Original Article

Synthesis and Fungicidal Activity of New 1,3,2-Oxazaphospholidine 2-Sulfides

Shigehiko TAIRA, Shinkichi TAWATA,^{*,**} Naotada KOBAMOTO,^{*}
Seizen TOYAMA^{*} and Masaaki YASUDA^{*}

*The United Graduate School of Agricultural Sciences, Kagoshima University, Koorimoto,
Kagoshima 890, Japan*

**College of Agriculture, University of the Ryukyus, Nakagami-gun, Okinawa 903-01, Japan*

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Geraniol and isothymol in the essential oil of *Alpinia speciosa* K. SCHUM. possess high antimicrobial activity against plant pathogenic bacteria. The twenty-three kinds of 1,3,2-oxazaphospholidine 2-sulfides were synthesized by reacting (S)-2-aminoalcohols, PSCl_2 and the components of essential oil; geraniol, isothymol, thymol, citronellol and eugenol. Among the prepared compounds, (4S)-2-citronelloxy-4-isopropyl-1,3,2-oxazaphospholidine 2-sulfide (**6**) and (4S)-2-geranioxy-4-isopropyl-1,3,2-oxazaphospholidine 2-sulfide (**5**) had the strongest antimicrobial activity against *Pythium* sp. and *Corticium* sp. respectively. L-Valine derivatives showed stronger activity than the other L-amino acids derivatives.

INTRODUCTION

Alpinia speciosa K. SCHUM. is one of the Zingibraceae species whose leaves emit a pleasure fragrance. These have been utilized traditionally in the packaging of rice cakes for many years in Okinawa. In the produced substances from *A. speciosa*, there are volatile and nonvolatile components. As the volatile components, there are organic acids and terpene derivatives such as geraniol, citronellol, isothymol, thymol and eugenol¹⁾; and as the nonvolatile components; cardamonin and alpinetin are obtained from the seeds.²⁾ Flavokawain B, dihydroflavokawain B, dihydro-5,6-dehydrokawain and 5,6-dehydrokawain are isolated from these rhizomes.³⁾ Since the essential oils showed some inhibitory effects on the growth or proliferation of bacteria, mold, parasites, and insects, these are possible components which may be used to make a new type of pesticide. Using each component of the essential oil contained in *A. speciosa*, we have investigated the antimicro-

bial activity against plant pathogenic bacteria to prepare a new series of compounds. The present paper reports the correlation between the chemical structure and the antimicrobial activity against plant pathogenic bacteria.

MATERIALS AND METHODS

1. Chemicals

The essential oils used are geraniol, isothymol, thymol, citronellol, and eugenol which were purchased from Wako Pure Chemical Industries, Co., Ltd. (Tokyo). Other reagents used were of the highest grade commercially available.

2. Antimicrobial Test

Pythium sp. and *Corticium* sp. were used as the test plant pathogenic bacteria. They were cultured on potato dextrose agar (agar 1.5%) for 5 days at 27°C and applied for the test. Antimicrobial activity was measured by the agar dilution method.⁴⁾ A negligible amount of acetone was added to each test compound to be able to suspend it in water. The concentration of all samples were regulated to 10,000 and 1000 ppm, then each 1.0 ml was

^{**} To whom correspondence should be addressed.

poured into a Petri dish (9 cm i.d.). Potato dextrose agar (9.0 ml, agar 1.5%) was cooled to 50–60°C and added to the Petri dish to make gel. After shaking, the nutrient medium settled to 1000 and 100 ppm. A mycelial disk (5 mm i.d.) from the planar cultured *Pythium* sp. or *Corticium* sp. was placed on a potato dextrose agar plate containing a test compound at 1000 or 100 ppm. After incubation for 4 days at 27°C, the inhibition of mycelial growth was measured percentagewise in comparison with the control. The bioassay was conducted with two replicates for 1000 ppm and four replicates for 100 ppm treatment. Data obtained from repetition of the experiments were combined to calculate the mean values.

