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Studies on the Synthesis of 3-oxo-1, 2-benzisothiazole-1, 1-dioxide Derivatives and their Antifungal Activity against *Pyricularia oryzae*

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3-Oxo-1, 2-benzisothiazole-1, 1-dioxide 유도체들의 합성및 *Pyricularia oryzae*에 대한 항균성에 관한 연구

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抄 錄

도열병균에 의한 벼의 목 및 잎도열병에 효과가 좋은 새로운 살균제의 개발을 시도하였다. 농약으로 예상되는 몇몇 3-oxo-1, 2-benzisothiazole-1, 1-dioxide의 새로운 유도체들을 합성하고, 이들 유도체들의 도열병균 (*Pyricularia oryzae*)에 대한 항균성을 agar medium dilution 방법에 의해 측정하였다.

3-oxo-1, 2-benzisothiazole-1, 1-dioxide의 5원자 고리의 3개 구조 단위중에서 가장 항균성이 큰 단위는 $R-S-\overset{|}{C}=N-SO_2-$ 단위이며, 3개 구조 단위의 항균성 순서는 $RS-\overset{|}{C}=N-SO_2- \geq RO-\overset{|}{C}=N-SO_2- > -\overset{O}{\overset{\|}{C}}NR-SO_2-$였다.

30개 후보화합물 가운데서 14개의 유도체가 도열병균에 효능이 좋은 것으로 알려진 oryzemate 보다 우수한 항균성을 나타냈다.

Introduction

It is well known that some 2- or 3-substituted 3-oxo-1, 2-benzisothiazole-1, 1-dioxide (henceforward saccharin) derivatives have a high antifungal activities against some fungi, such as *Pyricularia oryzae*[1], *Alternaria so-*

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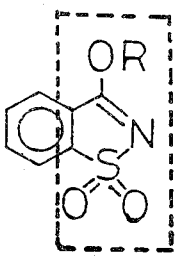
lani, Monilia fructicolar, Stemphylium sarcinaeforme[2] and others.[3][4]

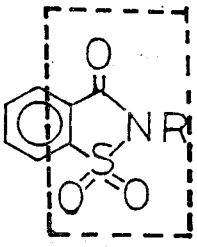
Furthermore, it was also reported that 2-alkyl (or aryl) derivatives[5] and N-methyl saccharin d, 1-trans-chrysanthemate[6] have the insecticidal activities.

Becaues that leaf and neck blast became a serious problem in Korea recently, we attempted to develop a new effective fungicide for this disease from 3-oxo-1, 2-benzisothiazole-1, 1-dioxide derivatives.

According to our preliminary studies[7][8] on the relationships between the structures of some saccharin derivatives and antifungal activities against *Pyricularia oryzae* and *Fusarium oxysporum* f. s.p. *cucummerinum*, we observed that the antifungal activity of their derivatives aganinst these fungi originated from the structural unit I and II on the five membered ring.



Structural unit I



Structural unit II

We have also known that the structural unit I was shown to be more active than the structural unit II for these fungi.

As part of a continuous program to develop more effective and selective fungicides against *Pyricularia oryzae*, we studied on the synthesis and the relationship between the structures and antifungal activities of 30 derivatives with different groups at 2- and 3-positions.

In this paper, we report the results of our studies on the synthesis of some saccharin derivatives and their antifungal activities against *Pyricularia oryzae*. We also discussed the relationship between the structures and antifungal activities.

Materials and Methods

1. Synthesis of the candidate compounds

Melting points were determined by capillary method and not corrected. Infrared and proton magnetic resonance spectra were determined on a Beckman model ACCLAB 9 spectrophotometer and Brucker 80MHz spectrometer, respectively. Tetramethylsilane (TMS) was used as the internal standard for proton NMR.

2-Thiocyanomethyl saccharin (36), pseudosaccharin chloride(2), N-hydroxymethyl saccharin(23), and N-chloromethyl saccharin (24) were synthesized by Yoon's procedures.[9]

3-Alkoxy and aryloxy derivatives (3~12) : Pseudosaccharin chloride(2) (0.01 mole), the corresponding alcohol (0.011 mole) and the base(0.01 mole), such as K_2CO_3, Na_2CO_3, NaOH or pyridine were dissolved in a suitable solvent, such as acetone (20~30m*l*), DMF(10~15m*l*), MeOH, EtOH and benzene. The reaction mixture was refluxed or stirred at room temperature, poured into cold water, filtered, washed with water and dried in air to give the corresponding products(3~12) as the power or crystal. The reaction conditions, melting points, yields and spectral data were shown in Table 1.

