抗菌性L-5-Alkylthiomethylhydantoin S-oxidesおよび関連化合物の合成

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Synthesis of Antimicrobial L-5-Alkylthiomethylhydantoin *S*-Oxides and Related Compounds*

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Ten L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides (alkyl or alkenyl : methyl, ethyl, propyl, isopropyl, allyl, butyl, isobutyl, *sec*-butyl, pentyl and hexyl) and some related compounds were prepared from L-cystine. L-5-Propylthiomethylhydantoin *S*-oxide (L-(±)-PHSO) was further split into L-(+)-PHSO and L-(−)-PHSO. L-5-Alkyl- and alkenylthiomethylhydantoin *S*-oxides exhibited antimicrobial activities, and L-(±)-PHSO and L-5-isopropylthiomethylhydantoin *S*-oxide were most active against *Escherichia coli* AHU 1041. There was no difference in activity between the two stereoisomers, L-(+)-PHSO and L-(−)-PHSO. Yeasts were much less sensitive to L-(+)-PHSO than bacteria. Although (±)-PHSO had potent inhibitory action against *E. coli*, the deoxy compound, L-5-propylthiomethylhydantoin did not have any activity and the *S,S*-dioxide had only a weak activity. Both *N*-carbamoyl-L-cysteine and its sulfoxide had no inhibitory action. From these results it has been suggested that the structure required for antibacterial activity involves both hydantoin ring and sulfoxide function.

INTRODUCTION

The authors have found that L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides have remarkable antibacterial activity.[1] These are hydantoin derivatives of naturally occurring sulfur-containing amino acids and related compounds. The hydantoin ring is easily degraded by microorganisms[2] and therefore, L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides would be a candidate for nonpersistent and biodegradable fungicides.

This paper deals with preparation of L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides and bioassays for their antimicrobial activities.

MATERIALS AND METHODS

1. *Instrumental Analyses*

Infrared spectra were measured with a Hitachi Model 285 infrared spectrometer. Mass spectral data were obtained by using Hitachi Model RMS-4 mass spectrometer and also by the method of GC-MS combination (Hitachi Model K-53 GLC-RMS-4). Partly, JEOL JMS-D300 mass spectrometer was also employed. To analyze volatile components, Yanagimoto GCG-550FP(FID) was used. The measurements of specific rotations were carried out on a Hitachi Model 047-2 polarimeter. ^{1}H NMR spectral data were obtained from a Hitachi R-22 apparatus (90 MHz). The growth of microorganisms was estimated by measuring optical densities at 610 nm with a Hitachi Model 101 spectrophotometer.

2. *Preparations of L-5-Alkylthiomethylhydantoin S-Oxides and Related Compounds*

S-Alkyl- and alkenyl-L-cysteines were prepared from L-cystine and alkyl or alkenyl halides by the methods of du Vigneaud *et al.*,[3] and Armstrong and Lewis.[4] *S*-Alkyl- and alkenyl-L-cysteines were converted into their hydantoin derivatives by application of the method of Dakin.[5] The hydantoin derivatives

* Hydantoin Derivatives of *S*-Alkyl- and Alkenyl-L-cysteine-*S*-oxides (Part I).

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were then oxidized to sulfoxides by the treatment of 30% H_2O_2 in aqueous ethanol or acetone.

S-Propyl-L-cysteine-*S*-oxide was prepared from *S*-propyl-L-cysteine by oxidation with 30% H_2O_2 in glacial acetic acid. *N*-Carbamoyl-*S*-propyl-L-cysteine-*S*-oxide was also prepared from *N*-carbamoyl-*S*-propyl-L-cysteine, the intermediate in the hydantoin synthesis, by the treatment of 30% H_2O_2 in aqueous acetone. The preparation of L-5-propylthiomethylhydantoin *S,S*-dioxide was achieved by oxidizing the L-5-propylthiomethylhydantoin with a large excess (5 eq) of 30% H_2O_2 in aqueous acetone. Further, L-5-propylthiomethylhydantoin (±)-*S*-oxide was split into the (+)- and (−)-*S*-oxides by fractional crystallization.