3. Thin Layer Chromatography

Each synthesized product was developed with benzene–chloroform (1:1 v/v) using a pre-coated silica gel glass plate (Kieselgel 60 PF₂₅₄, 20×20 cm, 2.0 mm layer thickness, Merck). The objective compound was detected by ultraviolet light, and extracted by benzene. The filtrate was evaporated *in vacuo*. The residue was applied to instrumental analysis.

4. Instrumental Analysis

Structures of the compounds were confirmed by IR (Analect RFX-30), ¹H NMR and ¹³C NMR in CDCl₃ with TMS as internal standard (JEOL JNM-GSX 270), and EI-MS with 70 eV as ionizing energy (JEOL JMS-DX 300). Refractive indexes are uncorrected. The following are examples of general synthetic procedures.

5. Synthesis of 1,3,2-Oxazaphospholidine 2-Sulfides

Compounds were synthesized as shown in Fig. 1. A mixture of (S)-(+)-leucinol (3.8 mmol) and triethylamine (7.6 mmol) in dichloromethane (50 ml) was added in drops to a stirred solution of thiophosphoryl chloride (3.8 mmol) in dichloromethane (50 ml) at 10°C. The reaction mixture was maintained with stirring at room temperature for 3 hr. After the completion of the reaction, the solution was evaporated *in vacuo*. The residue was mixed with benzene (100 ml) and the precipitate was

Fig. 1 Synthetic route of 1,3,2-oxazaphospholidine 2-sulfides.

removed by filtration. (4S)-2-chloro-4-isobutyl-1,3,2-oxazaphospholidine 2-sulfide was obtained by the evaporation of the filtrate.⁵⁾ Then a mixture of geraniol (3.5 mmol) and triethylamine (3.5 mmol) in dichloromethane (50 ml) was added in drops to the reaction mixture with stirring in dichloromethane (50 ml) at 10°C for 3 hr. After the completion of the reaction, the mixture was treated by the above mentioned method. The prepared compound was purified by the method described above to give 0.19 g (16%) of (4S)-2-geranioxy-4-isobutyl-1,3,2-oxazaphospholidine 2-sulfide (**10**) as a colorless oil, n_D^{25} 1.4933. MS m/z (rel. int): 331 (M⁺) (15), 279 (21), 262 (27), 197 (93), 137 (100). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 998 (P–O–C), 829 (P–O), 709 (P=S). ¹H NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 0.89 (6H, m, 2×CH₃), 1.32 (2H, m, CH₂), 1.56 (1H, m, CH), 1.60 (3H, s, CH₃), 1.68 (3H, s, CH₃), 1.72 (3H, s, CH₃), 2.09 (4H, m, 2×CH₂), 3.75 (1H, m, NHCH), 3.83–4.44 (2H, m, OCH₂), 4.58 (2H, m, OCH₂), 5.10 (1H, t, $J=7$ Hz, CH), 5.39 (1H, t, $J=7$ Hz, CH). ¹³C NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 16.5 (s, CH₃), 17.6 (s, CH₃), 22.0 (d, CH₃), 22.1 (d, CH₃), 22.8 (d, CH₃), 23.0 (d, CH₃), 25.0 (s, CH₃), 25.6 (s, CH), 26.2 (s, CH₂), 39.8 (s, CH₂), 43.2 (d, CH₂), 43.7 (d, CH₂), 53.5 (d, NHCH), 53.7 (d, NHCH), 64.9 (d, OCH₂), 72.6 (s, OCH₂), 73.3 (s, OCH₂), 118.9 (d, CH), 119.1 (d, CH), 123.7 (s, CH), 131.6 (s, C), 142.0 (d, C).

Analytical data of L-leucine derivatives (**11**–**14**) are shown below.