Thiosaccharin(14) : Method A) The mixture of saccharin(1) (0.01 mole, 1.83g), and P_2S_5 (0.011 mole, 2.44g) was heated up to 170°C, and then reacted at the same temperature for 30 min. The reaction mixture was cooled to room temperature. The product was extracted with benzene (20m*l*×3times). After the benzene layer was washed with water (50m*l*×2times), the organic layer was dried over $MgSO_4$ anhydrous, and then concentrated under reduced pressure to give the product(14) as yellow crystals in poor yield. mp 176~177°C (lit. mp 178~178.5°C).[10]

Method B) To the mixture of saccharin sodium salt(13) (0.05 mole, 11.2g), P_2S_5 (0.051 mole, 12.2g) and pyridine (50m*l*) were added

slowly with stirring in ice bath. The reaction mixture was stirred at room temperature for 30 min, and then poured into the mixture of cone-hydrochloric acid(20m*l*) and cold water(200m*l*) with stirring. The crystals were filtered and dried to give the product (14) as yellow needles in 94% yield. mp 177 ~178°C(lit. mp 178~178.5°C).[10]

3-Alkyl(or aryl) thiooxo saccharin (16~21) : Thiosaccharin sodium salt(15) (0.01 mole) was dissolved in DMF(10~15m*l*), and the corresponding halide was then added. The reaction mixture was refluxed with stirring or stirred at room temperature, poured into cold water, filtered, washed with water and dried to give the corresponding product(16~21). The reaction conditions, melting points, yields and spectral data were shown in Table 2.

3-Benzothiazoyl-1, 2-benzisothiazole-1, 1-dioxide (22) : The mixture of pseudosaccharin chloride (2) (0.01 mole), acetone(10m*l*), 2-mercaptobenzothiazole (0.01 mole) and pyridine (1m*l*) was stirred at room temperature for 20 min. The reaction mixture was poured into cold water, filtered, washed with water and dried in air to give the product(22) in 90% yield. Melting point and spectral data were shown in Table 2.

N-Methyl (25), N-alkyl ester (26), N-benzyl (27, 28, 29) and N-benzoyl derivatives (31, 32) : Saccharin sodium salt(13) (0.01 mole) was dissolved in DMF(10~15m*l*). The corresponding chloride (0.01 mole) was added to above DMF solution. After refluxing the reaction mixture for 10min-4 hrs, the mixture was poured into water with stirring. The precipitates were filtered, washed with water and dried in air to give the corresponding product. Melting points and spectral data were shown in Table 3.

N-Benzoyl saccharin(30) : N-Hydroxymethyl saccharin(23) (0.01 mole, 2.1g) was dissolved in acetone (10m*l*). After adding the benzoyl chloride (0.01 mole) to acetone solution, 1m*l* of pyridine was then added slowly. The reaction mixture was stirred at room temperature for 30min, and then poured into ice water stirring. The precipitates were filtered, washed with water and dried to give the compound (30) in 80% yield. Melting point spectral data were in Table 3.

N-Benzyloxymethyl saccharin(33) and N-methyl saccharin p-nitrobenzoate(35) : After N-hydroxymethyl saccharin(23) (0.01 mole, 2.1g) was dissolved in acetone (10~15m*l*) or DMF(10~15m*l*), the corresponding chloride (0.01 mole) and the base (0.011 mole), such as pyridine, K_2CO_3 or Na_2CO_3 were added to the above solution. The reaction mixture was refluxed for 20min-2hrs with stirring. The mixture was cooled to room temperature and then poured into water with stirring, filtered, washed with water and dried in air to give the corresponding ether compound(33 or 35). The experimental conditions, yields, melting points and spectral data were shown in Table 3.

N-(p-nitrophenyloxy) methyl saccharin(34) : The mixture of p-nitrophenol(8.66×10^{-3}moles) and KOH(0.5g) was dissolved in DMF(15m*l*). The reaction mixture was heated to 110°C in order to form potassium phenolate, and then cooled to room temperature N-chloromethyl saccharin(24) (8.66×10^{-3} moles) was added to the above mixture. The reaction mixture was stirred at room temperature for 30min, and then poured into water, filtered, washed and dried in air to give the product (34) in 62% yield. Melting point and spectral data were shown in Table 3.