3. Bioassay

Antimicrobial activities of L-5-alkylthiomethylhydantoin *S*-oxides and related compounds were assayed by measuring the inhibitory effects on the growth of microorganisms. The microorganisms used are as follows: *Escherichia coli* AHU 1041, *Bacillus subtilis* AHU 1036, *Staphylococcus aureus* AHU 1142, *Sarcina flava* AHU 1481, *Saccharomyces cerevisiae* var. *sake* AHU 3142 and *Sporobolomyces roseus* AHU 3980.

Semi-synthetic medium for *E. coli* contained glucose 2.00 g, L-asparagine monohydrate 2.00 g, meat extract (Riken Vitamin Oil Co., Ltd.) 0.50 g, $(NH_4)_2SO_4$ 4.72 g, NaCl 5.00 g, KH_2PO_4 5.44 g, and trace amounts of $MgCl_2$, $FeCl_2$ and $CaCl_2$ (1 ml of the mixture, 0.5% each) in 1 liter of deionized water (adjusted to pH 6.8). Nutrient broth for the bacteria consisted of 1% meat extract, 1% peptone (Daigo Eiyo Kagaku Co., Ltd.) and 0.5% NaCl, and pH of the medium was adjusted to 6.6–6.8. Yeasts were grown on 10% malt extract (Difco Laboratories) adjusted to pH 5.8–6.0.

Each test sample was added aseptically to the autoclaved medium before inoculation.

RESULTS

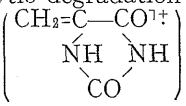
1. Compounds Prepared

Melting points, specific rotations and elemental analysis data of ten L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides synthesized are shown in Table 1. Intermediate products were confirmed by *tlc*, IR and MS. IR spectra of the hydantoins showed characteristic bands near 3,200 and 3,100 cm^{-1} due to N-H stretching with hydrogen bonding, and near 1,780 and 1,740 cm^{-1} due to C=O stretching. IR spectra of the sulfoxide derivatives showed strong absorption bands at 980–1,040 cm^{-1} due to S=O stretching.

In MS spectra of L-5-alkyl- and alkenylthiomethylhydantoins, molecular ion peaks (M^+) were observed and their base peaks were mostly M^+–99($C_3H_3N_2O_2$) showing easy cleavage at the C-C bond between the hydantoin ring and alkyl or alkenylthiomethyl side chains.

Table 1 Melting points, specific rotation and elementary analyses of L-5-alkyl-and alkenylthiomethylhydantoin *S*-oxides prepared.

Compound alkyl or alkenyl group	Mp °C (dec.)	$[\alpha]_D$ (°C) c=1.0, H_2O	Found (%)			Calcd. (%)		
			C	H	N	C	H	N
Methyl	120–122	−46° (21)	32.28	4.63		34.08	4.58	
Ethyl	123–125	−51° (22)	35.58	5.32		37.88	5.30	
Propyl (−)	146–147	−122° (15)	40.90	5.91	13.75	41.16	5.92	13.72
Propyl (+)	142–143	+38° (12)	40.96	5.92	13.90	41.16	5.92	13.72
Propyl (±)	129–130	−45° (12)						
Isopropyl	128–129	−61° (10)	41.16	5.90	13.77	41.16	5.92	13.72
Allyl	73– 75	−42° (10)	41.44	5.00	13.98	41.57	4.98	13.86
Butyl	109–111	−56° (21)	42.86	6.47		44.02	6.47	
Isobutyl	104–106	−58° (10)	44.57	6.52	13.05	44.02	6.47	12.84
sec-Butyl	84– 86	−53° (10)	43.85	6.49	12.95	44.02	6.47	12.84
Pentyl	99–101	−44° (21)	46.31	6.98	12.05	46.53	6.94	12.06
Hexyl	111–113	−45° (19)	48.65	7.47	11.35	48.76	7.37	11.38

On the other hand, MS spectra of the sulfoxide derivatives scarcely showed M^+, and it seems that in a sample heater pyrolytic degradation of the sulfoxides gave *m/e* 112  and M^+–112.

As a few examples, syntheses of L–5–propylthiomethylhydantoin *S*–oxide and related compounds are shown below.