(4S)-2-Citronelloxy-4-isobutyl-1,3,2-oxazaphospholidine 2-sulfide (**11**). Yield 0.23 g, 19%. n_D^{25} 1.4918. MS m/z (rel. int): 333 (M⁺) (26), 327 (23), 197 (100), 154 (41), 138 (65). IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 985 (P–O–C), 825 (P–O), 707 (P=S). ¹H NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 0.90 (9H, m, 3×CH₃), 1.13 (2H, m, CH₂), 1.31 (5H, m, CH, CH₂, CH₂), 1.45 (1H, m, CH), 1.60 (3H, s, CH₃), 1.68 (3H, s, CH₃), 1.96 (2H, m, CH₂),

3.87 (1H, m, NHCH), 4.02–4.42 (2H, m, OCH₂), 5.09 (2H, t, $J=7$ Hz, OCH₂). ¹³C NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 17.6 (s, CH₃), 19.3 (s, CH₃), 22.0 (d, CH₃), 22.9 (d, CH₃), 25.2 (d, CH₃), 25.7 (s, CH₂), 29.0 (d, CH), 36.9 (d, CH₂), 37.1 (d, CH₂), 43.2 (d, CH₂), 43.7 (d, CH₂), 53.6 (d, NHCH), 53.7 (d, NHCH), 66.8 (d, OCH₂), 72.6 (d, OCH₂), 73.4 (d, OCH₂), 124.5 (s, CH), 131.2 (s, C).

(4S)-4-Isobutyl-2-isothymoxy-1,3,2-oxazaphospholidine 2-sulfide (**12**). Yield 0.35 g, 28%. $n_D^{25.4}$ 1.5232. MS m/z (rel. int): 327 (M⁺) (78), 270 (19), 242 (22), 228 (44), 135 (100). IR $\nu_{\text{max}}^{\text{Neat}}$ cm⁻¹: 993 (P–O–C), 827 (P–O), 713 (P=S). ¹H NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 0.85 (6H, m, 2 × CH₃), 1.17 (3H, s, CH₃), 1.21 (3H, s, CH₃), 1.37 (1H, m, CH), 1.56 (2H, m, CH₂), 2.27 (3H, s, CH₃), 2.84 (1H, m, CH), 3.66 (1H, m, NHCH), 3.85–4.31 (2H, m, OCH₂), 6.94–7.13 (3H, m, aromatic). ¹³C NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 16.4 (d, CH₃), 22.0 (d, CH₃), 22.2 (d, CH₃), 22.7 (d, CH₃), 22.9 (d, CH₃), 23.9 (d, CH₃, CH₃), 25.2 (d, CH), 33.5 (s, CH), 43.1 (d, CH₂), 43.7 (d, CH₂), 53.5 (d, NHCH), 53.6 (d, NHCH), 73.2 (s, OCH₂), 73.8 (s, OCH₂), 119.4 (d, CH), 119.8 (d, CH), 123.3 (d, CH), 127.4 (d, C), 127.5 (d, C), 130.9 (d, CH), 147.8 (d, C), 147.9 (d, C), 149.6 (d, C), 149.7 (d, C).

(4S)-4-Isobutyl-2-thymoxy-1,3,2-oxazaphospholidine 2-sulfide (**13**). Yield 0.28 g, 24%. $n_D^{25.8}$ 1.5229. MS m/z (rel. int): 327 (M⁺) (32), 280 (12), 196 (12), 164 (15), 135 (97), 132 (100). IR $\nu_{\text{max}}^{\text{Neat}}$ cm⁻¹: 989 (P–O–C), 836 (P–O), 730 (P=S). ¹H NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 0.86 (6H, m, 2 × CH₃), 1.16 (3H, s, CH₃), 1.20 (3H, s, CH₃), 1.35 (1H, m, CH), 1.59 (2H, m, CH₂), 2.34 (3H, s, CH₃), 3.31 (1H, m, CH), 3.75 (1H, m, NHCH), 3.92–4.52 (2H, m, OCH₂), 6.95–7.18 (3H, m, aromatic). ¹³C NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 20.8 (s, CH₃), 21.9 (d, CH₃), 22.8 (d, CH₃), 23.1 (d, CH₃), 23.2 (d, CH₃), 25.2 (d, CH), 26.6 (d, CH), 43.1 (d, CH₂), 43.8 (d, CH₂), 53.6 (d, NHCH), 73.1 (s, OCH₂), 73.8 (s, OCH₂), 121.7 (d, CH), 122.0 (d, CH), 126.2 (d, CH), 126.4 (d, CH), 136.2 (d, C), 136.3 (d, C), 137.3 (d, C), 148.3 (d, C), 148.4 (d, C).

