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Synthesis and Antifungal Activity of 3-Oxo-1, 2-benzisothiazole-1, 1-dioxide Derivatives

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3-Oxo-1, 2-benzisothiazole-1, 1-dioxide유도체의 합성 및 항균성

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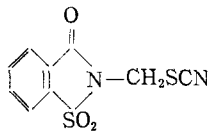
抄 錄

3-Oxo-1, 2-benzisothiazole-1, 1-dioxide의 몇몇 유도체를 합성하고 이들 유도체의 *Pyricuria oryzae*에 대한 항균성을 조사하였다. 이들 유도체의 I_{50}값은 각각 다음과 같다 ; 3-chloro (37.8ppm), 2-chloro (318.7ppm), MCS (20.1ppm), 3-(p-nitrophenyloxy) (35.4ppm), 3-(o-nitrophenyloxy) (11.8ppm), 3-(p-aminophenyloxy) (1643.2ppm), 2-allyl (946.2ppm), 2-(hydroxymethyl) (248.4), 2-chloromethyl 유도체(192.7ppm)

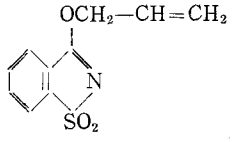
Introduction

It was reported that 2-thiocyanomethyl-1, 2-benzisothiazolin-3-one-1, 1-dixide(I) has a high antifungal activity against some fungi, such as *Alternaria solani, Monolinia fructicola* and *Stemphlium sarcinaeforme.*[1] Further, the fungicidal activities of 2-alkyl[2] and 2-(aryl) alkyl carbamoyl[3] derivatives have been reported.



I

Among the 3-substituted sulfonazole derivatives, 3-allyloxy-1, 2-benzisothiazole-1, 1-dioxide (Oryzamate, Ⅱ) has been reported to show a high antifungal activity especially against *Pyricularia oryzae.*[4]



Ⅱ

Recently, leaf and neck blast disease of rice plants by *Pyricularia oryzae* became a serious problem in Korea. In view of this situation, it seemed urgent to develop a new effective fung-

icide against this disease. Thus, some derivatives of 3-oxo-1, 2-benzisothiazole-1, 1-dioxide were synthesized, and their antifungal activity against *Pyricularia oryzae* has been tested by the agar medium dilution method.

Material and Methods

1. Synthesis of the candidate compounds

Melting points of the ccmpounds were not corrected. Infrared spectra and PMR spectra were determined on a Beckman Model ACCLAB 9 spectrophotcmeter and the Varian Associated A-60 protcn NMR spectrcmeter, respectively. Tetramethyl silane(TMS) was used as the internal standard for proton NMR. 3-Allyloxy derivative(Ⅱ), 3-chloro(Ⅲ) and multichlorinated(MCS, XII) derivatives were synthesized by an established method.[5]

1.1 3-Oxo-2-chloro-1, 2-benzisothiazole-1, 1-dioxide(Ⅳ) : The mixture of (Ⅴ)(0.5mole) or its sodium salt(0.5mole) and 20～30m*l* of $POCl_3$ was refluxed with stirring for 3 hours. The excess $POCl_3$ was than distilled under reduced pressure. The residue was pcured into 400m*l* of the cold water, filtered and dried in air. The structure was confirmed by IR and PMR spectra: 70% yield; mp 216～217C°(lit. mp215～216°C).[11,12] IR(nujol) 1680, 1585, 1304, 1150 cm^{-1}; H-NMR($CDCl_3$)δ8.0ppm(s, 4H).

1.2 3-Nitro and aminoaryl-1, 2-benzisothiazole-1.1-dioxide: 0.02 mole of(Ⅱ) was reacted with the corresponding aryl alcohol(0.03 mole) at the room temperature for 2～3 hours in acetone under the basic condition. The reaction mixture was poured into 400m*l* of the cold water with stirring. The product was filtered and dried in air. The followings are physical characteristics and yields of the isolated products.