1.1 S–Propyl–L–cysteine

S–Propyl–L–cysteine was prepared in about 85% yield from L–cystine by reduction with metallic sodium in liquid ammonia, followed by the treatment with 1–bromopropane; mp 232–4°C(dec.). *Anal.* Found: C, 44.22; H, 7.95. Calcd. for $C_6H_{13}NO_2S$: C, 44.15; H, 8.03%. IR ν_{max}^{KBr} cm^{-1}: 1622(δ_{as} NH_3^+), 1590 (ν_s COO^-), 1480 (δ_s NH_3^+), 1412 (δ_s S–CH_2 and ν_s COO^-). MS *m/e*(%): 165(M^+ +2, 0.9), 164(M^+ +1, 2.7), 163(M^+, 8.8), 118(M^+ –CO_2H 14.2), 90($C_3H_7S^+CH_3$ 32.6), 89(M^+ –CH(NH_2)–CO_2H, 80.6), 74(31.0) 61(36.0), 47(34.2), 43 ($C_3H_7^+$, 100).[6]

1.2 S–Propyl–L–cysteine–(+)–S–oxide

The *S*–oxide yielded almost quantitatively from S–propyl–L–cysteine, mp 139–140°C(dec.). *Anal.* Found: C, 39.94; H, 7.40; N, 7.68. Calcd. for $C_6H_{13}NO_3S$: C, 40.20; H, 7.31; N, 7.82%. IR ν_{max}^{KBr} cm^{-1}: 1640–1610(δ_{as} NH_3^+), 1580(ν_{as} COO^-), 1020(νSO). MS *m/e*(%): 179(M^+, 0), 92($C_3H_7SOH^{+\cdot}$, 14.8), 75(18.0), 63(CH_2SOH^+, 20.6), 45(17.6), 44($CO_2^{+\cdot}$, 69.8), 43($C_3H_7^+$, 100), 42(18.5), 41($C_3H_5^+$, 65.3), 39 ($C_3H_3^+$, 25.2). The mass spectrum is accompanied with thermal decomposition of the sulfoxide.[6]

1.3 N–Carbamoyl–S–propyl–L–cysteine

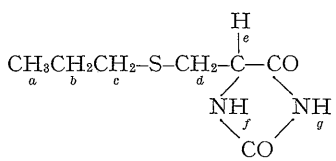
N–Carbamoyl–*S*–propyl–L–cysteine was obtained as an intermediate in hydantoin synthesis from *S*–propyl–L–cysteine by the treatment with 1.5–2.0 mol eq of potassium cyanate and by the adjustment of pH to 3.0 with 10% HCl, mp 153–4°C(dec.). *Anal.* Found: C, 40.88; H, 6.80; N, 13.77. Calcd. for $C_7H_{14}N_2O_3S$: C, 40.76; H, 6.84; N, 13.58%. IR ν_{max}^{KBr} cm^{-1}: 3450 & 3300(νNH's), 2450(broad), 1900(broad), 1690(νCO of –$CONH_2$) 1630(δNH), 1560(δ_{as} COO^-), 1290(νC–N). MS *m/e*(%): 206(M^+, 0), 188(M^+–H_2O, 11). 89($C_3H_7S^+$=CH_2, 100), 61 ($C_2H_4S^+H$, 29), 47(CH_2=S^+H, 31), 44(CONH_2^+, 30), 43($C_3H_7^+$, 80), 28(23), 27(24).

1.4 N–Carbamoyl–S–propyl–L–cysteine–S–oxide

The *S*–oxide was obtained in more than 80% yield from *N*–carbamoyl–*S*–propyl–L–cysteine; mp 129–130°C(dec.). *Anal.* Found: C, 37.62; H, 6.38; N, 12.77. Calcd. for $C_7H_{14}N_2O_4S$: C, 37.82; H, 6.35; N, 12.61%. IR ν_{max}^{KBr} cm^{-1}: 3400, 3300 & 3280(νNH's), 2450(broad), 1900 (broad), 1685(νCO of –$CONH_2$), 1635(δNH_2), 1560(δ_{as} COO^-), 1320 & 1280 (νC–N), 1015(ν–SO). MS (*m/e*(%): 222(M^+, 0), 166(C_3H_7–$SOSC_3H_7^{+\cdot}$, 3.0), 150 ($C_3H_7SSC_3H_7^+$, 1.9), 124(7.8), 108(2.2), 106(3.1), 92($C_3H_7SOH^{+\cdot}$, 3.6), 82 (3.6), 75(13.0), 63(CH_2SOH^+, 5.6), 59(6.6), 47(8.6), 45(CO_2H^+ & HCS^+, 12.5), 44($CONH^+$ & $CO_2^{+\cdot}$, 27.6), 43($C_3H_7^+$, 100), 41($C_3H_5^+$, 44.1), 39($C_3H_3^+$, 12.8), 27(22.0). The mass spectrum is also accompanied with thermal decomposition.[6]