2. Antifungal Activity

The stock solutions(2,000ppm) of each of the candidate compounds were made by dissolving in DMF. For the activity test, the stock solutions were diluted with water to the appropriate concentrations. The activity test was carried out at a range from 0.05ppm to 160 ppm. *Pyricularia oryzae* was isolated from the Agricultural Experimental Station, College of Agriculture, Gyeongsang National Univer-

sity, Chinju, Korea in 1984. This fungus was allowed to sporulate on Misatos's medium at 25~28°C for 5~7 days.

Antifungal activities of the candidate compounds against *Pyricularia oryzae* were determined by the agar medium dilution method. The cultivation was performed at 25~28°C for 15~20hrs.

I_{50} (the concentration for 50% inhibition of germination) values were estimated by the method of Finney[11] using PDP 1, 134 computer (DEC Co.).

Results and Discussion

1. Syntesis of the candidate compounds

An outline of the pathway for pathway for the synthesis of 30 derivatives used in this research is given in Scheme I~III.

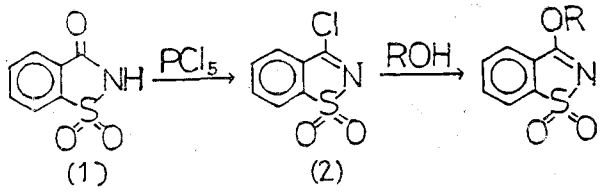
3-Alkoxy or 3-aryloxy derivatives(3~12) were synthesized according to Yoon's methods[9] from pseudosaccharin chloride(2) and the corresponding alcohols. The reaction conditions, melting points and spectral data were shown in Table 1. All analytical data, such as melting points in case of some compounds, proton NMR and IR spectra of synthetic compounds were agreed perfectly.

On the other hand, thiosaccharin (14) was prepared from saccharin sodium salt(13) and P_2S_5 in pyridine in 94% yield.

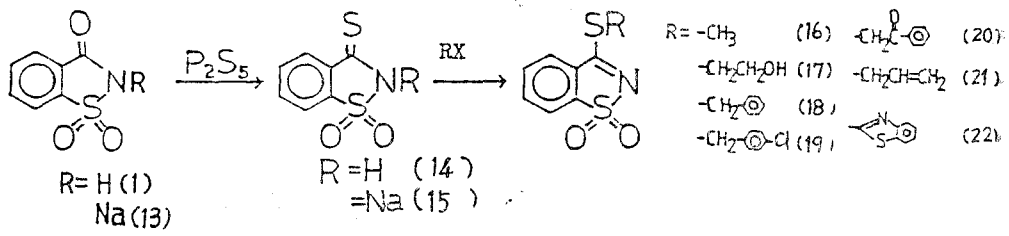
In order to synthesize 3-alkyl or 3-aryl thiooxo derivatives, we can use two possible procedures, that is, one is the method that pseudosaccharin chloride(2) is reacted with the corresponding mercaptans, and the other is that thiosaccharin sodium salt(15) is reacted with the corresponding halides.[12] Because of the economical efficiency, we chose the latter, but only compound(22) was synthesized from pseudosaccharin chloride(2) and 2-mercaptobenzothiazole. All analytical data of these compounds were agreed perfectly. The reaction conditions, melting points, proton NMR and IR spectra were shown in Table 2.

In addition, we attempted to synthesize N-alkyl or N-aryl derivatives according to scheme III. Reaction of saccharin sodium salt(13)

