable for their effect to be represented by different steric parameters in Eqs. (6) and (7). Moreover, the two separated "parallel" parabolic relationships in Fig. 3 are not conceivable in Eq. (7). We believe that Eqs. (3) and (5) with steric outliers are capable of rationalizing the structure-activity relationship of this series of compounds better than Eqs. (6) and (7), respectively.

Equation (8) shows a good linear relationship of log k' value to the π value of the alkyl group in alkyl-thio substituents.

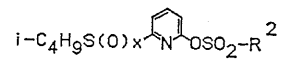
$$\log k' = \underset{(0.033)}{0.411}\pi \underset{(0.066)}{-0.462} \quad (8)$$

$n=18$, $s=0.420$, $r=0.989$, $F_{1,16}=688.47$

The π value is the hydrophobicity substituent parameter for aliphatic substituents based on the log P value, P being the partition coefficient in the 1-octanol/water system.

Table 3 demonstrates the activity of 6-*i*-$C_4H_9S(O)_x$-substituted 2-pyridyl alkanesulfonates. Methane- (**9–11**), ethane- (**29–31**) and chloromethane-sulfonates (**44** and **45**), and the sulfide form of *n*-propanesulfonate (**32**) showed 100% mortality to *N. cincticeps*, *N. lugens* and *C. pipiens* at the dose of 200 ppm. The sulfone form of *n*-propanesulfonate (**33**) remarked 100% mortality only to *N. cincticeps*. Other higher alkanesulfonates were either very weakly active or inactive to *N. cincticeps*. Although the sulfide form of trifluoromethanesulfonate (**41**) was inactive, its sulfoxide (**42**) and sulfone (**43**) were very active to *N. lugens*. 2-Propanesulfonate (**34**) and 3-chloropropanesulfonate (**45**) in a sulfide form, and trifluoromethanesulfonates (**41–43**) remarked high mortality to *C. pipiens*. Methanesulfonates (**9–11**) and chloromethanesulfonates (**44** and **45**) exhibited acaricidal activity.

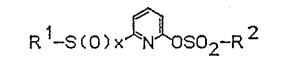
Table 3 Insecticidal and acaricidal activities of 6-*i*-$C_4H_9S(O)_x$-substituted 2-pyridyl alkanesulfonates.



No.	R^2	x	mp (°C) n_D^{25}	Mortality (%)[a]				
				N. c.[b] 200	*N. l.*[c] 200	*P. x.*[d] 200	*C. p.*[e] 1	*T. u.*[f] 200 ppm
9	CH_3	0	40–40.5	100	100	0	100	++
10	CH_3	1	87.5–88.5	100	100	0	100	+
11	CH_3	2	1.5156	100	100	0	100	+
29	C_2H_5	0	1.5332	100	100	0	100	—
30	C_2H_5	1	1.5256	100	100	0	100	—
31	C_2H_5	2	48.5–49.5	100	100	0	100	—
32	*n*-C_3H_7	0	1.5291	100	100	10	100	—
33	*n*-C_3H_7	2	1.5086	100	30	20	20	—
34	*i*-C_3H_7	0	1.5291	20	90	0	100	—
35	*i*-C_3H_7	1	1.5201	0	40	10	10	—
36	*i*-C_3H_7	2	1.5079	0	0	0	0	—
37	*n*-C_5H_{11}	0	1.5228	0	10	0	20	—
38	*n*-C_5H_{11}	1	1.5147	0	10	10	0	—
39	*n*-C_5H_{11}	2	1.5406	0	10	30	0	—
40	*n*-C_8H_{17}	0	1.5128	0	50	10	0	—
41	CF_3	0	1.4827	0	0	10	100	—
42	CF_3	1	1.4789	0	100	0	100	—
43	CF_3	2	1.4707	0	100	10	100	—
44	$ClCH_2$	0	1.5430	100	100	30	100	++
45	$ClCH_2$	2	1.5240	100	100	10	100	++
46	$ClCH_2CH_2CH_2$	0	1.5412	0	30	10	90	—
47	$ClCH_2CH_2CH_2$	1	44–46	0	10	20	0	—
48	$ClCH_2CH_2CH_2$	2	66–67	0	20	0	0	—

[a]–[f] See footnote [a]–[f] of Table 1.

Table 4 Inhibition of 6-R^1-$S(O)_x$-substituted 2-pyridyl alkanesulfonates to acetylcholinesterase preparations from *Nephotettix cincticeps* and *Nilaparvata lugens*.