1.5 L–5–Propylthiomethylhydantoin

N–carbamoyl–*S*–propyl–L–cysteine was converted into hydantoin derivative in 10% HCl on a boiling water bath in a 78% yield from *S*–propyl–L–cysteine; mp 114–6°C, $[\alpha]_D^{12}$ −112° (*c*=1.0, H_2O). *Anal.* Found: C, 44.41; H, 6.40; N, 14.89; S, 16.93. Calcd. for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88; S, 17.03%. IR ν_{max}^{KBr} cm^{-1}: 3200 & 3050 (νNH's), 1780 & 1740 (νCO's). MS *m/e*(%): 188(M^+, 9.0), 112(8.5), 89(M^+–99, 100), 76($C_3H_5S^+H$, 17.0), 61(C_2H_4–S^+H, 27.8), 47(CH_2=S^+H, 35.9), 43($C_3H_7^+$, 62.6), 41($C_3H_7^+$, 48.4), 27(13.5). NMR$\delta_{DSS}^{(CD_3)_2SO}$: 0.92 (*a*, t, *J*=7 Hz), 1.53(*b*, *sex.*, *J*=7 Hz), 2.53(*c*, t, *J*=7 Hz), 2.82(*d*, d, *J*=4.5 Hz), 4.29(*e*, t, *J*=4.5 Hz), 7.82 (*f*, bs), 10.75 (*g*, bs).



NMR spectral signals were assigned by comparing with the data of L–5–methylthioethylhydantoin reported by Suzuki *et al.*[7]

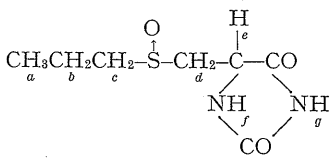
1.6 L–5–Propylthiomethylhydantoin S–oxide (L–(±)–PHSO)

L–(±)–PHSO was yielded almost quantitatively from L–5–propylthiomethylhydantoin, and melting point, specific rotation and elementary analysis data are shown in Table 1. MS *m/e*(%): 204(M^+, 0), 124(12.7), 112(35.3),

92(M^+–112, 12.3), 75(19.6), 63(CH_2SOH^+, 16.6), 47(10.5), 45(HCS^+, 10.6), 43($C_3H_7^+$, 100), 41($C_3H_5^+$, 88.1), 39($C_3H_3^+$, 16.6), 27(20.5).

1.7 Resolution of L–(±)–*PHSO*

Recrystallization from aqueous ethanol gave first L–(−)–PHSO as colorless needles; $[\alpha]_D^{15}$ −122° (c=1.0, H_2O), IR ν_{max}^{KBr} cm^{-1}: around 3200(νNH's), 1765 & 1730 (νCO's), 1030–980 (νSO). L–(+)–PHSO was also obtained from mother liquor by the addition of ethanol as colorless plates; $[\alpha]_D^{12}$ +38° (c=1, H_2O). IR ν_{max}^{KBr} cm^{-1}: 3325 & 3120(νNH's), 1780 & 1720 (νCO's), around 985(νSO). NMR $\delta_{DSS}^{(CD_3)_2SO}$: 1.10 (*a*, t, J=7 Hz), 1.70(*b*, *sex.*, J=7 Hz), 2.78(*c*, t, J=7 Hz), 3.10(*d*, m), 4.48(*e*, bt), 7.87 (*f*, bs), 10.84(*g*, bs).