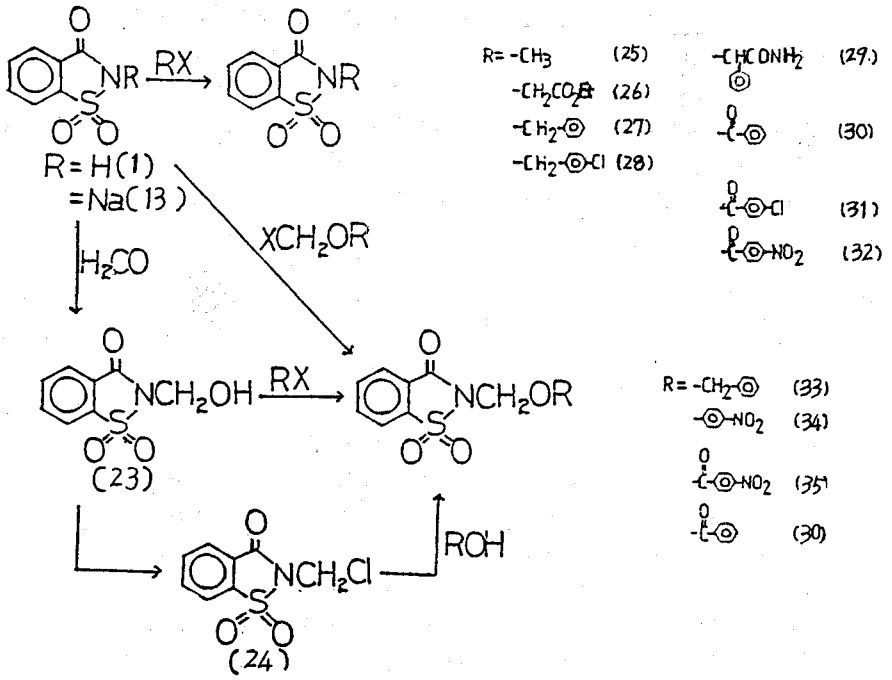
Scheme I



Scheme II



Scheme Ⅲ



with some corresponding halides afforded the corresponding alkyl or aryl derivatives. The experimental results were shown in Table 3. We exected to give the corresponding aryl esters when N-hydroxymethyl saccharin (23) was reacted with the corresponding acid halide, but we obtained only N-benzoyl saccharin(30) in excellent yield instead of the corresponding ester when N-hydroxymethyl saccharin(23) was reacted with benzoyl chloride in acetone. We also obtained N-benzoyl saccharin (30) in 75% yield when saccharin sodium salt was reacted with benzoyl chloride in DMF.

On the other hand, reaction of N-hydroxymethyl saccharin(23) with p-nitrobenzoyl chloride afforded the corresponding ester(35) in 15% yield (Scheme IV). Because of the academic interest, these reactions are under further investigation in our laboratory.

2. Relationship between the structures and antifungal activities(SAR)

The antifungal activities as I_{50}(ppm) of the candidate compounds were shown in Table 4.

Scheme Ⅳ

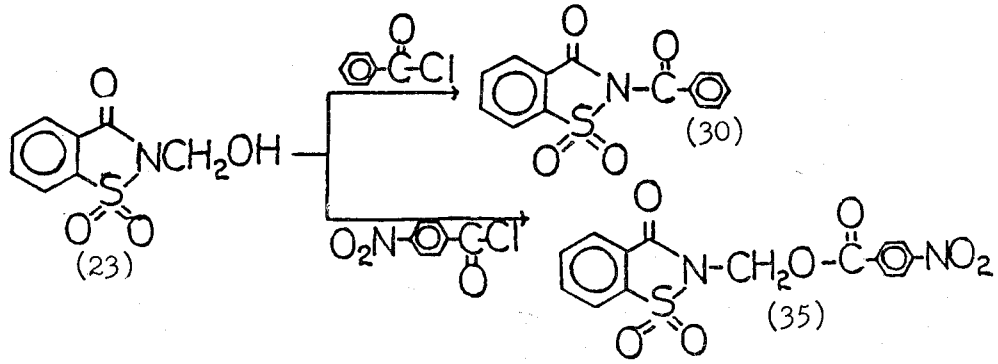
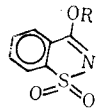
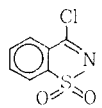
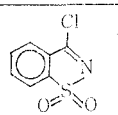
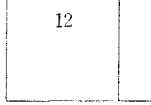
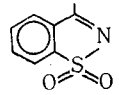


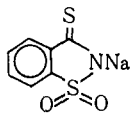
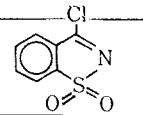
Table 1. Reaction conditions, mp, yield and spectral data of 3-alkyl(or aryl) oxy-1, 2-benzisothiazole-1, 1-dioxide derivatives(SOR series )