No.	R^1	x	R^2	I_{50} (M)		
				N. cincticeps		*N. lugens*
				Ageo	Izumi	Kaseda
3	*n*-C_3H_7	0	CH_3	$>1\times10^{-5}$	$>1\times10^{-5}$	9×10^{-7}
4	*n*-C_3H_7	1	CH_3	5×10^{-9}	3×10^{-8}	8×10^{-8}
5	*n*-C_3H_7	2	CH_3	2×10^{-9}	8×10^{-9}	
9	*i*-C_4H_9	0	CH_3	$>1\times10^{-5}$	$>1\times10^{-5}$	
10	*i*-C_4H_9	1	CH_3	2×10^{-9}	4×10^{-9}	
11	*i*-C_4H_9	2	CH_3	1×10^{-9}	2×10^{-9}	
31	*i*-C_4H_9	2	C_2H_5	4×10^{-9}	2×10^{-8}	
	Propoxur			1×10^{-8}	$>5\times10^{-5}$	5×10^{-8}

Along with Table 1, Table 3 shows that the activity of 6-R^1-$S(O)_x$-substituted 2-pyridyl alkane(R^2)sulfonates are fairly selective to *N. cincticeps*, *N. lugens* and *C. pipiens*, and that only a few compounds are active against *P. xylostella* and *T. urticae*.

Table 4 shows the inhibitory activity of 6-R^1-$S(O)_x$-substituted 2-pyridyl alkanesulfonates to acetylcholinesterase preparations from *N. cincticeps* and *N. lugens*. The inhibitory activity of methanesulfonates in a sulfide form (**3** and **9**) was very low against the acetylcholinesterase prepared from *N. cincticeps*, while the sulfoxide (**4** and **10**) and sulfone (**5**, **11** and **31**) derivatives of methane- and ethane-sulfonates were very high ($I_{50}=3\times10^{-8}$–1×10^{-9} M). Propoxur as the reference compound inhibited very strongly the acetylcholinesterase from the susceptible Ageo strain of green rice leafhopper, but did not inhibit the enzyme from the resistant Izumi strain at a concentration of 5×10^{-5} M. The sulfide (**3**), sulfoxide (**4**) derivatives and propoxur showed high inhibitory activity to the acetylcholinesterase prepared from the Kaseda strain of *N. lugens*.

DISCUSSION

We have found that the number of carbon atoms in the alkyl group (R) of alkylthio substituents and their oxidized relatives in 3-R-$S(O)_x$-substituted phenyl methanesulfonates ($x=0$, 1 and 2) required to show a remarkable insecticidal activity against *N. cincticeps* and *N. lugens* correspond to 2 to 4.[1] In the present series of pyridyl methanesulfonates, it was 1 to 6 as shown in Table 1. Likewise, the number of carbon atoms in the alkyl group of the alkanesulfonate moiety in highly insecticidal 3-*n*-Pr-$S(O)_x$-phenyl alkanesulfonates was 1 to 2. In the 6-*i*-Bu-$S(O)_x$-2-pyridyl analogs, it was 1 to 3. Chloromethanesulfonates also turned out to be active in a pyridyl series as indicated in Table 3. Although the present pyridyl compounds were applied on rice seedlings by "foliar spraying" different from previous "leaf dipping" for phenyl derivatives, the data in Tables 1 and 3 could be directly comparable with those in the previous paper.[1] The replacement of the benzene ring in phenyl alkanesulfonates with pyridine expanded the range of the alkyl group in alkylthio substituents as well as in alkanesulfonate moiety. This could partly be due to the fact that pyridyl derivatives are lower in hydrophobicity than the corresponding phenyl analogs. To make substituents and substructures more hydrophobic by increasing the carbon number would be permissible in pyridyl compounds to attain optimum hydrophobicity for the total series of aryl alkanesulfonates.