1.8 L*–5–Propylthiomethylhydantoin S,S–dioxide*

Mp 149–151°C(dec.), $[\alpha]_D^{15}$ −76° (c=1.0, H_2O). *Anal.* Found: C, 38.21; H, 5.44; N, 12.72. Calcd. for $C_7H_{12}N_2O_4S$:C, 38.17; H, 5.49; N, 12.72%. IR ν_{max}^{KBr} cm^{-1}: 3380, 3180 & 3070 (νNH's), 1765 & 1750 (νCO's), 1335, 1305 & 1275(ν_{as} SO_2), 1190 & 1135(ν_s SO_2). MS *m/e* (%): 220(M^+, 0), 112(M^+–$C_3H_7SO_2H$, 46.6), 108(M^+–$C_4H_4N_2O_2$, 4.0), 92(5.9), 76(10.7), 69 (6.6), 63(9.4), 47(6.2), 45(5.6), 44(5.4), 43($C_3H_7^+$, 65.0), 42(15.3), 41($C_3H_5^+$, 100), 40(14.7), 39 ($C_3H_3^+$, 17.0), 28(16.0), 27(30.5).

2. Antimicrobial Activities of L*–5–Alkylthiomethylhydantoin S–Oxides and Related Compounds*

Effects of L–5–alkyl– and alkenylthiomethylhydantoin *S*–oxides on the growth of *E. coli* were examined. The bacteria were cultured in test-tubes (18×180 mm) containing 6 ml of semi-synthetic medium with shaking. The results are shown in Tables 2 and 3. These hydantoin sulfoxides exhibited potent antibacterial activity. Furthermore, effects of L–(±)–PHSO, L–(+)–PHSO and L–(−)–PHSO on the growth of *E. coli* were tested by changing pH of the medium. As shown in Table 4, although there was no difference in activity between the two stereoisomers, it has appeared that much stronger activity was demonstrated in the medium adjusted to pH 6.0 and decreased with rising pH.

Table 2 Effects of L–5–alkylthiomethylhydantoin *S*–oxides on the growth of *Escherichia coli* AHU 1041.

Alkyl	OD_{610nm}*		
	0.00765	0.0153	0.0306 (mM)
Methyl		0.328	0.043
Ethyl		0.259	0.015
Propyl	0.683	0.091	0.002
Isopropyl	0.859	0.032	0.002
Butyl		0.322	0.076
Isobutyl		0.417	0.615
Pentyl		0.381	0.181
Hexyl		0.361	0.190
Control		0.844	

* Cultured at 37°C for 17 hr with shaking (110 rpm) and each OD value was the mean of three samples.

Table 3 Effects of L–5–alkyl–and alkenylthiomethylhydantoin *S*-oxides on the growth of *Escherichia coli* 1041.

Alkyl or alkenyl	OD_{610nm}*		
	0.00765	0.0153	0.0306 (mM)
Propyl	0.313	0.008	0.002
Isopropyl	0.495	0.001	0.001
Butyl	0.786	0.431	0.036
Isobutyl	0.763	0.477	0.088
sec–Butyl	0.779	0.013	0.001
Allyl	0.714	0.202	0.007
Control		0.987	

* Cultured at 37°C for 18 hr with shaking (110 rpm) and each OD value was the mean of three samples.

Effects of L–(+)–PHSO on the growth of other bacteria and yeasts were also examined (Tables 5 and 6). L–(+)–PHSO had much greater activity against *S. flava* and *B. subtilis* than against *E. coli* and *S. aureus* under given conditions. Antimicrobial activities of L–(+)–PHSO against *S. roseus* and *S. cerevisiae* var. *sake* were much less than against bacteria.

Among the related compounds which were prepared, L–5–propylthiomethylhydantoin *S,S*–

Table 4 Effects of L-5-propylthiomethylhydantoin *S*-oxides (PHSO) on the growth of *Escherichia coli* AHU 1041 by changing pH of the medium.