Compound No	Reaction condition: Reactant (Yield %)		Reaction condition: RX Temp. Time	Solvent base	mp ℃ (Lit. ℃)	NMR (δ) (Solvent)	IR (cm^{-1}) (Solvent)
3		$HOCH_3$ (80)	reflux 15min.	MeOH pyridine	185—187 (186) 13)		(KBr) 3100 (aroCH) 2295 (aliCH) 1330, 1170 (SO_2) 1180 (C-O-C)
4		$HOCH_2CH_3$ (75.8)	reflux 15min.	EtOH pyridine	216—219 (218) 14)		(nujzol) 3100 (aroCH) 1335 1170 (SO_2) 1188 (C-O-C)
5		$HOCH_2CH_2CH_3$ (79.5)	reflux 2h	Acetone Na_2CO_3	122—124 (125) 14)	(Acetone-d_6) 7.7 (aro, m) 4.5 (O-CH_2-, t) 1.9 (-CH_2-, t) 1.0 (-CH_3, t)	(nujzol) 3100 (aro CH) 1625 (aroC-C) 1340, 1180 (SO_2) 1190 (C-O-C)
6		$HOCH_2CH_2CH_2CH_3$ (83)	reflux 1h	Acetone pyridine	103—105 (96) 14)	($CDCl_3$) 7.8 (aro, m) 4.6 (O-CH_2-, t) 1-2 (-$CH_2CH_2CH_3$, m)	(nujzol) 1600 (aroC=C) 1340, 1140 (SO_2) 1160 (C-O-C)
7		$HOCH_2CH_2CH(CH_3)_2$ (75)	reflux 1h	DMF pyridine	62—63 (64) 14)	(Acetone-d_6) 7.8 (aro, m) 4.5 (O-CH_2-, t) 1.7 (-CH_2-CH<, m)	(nujzol) 3100 (aroCH) 1335, 1160 (SO_2) 1184 (C-O-C)
8		$HOCH_2CN$ (80)	reflux 15min.	Acetone pyridine	164—166	(Acetone-d_6) 7.8 (aro, m) 5.4 (O-CH_2-, s)	(nujzol) 3100 (aroCH) 1330, 1170 (SO_2) 1180 (C-O-C) 2243 (CN)
9		$HOCH_2CH_2Cl$ (100)	reflux 1h	Benzene	178—181	(Acetond-d_6) 7.7 (aro, m) 4.9 (O-CH_2-, t) 4.1 (-CH_2Cl, t)	(nujzol) 3100 (aroCH) 1339, 1180 (SO_2) 1186 (C-O-C)
10		NaO-⬡ (79.6)	R. T[a] 20min.	Acetone	177—179	(Acetone-d_6) 7.5-8.0 (aro, m)	(nujzol) 1618, 1600 (aroC=C) 1338, 1180 (SO_2) 1175 (C-O-C)
11		$HOCH_2$-⬡ (74)	R. T[a] 30min.	DMF pyridine	115-117	(Acetone-d_6) 7.5-8.0 (aro, m) 5.6 (-CH_2-, s)	(nujzol) 1626, 1615 (aroC=C) 1330, 1165 (SO_2) 1180 (C-O-C)
12		 (50)	100℃ 30min.	Acdtone NaOH	148—150	($CDCl_3$) 8.9-8.0 (aro, M)	(nujzol) 1635, 1600 (aroC=C) 1550, 1378 (NO_2) 1350, 1170 (SO_2)

a) Room temperature, b) KBr disc, c) Nujol mull.

Table 2. Reaction conditions, mp, yield and spectral data of 3-alkyl(or aryl) thicoxo-1, 2-benzoisothiazole-1, 1-dioxide derivatives (SSR series SR)