(4S)-2-Eugenoxo-4-isobutyl-1,3,2-oxazaphospholidine 2-sulfide (**14**). Yield 0.17 g, 10%. $n_D^{25.6}$ 1.5442. MS m/z (rel. int): 341 (M⁺) (79), 280 (24), 264 (5.0), 175 (100), 161 (20), 146 (20). IR $\nu_{\text{max}}^{\text{Neat}}$ cm⁻¹: 993 (P–O–C), 844 (P–O), 705

(P=S). ¹H NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 0.85 (6H, m, 2 × CH₃), 1.26 (2H, m, CH₂), 1.55 (1H, m, CH), 3.34 (2H, d, $J=7$ Hz, CH₂), 3.78 (1H, m, NHCH), 3.84 (3H, s, CH₃), 3.88–4.46 (2H, m, OCH₂), 5.09 (2H, m, =CH₂), 5.93 (1H, m, CH), 6.68–7.11 (3H, m, aromatic). ¹³C NMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ ppm: 21.9 (d, CH₃), 22.9 (d, CH₃), 25.1 (d, CH), 39.7 (d, CH₂), 39.9 (d, CH₂), 43.2 (d, CH₂), 43.7 (d, CH₂), 53.1 (d, NHCH), 53.3 (d, NHCH), 55.9 (d, CH₃), 56.0 (d, CH₃), 72.8 (d, OCH₂), 73.6 (d, OCH₂), 113.0 (s, CH), 116.1 (s, CH₂), 120.6 (d, CH), 120.8 (d, CH), 122.5 (d, CH), 137.0 (s, CH), 137.9 (d, C), 138.6 (d, C), 138.7 (d, C), 150.9 (d, C), 151.0 (d, C).

By using the same procedure, L-alanine derivatives (**1–4**), L-valine derivatives (**5–9**), L-isoleucine derivatives (**15–19**), and L-phenylalanine derivatives (**20–23**) were prepared. Spectral data, refractive indexes and yields of compounds are listed in Tables 2 and 3.

RESULTS AND DISCUSSION

1. Antimicrobial Activity of the Essential Oils

The essential oil from *Alpinia speciosa* K. SCHUM. was obtained by steam distillation of the leaves and analyzed by gas-chromatog-

Table 1 Antimicrobial activity of essential oils of *Alpinia speciosa*. (%)

Compound	Conc. (ppm)	<i>Pythium</i> sp.		<i>Corticium</i> sp.	
		100	1000	100	1000
Essential oil of <i>A.s.</i>			68.1		64.7
α -Terpineol	11.2	100		71.8	100
<i>p</i> -Cymene	0	0.2		14.4	13.6
Borneol	21.1	100		27.7	100
Geraniol	63.3	100		71.8	100
Citronellol	68.9	100		23.9	100
α -Pinene	4.0	0		0.8	46.3
Linalool	21.3	67.4		46.9	93.9
Terpinene-4-ol	7.1	98.3		0	98.3
Cineole	0	0.4		8.3	0
<i>d</i> -Camphor	0	9.3		0.4	22.1
β -Pinene	0	2.2		1.2	16.3
Isothymol	94.3	100		72.4	100
Thymol	93.0	100		71.0	100
Eugenol	92.7	100		67.6	100
Cuminaldehyde	14.0	100		22.0	100
Benzylacetone	24.5	100		30.5	100
Myrtenol	41.0	100		56.0	100
Methyl cinnamate	66.0	100		54.0	100

Table 2 IR, NMR and MS spectral data of 1, 3, 2-oxazaphospholidine 2-sulfides.