3-(p-nitrophenyloxy)-1, 2-benzisothiazole-1, 1-dioxide(Ⅵ) : mp 190～192°C(lit. mp 192°C)[6]; 90% yield; IR(nujol) 1570, 1500, 1310, 1345, 1150, 1240, 1025cm^{-1}; H-NMR(acetone-d_6)δ 7.4～8.4 ppm(m, 8H).

3-(o-nitrophenyloxy)-1, 2-benzisothazole-1, 1-dioxide(Ⅶ) : mp 232～234°C(lit. mp 236°C)[6]; 93% yield; IR(nujol) 1570, 1495, 1300, 1335, 1130, 1240, 1065cm^{-1}; H-NMR(acetone-d_6)δ 7.2～8.4 ppm(m, 8H). 3-(p-aminophenyloxy)-1, 2-benzisothiazole-1, 1-dioxide(Ⅷ) : mp275～280°C; 85% yield; IR(nujol) 3360, 3260, 1580, 1340, 1130, 1235, 1030cm^{-1}; H-NMR($CDCl_3$+DMSO-d_6)δ 4.0(s, 2H), 7.2～8.2 ppm(m, 8H).

1.3 2-Allyl-1, 2-benzisothiazolin-3-one-1, 1-dioxide(IX) : The mixture of(Ⅴ) (0.05 mole), NaOH(0.075 mole), allyl chloride(0.065 mole) and 30m*l* of DMSO was reacted at 100°C for 3 hours. The reaction mixture was cooled to the room temperature, and then poured into 300m*l* of cold water with stirring. The product was extracted with three 100m*l* protions of ether and dried over anhydrcus $MgSO_4$. The solvent was removed using the rotary evaporator. The crude product was recrystallized with benzene: 80% yield; mp 80～82°C; IR(nujol) 1710, 1600, 1575. 1350, 1170, 980, 930cm^{-1}; H-NMR($CDCl_3$) δ 4.45(d, NCH_2-), 5.35(d, C=CH_2), 6.0(m,CH=C), 8.0ppm(s, 4H).

1.4 2-Hydroxymethyl-1, 2-benzisothiazolin-3-one-1, 1-dioxide(X) : A slight mcdification of the method reported by Horst[7] was used for the synthesis of the title compound. The mixture of (Ⅴ) (0.1 mole), 8m*l* of formalin(37%) and 60 m*l* of H_2O was refluxed for 1 hour. The reaction mixture was then cooled to the room temperature and filtered. The crude product was washed with water, and dried in air: 90% yield; mp 126～127°C(lit. mp 128°C)[7]; IR(nujol) 3250, 1600, 1560, 1300, 1150cm^{-1}; H-NMR(acetone-d_6)δ 5.3(s, 2H), 6.0(s, 1H), 7.9ppm(s, 4H).

1.5 2-Chloromethyl-1, 2-benzisothiazolin-3-one-1, 1-dioxide(XI)

The mixture of (X) (0.1mole), 8m*l* of $SOCl_2$, 50m*l* of $CHCl_3$ as the solvent and the catalytic amount of $FeCl_3$ as the catalyst was refluxed for 1-1.5 hours. The solvent was then removed from the reaction mixture using aspirator. The residue was cooled to the room temperature and poured into 400m*l* of the cold water with stir-

ring, filtered and dried in air: 97% yield; mp 140~144°C(lit. mp 145~146°C)[7]; IR(nujol) 1710, 1565, 1300, 1160, 730cm^{-1}; H-NMR(acetone-d_6)δ 5.7(s, 2H), 8.1ppm(s, 4H).