Compd No	Reaction condition: Reactant (Yield %)		RX Temp. Time	Solvent base	mp ℃ (Lit. ℃)	MM'R (δ) (Solvent)	IR (cm^{-1}) (Solvent)
16		$I\text{-}CH_3$ (90.5)	R. T[a] 4h	DMF	226—228 12) (227.5—228.5)		(KBr) 3077 (aroCH) 2920 (ali CH) 1330, 1170 (SO_2)
17		$ClCH_2CH_2OH$ (40)	reflux 4h	DMF	oil	($CDCl_3$) 7.9 (aro, m) 4.0 $S\text{-}CH_2\text{-}t$) 3.3 (-OH, s) 3.0 ($\text{-}CH_2\text{-}O$, m)	(neat) 3400 (OH) 1330, 1185 (SO_2) 755 (C-S-C)
18		$ClCH_2$-⬡ (100)	R. T[a] 3h	DMF	142—144 10) (141-142)	(Acetone-d_6) 7.9-7.7 (aro, m) 4.6 ($S\text{-}CH_2\text{-}$, s)	(KBr) 3100, 3065 (aroCH) 1170, 1330 (SO_2) 720 (C-S-C)
19		$ClCH_2$-⬡-Cl (86)	R. T[a] 20min.	DMF	118—120	($CDCl_3$) 8.0-7.3 (aro, m) 4.6 ($S\text{-}CH_2\text{-}$, s)	(nujzol) 3120, 3100 (aroCH) 1342-1185 (SO_2) 782 (C-S-C)
20		$ClCH_2$ -⬡ (88)	R. T[a] 20min.	DMF	194—195	(DMSO-d_6) 8.4-7.6 (aro, m) 5.4 ($S\text{-}CH_2\text{-}$, s)	(KBr) 1685 (C=O) 1600, 1585 (aroC=C) 757 (C-S-C)
21		$ClCH_2CH{=}CH_2$ (40)	R. T[a] 20min.	Acetone	113—114	($CDCl_3$) 7.9 (aro, m) 4.0 ($\text{-}CH_2CH{=}$, m) 300 (CH_2, m)	(KBr) 1630 (aroC=C) 1557 (vinyl) 1340, 1156 (SO_2) 756 (C-S-C)
22		HS-⬡ (90)	R. T[a] 3h	DMF pyridine	196—199	(DMSO-d_6) 8.3-7.8 (aro, m)	(nujzol) 1618, 1605 (aroC=C) 1345, 1175 (SO_2)
14	Saccharin sodium salt	P_2S_5	R. T[a] 1h	Pyridine	177—178 10) (178—178.5)	177—178	(KBr) 3340 (NH) 1580 (aroC=C) 1320, 1160 (SO_2)

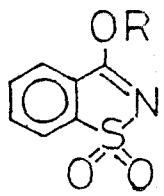
a) Room temperature, b) KBr disc, c) Neat, d) Nujol mull,

Table 3. Reaction conditions, mp, yield and spectral data of 3-oxo-2-alkyl(or aryl)-1, 2-benzoisothiazoline-1, 1-dioxide derivatives (SNR series)

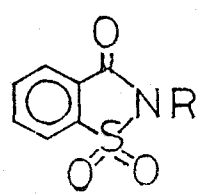
Compd No	Reaction condition			mp ℃ (Lit. ℃)	NMR (δ) (Solvent)	IR (cm^{-1}) (Solvent)
	Reactant (Yield %)	RX Temp. Time	Solvent base			
25	I-CH_3 (85)	reflux 1h	DMF	131–133 (134) 5)		(KBr) 3100 (aroCH) 1745 (C=O) 1330, 1180 (SO_2)
26	$ClCH_2$-C(=O)-OEt (83)	reflux 2h	DMF	103–104 15) (104–105)		(KBr) 1770, 1750 (C=O) 1330 1155 (SO_2)
27	$ClCH_2$-Ph (54.9)	reflux 10min.	DMF	164–167	(Acetone-d_6) 8.1-7.4 (aro, m) 4.9 ($-CH_2-$, s)	(nujol) 3080, 3060 (aroCH) 1725 (C=O) 1330, 1180) SO_2
28	$ClCH_2$-Ph-Cl (84.6)	reflux 20min.	DMF	148–151	(Acetone-d) 8.2-7.4 (aro, m) 4.9 ($-CH_2-$, s)	(nujol) 3100. 3080 (aroCH) 1735 (C=O) 1330, 1180 (SO_2)
29	Br-$CHCONH_2$-Ph (50.7)	reflux 4h	Acetone	149–153	(DMSO-d_6) 7.9-7.1 (aro, m) 5.9 ($-NH_2$, s) 5.6 ($-CH-$, s)	(nujol) 3250 ($-NH_2$) 1640 (C=O) 1340, 1160 (SO_2)
30	(80)	R. T° 30min.	Acetone pyridine	157–160 10) (165)	(Acetone-d_6) 8.3-7.4 (aro, m)	(nujol) 3100 (aroCH) 1690 (C=O) 1330, 1180 (SO_2)
31	(59.1)	100℃ 20min.	DMF	199–203 10) (205)	(Acetone-d_6) 8.1-7.6 (aro, m)	(nujol) 3100 (aroCH) 1690 (C=O) 1330, 1180 (SO_2)
32	(72.3)	100℃ 1h	DMF	189–191	(Acetone-d_6) 8.4-8.1 (aro, m)	(nujol) 3120, 3080 (aroCH) 1700 (C=O) 1330, 1180 (SO_2) 1470, 1550 (NO_2)
33	(60)	reflux 20min.	Acetone pyridine	111–113	(Acetone-d_6) 8.1-7.2 (aro, m) 4.9 ($N-CH_2-$, s) 3.5 ($O-CH_2-\phi$, s)	(nujol) 3100, 3080 (aroCH) 1745 (C=O) 1340, 1180 (SO_2) 1182 (C-O-C)
34	(62)	R. T° 30min.	DMF	250dec	(DMSO-d_6) 8.3-7.5 (aro, m) 5.9 ($-CH_2-$, s)	(nujol) 3100 (aroCH) 1740 (C=O) 1550, 1460 (NO_2)
35	(15)	reflux 2h	Acetone pyridine	160–162	(Acetone-d_6) 8.3-8.1 (aro, m) 6.2 ($-CH_2-$, s)	(nujol) 3100, 3080 (aroCH) 1750 (C=O) 1530, 1470 (NO_2)