Compound	IR ^{a)} $\nu_{\text{max}}^{\text{Neat}}$ cm ⁻¹			¹ H NMR ^{b)} (CDCl ₃) δ ppm		¹³ C NMR (CDCl ₃) δ ppm		EI-MS <i>m/z</i>
	$\nu_{\text{P=S}}$	$\nu_{\text{P-O}}$	$\nu_{\text{P-O-C}}$	>N-CH (4)	$\text{-O-CH}_2 \text{ (5)}$	>N-CH (4)	$\text{-O-CH}_2 \text{ (5)}$	
1	709 (s)	829 (vs)	998 (vs)	3.83 (m)	3.90–4.43 (m)	50.9	74.2	289 (M ⁺)
2	707 (s)	823 (vs)	993 (vs)	3.82 (m)	3.90–4.44 (m)	51.0	74.2	291 (M ⁺)
3	711 (s)	833 (vs)	991 (vs)	3.64 (m)	3.87–4.33 (m)	51.0	74.7	285 (M ⁺)
4	730 (s)	844 (vs)	997 (vs)	3.75 (m)	3.92–4.42 (m)	51.1	74.6	285 (M ⁺)
5	701 (s)	800 (vs)	1035 (vs)	3.42 (m)	3.95–4.37 (m)	60.8	71.2	319 (M ⁺)
6	700 (s)	836 (vs)	985 (vs)	3.41 (m)	3.94–4.45 (m)	60.8	71.2	321 (M ⁺)
7	711 (s)	829 (vs)	987 (vs)	3.82 (m)	4.03–4.29 (m)	60.9	71.5	315 (M ⁺)
8	731 (s)	844 (vs)	964 (vs)	3.93 (m)	4.09–4.37 (m)	60.9	71.5	315 (M ⁺)
9	694 (s)	850 (vs)	989 (vs)	3.96 (m)	4.07–4.43 (m)	60.6	71.4	329 (M ⁺)
10	707 (s)	806 (vs)	985 (vs)	3.75 (m)	3.83–4.44 (m)	53.7	72.6	331 (M ⁺)
11	707 (s)	825 (vs)	985 (vs)	3.87 (m)	4.02–4.42 (m)	53.7	72.6	333 (M ⁺)
12	713 (s)	827 (vs)	993 (vs)	3.66 (m)	3.85–4.31 (m)	53.6	73.8	327 (M ⁺)
13	730 (s)	836 (vs)	989 (vs)	3.75 (m)	3.92–4.52 (m)	53.6	73.8	327 (M ⁺)
14	705 (s)	844 (vs)	993 (vs)	3.78 (m)	3.88–4.46 (m)	53.1	72.8	341 (M ⁺)
15	703 (s)	800 (vs)	1022 (vs)	3.52 (m)	3.95–4.40 (m)	60.1	71.1	331 (M ⁺)
16	701 (s)	829 (vs)	993 (vs)	3.49 (m)	3.94–4.40 (m)	60.0	71.2	333 (M ⁺)
17	713 (s)	827 (vs)	997 (vs)	3.82 (m)	4.02–4.29 (m)	59.9	71.3	327 (M ⁺)
18	731 (s)	840 (vs)	966 (vs)	3.94 (m)	4.10–4.39 (m)	59.5	71.3	327 (M ⁺)
19	694 (s)	817 (vs)	997 (vs)	3.47 (m)	4.03–4.41 (m)	59.8	71.3	341 (M ⁺)
20	700 (s)	804 (vs)	1004 (vs)	4.03 (m)	4.13–4.42 (m)	56.5	71.9	365 (M ⁺)
21	700 (s)	825 (vs)	987 (vs)	3.85 (m)	4.00–4.42 (m)	56.6	71.9	368 (M ⁺)
22	701 (s)	827 (vs)	995 (vs)	3.83 (m)	4.02–4.47 (m)	56.6	72.4	361 (M ⁺)
23	701 (s)	846 (vs)	966 (vs)	3.93 (m)	4.09–4.49 (m)	56.6	72.4	361 (M ⁺)

a) vs: very strong, s: strong.

b) m: multiplet.

raphy for determining the constituents. Among the 105 kinds of compounds in the essential oil, 18 kinds of compounds were tested for antimicrobial activity against *Pythium* sp. and *Corticium* sp. Isothymol showed 94.3% inhibitory activity at the 100 ppm against *Pythium* sp. Geraniol and isothymol showed 71.8 and 72.4% respectively at 100 ppm against *Corticium* sp. The strongest active compound was isothymol and the next was thymol. Isothymol and geraniol are volatile in the natural environment. These were used as an exocyclic combining moiety of 1,3,2-oxazaphospholidine. Isothymol and the other active constituents can be converted into nonvolatile compounds.