Compound	pH	OD_{610nm}*	
		0.00765	0.0153 (mM)
L-(±)-PHSO**	6	0.263	0.001
	7	0.774	0.664
	8	0.925	0.589
L-(+)-PHSO***	6	0.244	0.001
	7	0.751	0.456
	8	0.691	0.602
L-(−)-PHSO****	6	0.168	0.001
	7	0.650	0.426
	8	0.760	0.492
Control	6	0.907	
	7	1.071	
	8	1.067	

* Cultured at 37°C for 16 hr with shaking (110 rpm) and each OD value was the mean of three samples.
** $[\alpha]_D^{12}-45°$ ($c=1$, H_2O).
*** $[\alpha]_D^{12}+38°$ ($c=1$, H_2O).
**** $[\alpha]_D^{12}-122°$ ($c=1$, H_2O).

dioxide only had a weak inhibitory effect against *E. coli* at the given concentration as shown in Table 7.

DISCUSSION

Ten L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides (alkyl or alkenyl: methyl, ethyl, propyl, isopropyl, allyl, butyl, isobutyl, *sec*-butyl, pentyl and hexyl) were prepared from L-cystine as shown in Scheme 1. L-(±)-PHSO was further split into L-(+)- and L-(−)-PHSO by fractional crystallization in aqueous ethanol.

L-5-Alkyl- and alkenylthiomethylhydantoin *S*-oxides exhibited antimicrobial activities, and L-(±)-PHSO and L-5-isopropylthiomethylhydantoin *S*-oxide were most active against *E. coli*. In the previous paper[1] the authors reported that L-(+)-PHSO showed much stronger inhibitory action than L-(−)-PHSO. However, it has subsequently been confirmed that there is no significant difference in antibacterial activity between the two stereoisomers as shown in Table 4.

It has not been found that antibacterial activity of a hydantoin sulfoxide against the

Table 5 Effects of L-5-propylthiomethylhydantoin(+)-*S* oxide [L-(+)-PHSO]* on the growth of bacteria in the nutrient broth.

Bacillus subtilis AHU 1036		*Escherichia coli* AHU 1041	
Concentration (μg/ml)	OD_{610nm}**	Concentration (μg/ml)	OD_{610nm}**
2.5	1.482	3.5	1.494
3.5	1.174	5.0	1.266
5.0	0.069	7.0	0.438
7.0	0.015	10.0	0.012
Control	1.623	Control	1.617
Sarcina flava AHU1481		*Staphylococcus aureus* AHU 1142	
Concentration (μg/ml)	OD_{610mn}***	Concentration (μg/ml)	OD_{610nm}****
1.75	1.053	5.0	1.605
2.5	0.931	10.0	0.848
3.5	0.815	14.0	0.124
5.0	0.234	20.0	0.011
7.0	0.000	Control	2.172
Control	1.167		

* $[\alpha]_D^{12}+18°$ ($c=1$, H_2O).
** Cultured at 37°C for 15 hr; inoculation *ca.* 4×10^7 cells/6 ml medium.
*** Cultured at 37°C for $16\frac{1}{2}$ hr; inoculation *ca.* 4×10^7 cells/6 ml medium.
**** Cultured at 37°C for 15 hr; inoculation *ca.* 4×10^7 cells/6 ml medium. Each OD value was the mean of three samples.

Table 6 Effects of L-5-propylthiomethylhydantoin-(+)-*S*-oxide [L-(+)-PHSO]* on the growth of yeasts in the malt extract.

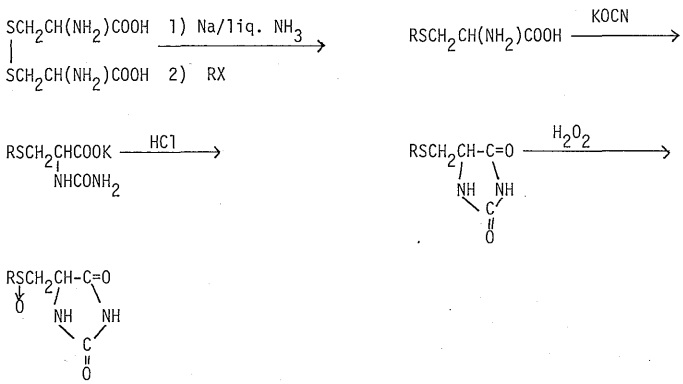
Sporobolomyces roseus AHU 3980		*Saccharomyces cerevisiae* var. *sake* AHU 3142	
Concentration (μg/ml)	OD_{610nm}**	Concentration (μg/ml)	OD_{610nm}***
6.25	2.228	12.5	5.336
12.5	1.772	18.75	3.384
25.0	0.160	25.0	0.128
37.5	0.024	37.5	0.000
Control	2.304	Control	6.048

* $[\alpha]_D^{32}+18°$ ($c=1$, H_2O). ** Cultured in 10% malt extract at 25°C for 43 hr.
*** Cultured in 10% malt extract at 25°C for 37½ hr. Each OD value was the mean of three samples.