a) Room temperature, b) KBr disc, c) Nujol mull.

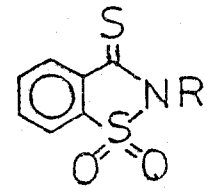
Each compound was classified into three structural units, such as SOR system containing $R-O-\overset{|}{C}=N-SO_2-$ unit, system containing $-C(=O)-NR-SO_2-$ unit and SSR system containing $R-S-\overset{|}{C}=N-SO_2-$ or $-C(=S)-NR-SO_2-$ unit on the five membered ring of saccharin moiety.

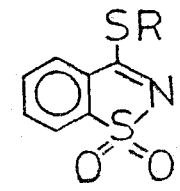


SOR system



SNR system



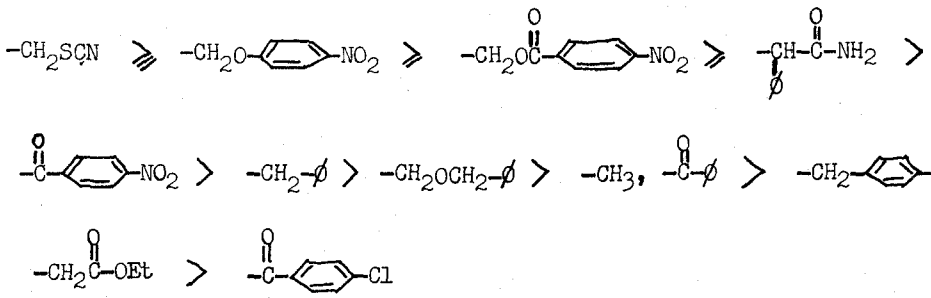


SSR system

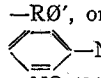
The order of the antifungal activity of the three systems was shown as the followings:

SSR≥SOR>SNR

Among the three structural units, the order of activity of SNR which has the lowest antifungal activity was as follows:



Among eleven derivatives of SNR system, the strongest antifungal activity was shown by N-CH_2SCN. It was reported that compound has a high antifungal activity against *Alternaria solani, Monilia fructicolar* and *Stemphylium sarcinaeforme* by Chien-pen Lo.[2] This compound also has a high antifungal activity against *Pyricularia oryzae* according to our research.

On the other hand, we attempted to change R-groups of the structural unit of SNR system in order to increase the antifungal activity. When R-groups of C=NR unit in this system were changed to alkyl, $-CH_2COOR$, $-CH_2-$aryl, $-CO-Ø-R'$, $-OR$ and $-CH_2OCO-RØ'$, only two groups, such as $-CH_2O-$  $-NO_2$(13.8ppm) and $-CH_2OCO-$$-NO_2$(24.0ppm) increased the antifungal activity against *Pyricularia oryzae.*

In SOR system, the strongest antifungal activity was shown by 3-phenyloxy derivative (10). The order of the antifungal activity of SOR system was as follows:

$-Ø \geqq -CH_2Ø > -CH_2CH_2CH-(Me)_2 \geq$ 2,4,6-trinitrophenyl$> -CH_2CN > -(CH_2)_3CH_3 > -CH_2CH_3 > -CH_3 > -CH_2CH_2Cl > -$(n-propyl)$> -CH_2COOEt$

In SOR system, compounds(3~6) containing small n-alkyl groups, such as methyl, ethyl, n-proryl and n-butyl did not show a high antifungal activity, whereas the compound(7) containing isoamyl group was shown to be more effective than these compounds containing small n-alkyl groups (about 20 times).