2. Synthesis of 1,3,2-Oxazaphospholidine 2-Sulfides

L-Amino acid methyl esters were reduced to make (S)-2-aminoalcohols by sodium borohydride. The L-amino acids used were L-

Fig. 2 ¹H-¹H COSY spectrum of compound **10**.

alanine, L-valine, L-leucine, L-isoleucine, and L-phenylalanine. The 2-aminoalcohols reacted with phosphorus thiochloride to make 2-chloro-1,3,2-oxazaphospholidine derivatives.⁵⁾ 2-Chloro derivatives reacted with the essential oils geraniol, citronellol, isothymol, thymol, and eugenol. Twenty-three kinds of 1,3,2-oxazaphospholidine 2-sulfides were prepared and listed the IR, NMR and MS spectral data in Table 2. IR spectra of the compounds showed the existence of P=S, P=O, and P=O-C groups. ¹H NMR and ¹³C NMR data show the chemical shift values of endocyclic methine and methylene on positions 4 and 5, respectively.

3. ¹H-¹H COSY Spectrum of 1,3,2-Oxazaphospholidine 2-Sulfides

¹H-¹H COSY spectrum of (4S)-2-geranioxy-

4-isobutyl-1,3,2-oxazaphospholidine 2-sulfide (**10**) is shown in Fig. 2. Methyl protons "a" and "b" of isobutyl group are coupling with methine proton "d", but the proton "d" overlaps with the signals of the methyl protons "e, f, and g" of geranyl group. Methylene protons "c" are coupling with methine proton "j" and the proton "j" is coupling with methylene protons "k" in which two protons of the methylene are separated into two signals (δ 3.9 and 4.4 ppm) due to the fact that the neighboring carbon of position 4 is chiral. Methylene protons "i" of geranyl group are coupling with methine proton "m", and methylene protons "l" are coupling with methine proton "n". This ¹H-¹H COSY spectrum supports the chemical structure of compound **10**.

Table 3 Antimicrobial activity of 1, 3, 2-oxazaphospholidine 2-sulfides.

Compound	R ¹	R ² OH	n _D (°C)	Yield (%)	Pythium sp. (%)		Corticium sp. (%)	
					100 (ppm)	1000 (ppm)	100 (ppm)	1000 (ppm)
1	CH ₃	Geraniol	1.5102 (25.2)	8	20.2		22.7	
2	CH ₃	Citronellol	1.4665 (24.7)	14	0		0	
3	CH ₃	Isothymol	1.5021 (25.3)	11	10.8		31.7	
4	CH ₃	Thymol	1.4716 (24.4)	14	0		0	
5	CH(CH ₃) ₂	Geraniol	1.4667 (25.9)	9	68.2		68.6	
6	CH(CH ₃) ₂	Citronellol	1.4945 (24.9)	14	87.3		42.6	
7	CH(CH ₃) ₂	Isothymol	1.5301 (25.3)	16	24.3		0	
8	CH(CH ₃) ₂	Thymol	1.5331 (25.7)	15	29.8		18.7	
9	CH(CH ₃) ₂	Eugenol	1.5459 (22.8)	18	53.9		37.5	
10	CH ₂ CH(CH ₃) ₂	Geraniol	1.4933 (25.2)	16	35.4	100	26.7	97.9
11	CH ₂ CH(CH ₃) ₂	Citronellol	1.4918 (25.3)	19	24.7	53.9	26.7	82.9
12	CH ₂ CH(CH ₃) ₂	Isothymol	1.5232 (25.4)	28	11.7	58.2	14.6	64.3
13	CH ₂ CH(CH ₃) ₂	Thymol	1.5229 (25.8)	24	19.8	36.1	36.8	77.1
14	CH ₂ CH(CH ₃) ₂	Eugenol	1.5442 (25.6)	10	9.9		0.8	
15	CH(CH ₃)CH ₂ CH ₃	Geraniol	1.4464 (24.3)	11	0		0	
16	CH(CH ₃)CH ₂ CH ₃	Citronellol	1.4596 (24.8)	13	0		0	
17	CH(CH ₃)CH ₂ CH ₃	Isothymol	1.4760 (24.1)	14	12.5		0	
18	CH(CH ₃)CH ₂ CH ₃	Thymol	1.4678 (24.1)	14	3.7		0	
19	CH(CH ₃)CH ₂ CH ₃	Eugenol	1.4758 (24.1)	10	41.7		25.3	
20	Benzyl	Geraniol	1.5311 (25.5)	18	4.0	16.9	28.5	60.4
21	Benzyl	Citronellol	1.5293 (25.1)	18	1.6	30.8	21.1	66.8
22	Benzyl	Isothymol	1.5542 (25.1)	21	9.4	58.2	15.3	36.0
23	Benzyl	Thymol	1.5532 (25.4)	21	19.8	46.0	33.8	41.0