Table 7 Effects of L-5-propylthiomethylhydantoin (±)-*S*-oxide (L-(±)-PHSO) and related compounds on the growth of *Escherichia coli* AHU 1041.

Compound	Conc. (μg/ml)	OD_{610nm}*
Control	—	0.754
L-Cysteine	100	0.484
S-Propyl-L-cysteine	100	0.674
S-Propyl-L-cysteine-*S*-oxide	100	0.676
N-Carbamoyl-*S*-propyl-L-cysteine	25	0.704
N-Carbamoyl-*S*-propyl-L-cysteine-*S*-oxide	25	0.692
L-5-Propylthiomethylhydantoin	100	0.792
L-(±)-PHSO	6.25	0.009
L-5-Propylthiomethylhydantoin *S*, *S*-dioxide	12.5	0.404

* Cultured in the semi-synthetic medium at 37°C for 16 hr with shaking and each OD value was the mean of three samples.



Scheme 1 Synthetic route of L-5-alkyl- and alkenylthiomethylhydantoin *S*-oxides.
R: CH_3, C_2H_5, $CH_3(CH_2)_2$, $(CH_3)_2CH$, $CH_2=CHCH_2$, $CH_3(CH_2)_3$, $(CH_3)_2CHCH_2$, $CH_3CH_2(CH_3)CH$, $CH_3(CH_2)_4$, $CH_3(CH_2)_5$.

Gram negative *E. coli* differs from those against the Gram positive bacteria (Table 5). As shown in Table 6, yeasts were much less sensitive than bacteria. It might be dependent on bioassay conditions.

As described in the previous paper,[1] the minimum inhibitory concentrations (MIC) of L-(+)-PHSO compared with chloramphenicol in nutrient broth are as follows: *S. aureus*, 3.0 μg/ml (chloramphenicol), 15.0 μg/ml (L-(+)-PHSO); *E. coli* 1.0 μg/ml (chloramphenicol), 15.0 μg/ml (L-(+)-PHSO).

Effects of L-(±)-PSHO and related compounds on the growth of *E. coli* were examined as shown in Table 7. L-(±)-PHSO has potent inhibitory action, while the deoxy compound, L-5-propylthiomethylhydantoin does not have any activity. The *S,S*-dioxide has only a weak activity. Both *N*-carbamoyl-L-cysteine and its sulfoxide have no inhibitory action. From these experimental results it has been suggested that the structure required for antibacterial activity involves both hydantoin ring and sulfoxide function. We were naturally interested in studying structure-activity relationship further. The structure-activity relationship study will be presented in a subsequent paper.

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要　　約

抗菌性 L-5-Alkylthiomethylhydantoin *S*-oxides および関連化合物の合成

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10 種類の L-5-alkyl- および alkenylthiomethylhydatoin *S*-oxides (alkyl または alkenyl: methyl, ethyl, propyl, isopropyl, allyl, butyl, isobutyl, *sec*-butyl, pentyl および hexyl), ならび関連化合物を調製した．L-5-Propylthimethylhydatoin (±)-*S*-oxide (L-(±)-PHSO) を中心に強い抗菌活性が見いだされた．L-(±)-PHSO はさらに L-(+)-PHSO と L-(−)-PHSO に分割されたが，活性に差異は認められなかった．細菌類は L-(+)-PHSO に対する感受性が高く，酵母類はより低い感受性を示した．

(±)-PHSO および関連化合物の *Escherichia coil* AHU 1041 に対する抗菌力を調べたところ，デオキシ化合物は活性がなく，スルホンは弱い活性を示した．また，*N*-carbamoyl-L-cysteine やそのスルホキシドは抗菌活性を示さなかった．これらの結果から，抗菌活性をもつためにはヒダントイン環とスルホキシド基の存在の必要性が示唆された．