Among eight compounds of SSR system, the antifungal activity of thiosaccharin against *Pyricularia oryzae* was shown to be similar that of the derivatives which have a low act-

Table 4. I_{50} values of each compound against *Pyricularia oryzae**

Compound No	SOR series	
	R	I_{50}(ppm)
3	$-CH_3$	44.19
4	$-CH_2CH_3$	43.31
5	$-CH_2CH_2CH_3$	52.47
6	$-CH_2CH_2CH_2CH_3$	42.24
7	$-CH_2CH_2CH(CH_3)_2$	2.09
8	$-CH_2CN$	34.78
9	$-CH_2CH_2Cl$	45.22
10	$-C_6H_5$	0.21
11	$-CH_2C_6H_5$	1.56
12	$-C_6H_2(NO_2)_3$	2.41

Compound No	SSR series	
	R	I_{50}(ppm)
14	Thiosaccharin	44.44
16	$-CH_3$	2.53
17	$-CH_2CH_2OH$	0.83
18	$-CH_2C_6H_5$	0.16
19	$-CH_2C_6H_4Cl$	2.05
20	$-CH_2C(=O)C_6H_5$	2.70
21	$-CH_2CH=CH_2$	2.30
22		4.18

Compound No	SNR series	
	R	I_{50}(ppm)
36	$-CH_2SCN$	1.37
25	$-CH_3$	48.43
26	$-CH_2CO_2Et$	70.24
27	$-CH_2C_6H_5$	39.46
28	$-CH_2C_6H_4Cl$	57.29
29	$-CHCONH_2$ 	35.86
30	$-C(=O)C_6H_5$	48.43
31	$-C(=O)C_6H_4Cl$	79.10
32	$-C(=O)C_6H_4NO_2$	38.32
33	$-CH_2O-CH_2C_6H_5$	44.01
34	$-CH_2O-C_6H_4NO_2$	13.87
35	$-CH-O-C(=O)-C_6H_4NO_2$	24.08

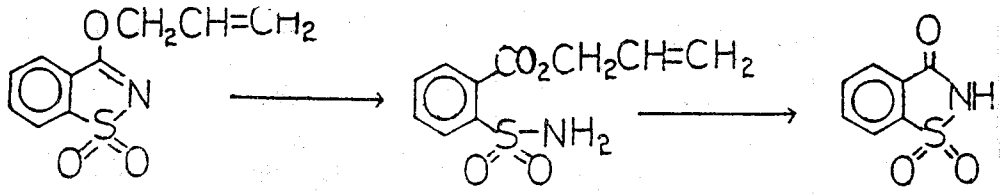
*In order to compare with other compounds, I_{50} value of Oryzemate was determined under the same conditions. I_{50} (ppm) = 39.66.

ivity in SNR and SOR systems, whereas the compounds containing $RS-\overset{|}{C}=N-SO_2-$ structural unit on the five membered ring were shown to be more effective than oryzemate (from about 250 to 10 times). The order of the antifungal activity of SSR system was as follows:

$-CH_2\emptyset$> $-CH_2CH_2OH$> p-chlorobenzyl> allyl> methyl> $-CH_2CO\emptyset$> 3-benzothiazolyl≧ thiosaccharin

In conclusion, the most active structural unit is $R-S-\overset{|}{C}=N-SO_2-$ on the five-member-

Scheme V



ed ring among the three structural units.

According to Uchiyama[1] and Hiroyasu,[16] saccharin which is a final stable degradation product of Oryzemate containing allyloxy group at 3-position is converted from allyl-o-sulfaminobenzoate formed by ring-opening hydrolysis of Oryzemate in plants (scheme V). Thus, we can think that the antifungal activity of these derivatives is related to the rate of their hydrolysis in plants or in testing systems. It was also reported by Meadow and his co-worker[10] that the hydrolysis for these three systems was as follows; SSR SOR SNR.

On the other hand, Hettler[13] has reported CHAPMAN-MUMM rearrangement of some S-OR derivatives at high temperature to the corresponding SNR derivatives, whereas the similar rearrangement of SSR derivatives to the corresponding N-substituted thiosaccharin is not easy. Therefore, SSR derivatives are more effective than SOR and SNR derivatives.

In summary, the antifungal activity of each structural system is intimately related to the rate of hydrolysis in plants or in testing systems and the rearrangement to other derivatives which have a low activity or are inactive.

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