4. Antimicrobial Activity of 1,3,2-Oxazaphospholidine 2-Sulfides

For the antimicrobial activity of 1,3,2-oxazaphospholidine 2-sulfides against plant pathogenic bacteria, L-valine derivatives showed stronger activity than the other L-amino acids derivatives. Compound **6** showed the strongest activity 87.3%, and the next was **5** as shown 68.2% at 100 ppm against *Pythium* sp. Against *Corticium* sp., **5** and **6** showed 68.6 and 42.6% respectively. Isothymol showed the strongest activity against *Pythium* sp. and *Corticium* sp., but the synthesized compounds **3**, **7**, **12**, **17**, and **22** did not show such strong activity. Geraniol showed a moderate amount of strong activity and its derived compound **5** showed stronger activity than the starting material geraniol. In conclusion, L-valine derivatives showed stronger activity than the other L-amino acids *i.e.*, isopropyl group on position 4 had stronger activity than the other methyl or isobutyl groups.

For the insecticidal activity (4S)-4-isobutyl-2-methoxy-1,3,2-oxazaphospholidine 2-sulfide derived from L-leucine and the 4-isopropyl homolog derived from L-valine have already been reported to show remarkably stronger activity against resistant strains of houseflies.⁶⁾ In the matter of antimicrobial substances, organophosphorus compounds involved the organothiophosphoric acid esters and thiophosphonic acid esters such as Kitazin-P and Pyrazophos. Both of these were known to inhibit the biosynthesis of chitin and break the cell wall.⁷⁾ Since the newly synthesized compounds show relatively strong activity, the result suggests that a stronger active compound could be synthesized in the L-valine derivatives by the conversion of exocyclic substituents.

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要 約

新規 1,3,2-Oxazaphospholidine 類の合成および抗カビ活性

平良栄彦, 多和田真吉, 小波本直忠
当山清善, 安田正昭

ゲットウ精油成分中には, geraniol や isothymol など植物病原菌に対してかなりの抗菌活性をもつ成分のいることがわかったので, これらの精油成分を用いてより活性の強い化合物の合成を試みた. アミノ酸の L-ロイシンや L-バリンを還元して得られる (S)-2-amino-alcohol 類と PSCl_3 を反応させて五員環リン酸アミド化合物を合成し, これに環外置換基として精油成分である geraniol, citronellol, isothymol, thymol および eugenol とを反応させることにより 1,3,2-Oxazaphospholidine 類を 23 種類合成した. 合成化合物の植物病原菌に対する抗菌活性では, ピシウム菌および白絹病菌に対してそれぞれ (4S)-2-citronelloxy-4-isopropyl-1,3,2-oxazaphospholidine 2-sulfide (**6**) および (4S)-2-geranioxy-4-isopropyl-1,3,2-oxazaphospholidine 2-sulfide (**5**) がもっとも強い抗菌活性を示し, L-バリン誘導体は他の L-アミノ酸誘導体よりも比較的強い抗菌活性を有することが明らかとなった.