The existence of hydrophobicity optimum in insecticidal activity was clearly substantiated by examinations of quantitative structure/activity relationships shown in Eqs. (3) and (5) for alkylthiopyridyl methanesulfonates. The parabolic dependence on hydrophobicity in these equations indicates that the compounds would take a traverse through a number of lipoidal-aqueous interfaces to reach a critical site of biological activity. The findings that the sulfide form was inactive while the sulfoxide and sulfone forms were highly active in inhibiting acetylcholinesterase preparations from green rice leafhoppers (Table 4), and that they were equally insecticidally active *in vivo* (Table 1) indicate that the sulfide form must be oxidized *in vivo* perhaps by mixed-function oxidases before it inhibits acetylcholinesterase. The alkylthio group on the aromatic ring would not be electron-withdrawing enough for this series of compounds to efficiently sulfonylate the serine-OH group of acetylcholinesterase. Since the sulfide form was much more hydrophobic than either sulfoxide or sulfone form, the sulfide form is assumed to be a form in which molecules traverse barriers. That is, the rate-limiting and/or critical process(es) for this series of compounds to exhibit activity is transport to organs where they are activated by oxidases.

The activity lower than expected from Eqs. (3) and (5) for the *t*-butylthio and benzylthio derivatives was attributed to steric limitation. The steric limitation could be found in the interaction with oxidases as well as with acetylcholinesterase regardless of strains. Another steric factor was observed in the activity to the resistant green rice leafhoppers in Eq. (5). That is the effect of the alkyl groups in alkylthio substituents the steric bulk of which

is either too low or too high. The activity of compounds having alkyl groups of intermediate bulk was analyzed by using the indicator variable. Alkylthio compounds having alkyl substituents smaller than the intermediate range could be too easily oxidized to sulfoxides and sulfones because of a lack of significant steric hindrance. Their hydrophobicity is lowered and the transport to the nervous system is not easy. Hydrolytic inactivation that may be started spontaneously and by nonspecific hydrolases would be important in the sulfoxide and sulfone forms more than in the sulfide form, because of higher electron withdrawing property of oxidized substituents. On the other hand, compounds having bulkier alkyl groups could not easily be activated by oxidases. They would also have a difficulty fitting acetylcholinesterase. As a result, compounds having a moderate steric bulk in terms of E_S are well balanced in their physicochemical properties to show higher activity. The extra steric factor is significant only in the activity to resistant strains. This is reasonable since a mixed-function oxidase system would be developed more widely in resistant strains than in susceptible insects,[10] and enzymatic oxidation operating as detoxication would also work as a bioactivation mechanism.

High inhibitory activity of *n*-propylthiopyridyl methanesulfonate in a sulfide form against the acetylcholinesterase preparation from *N. lugens* contrasted to very low activity against the enzyme from *N. cincticeps*. Such phenyl analogs as 3-*n*-Pr-thiophenyl methanesulfonate were inactive as found previously.[1] The *n*-propylthiopyridyl compound itself may interact with a acetylcholinesterase preparation from *N. lugens* much stronger than with esterase from *N. cincticeps*. Another reason could be that the enzyme preparation was not purified containing some oxidases to activate sulfide.

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要　　約

6-アルキルチオ-2-ピリジル アルカンスルホナート類の化学構造と殺虫，殺ダニ活性*

加藤彰一，桝井昭夫，石田秀弐

6-アルキルチオ-2-ピリジル　アルカンスルホナート，それらのスルホキシド体，そしてスルホン体を合成し，5種類の害虫およびハダニに対する致死活性を調べた．1から6個の炭素原子を有する6-アルキル-チオ，-スルフィニルおよび -スルホニル基を持つメタンスルホナートはツマグロヨコバイ，トビイロウンカおよびチカイエカに対して高活性を示した．有機リン剤およびカーバメート剤に感受性および抵抗性の2系統のツマグロヨコバイに対する6-アルキルチオ-2-ピリジル　メタンスルホナートの殺虫活性は分子の疎水性とパラボリックな関係にあり，いずれの系統においても C_3 ないし C_4 のアルキル-チオ基が最適であった．6-イソブチルチオ-2-ピリジル　アルカンスルホナート，それらのスルホキシド体

* メタンスルホナート殺虫剤の構造活性相関(第2報)

およびスルホン体の中では，メタン-，エタン-およびクロロメタン-スルホナートが，より高級なアルカン-スルホナートに比べて高活性を示した．6-*n*-プロピルスルフィニル-，-スルホニル-，6-イソブチル-スルフィニル-および-スルホニル-2-ピリジル　メタンスルホナート，そして6-イソブチルスルホニル置換のエタンスルホナートはツマグロヨコバイの有機リン剤およびカーバメート剤に対して感受性あるいは抵抗性の二つの系統から得たアセチルコリンエステラーゼを強く阻害した．