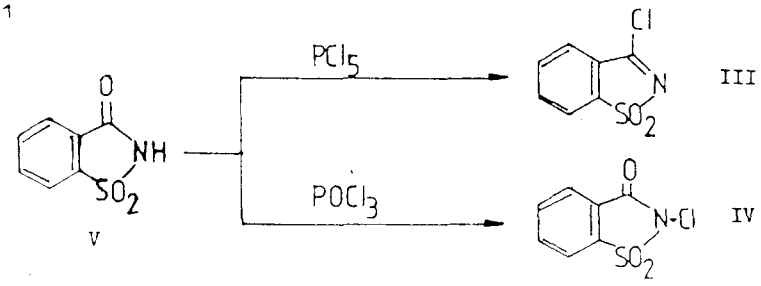
2. Antifungal activity

The stock solution(1,000 and 10,000ppm) of each of the candidate compounds synthesized were made by dissolving them in acetone. For the activity test, the stock solution were diluted to the appropriate concentrations. The activity test was carried out at the range from 6.25ppm to 4,000ppm.

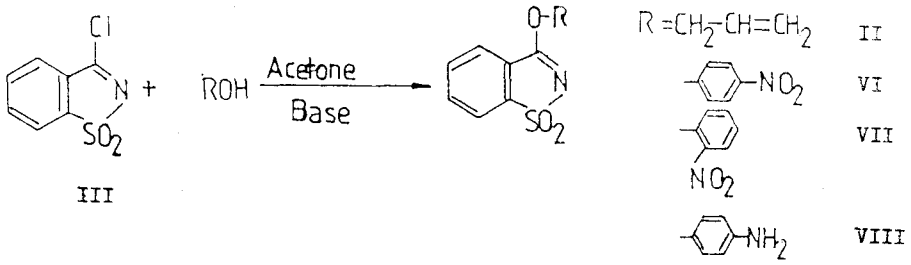
Pyricularia oryzae was isolated from the Agricultural Experimental Station, College of Agriculture, Gyeongsang National University, Jinru, Korea in 1983. This fungus was allowed to sporulate on Misato's medium[8] for 2 weeks at 28°C.

Antifungal activity of the candidate compounds against *Pyricularia oryzae* was determined by the agar medium dilution method. The cultivation was performed for 12 hours at 28°C. I_{50}(the concentration for 50% inhibition of ger-

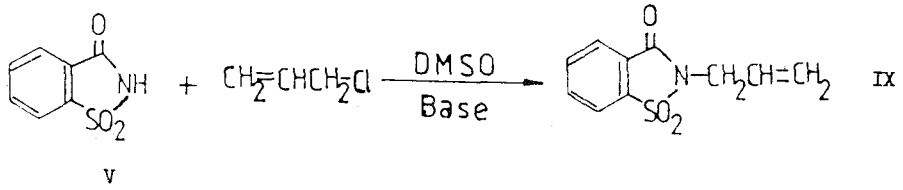
Scheme 1



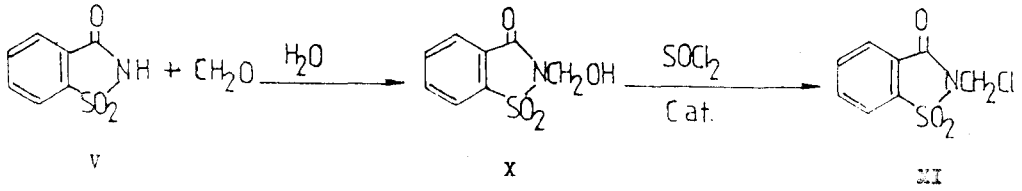
Scheme 2



Scheme 3



Scheme 4



mination) values were estimated by the method of Finney[9] and Fischer et al.[10] using PDP 1134 (DEC Co.) computer.

Results and Discussion

An outline of the synthetic pathways for the synthesis of nine derivatives used in this study is given in Scheme 1 to 4.

The antifungal activities of the candidate compounds were shown in Table 1.

Among ten derivatives, 3-(o-nitrophenyloxy), MCS, 3-(p-nitrophenyloxy) and 3-chloro analogues were highly effective against *Pyricularia oryzae*. The order of activity of the derivatives was as follows;

3-(o-nitrophenyloxy)>MCS>3-(p-nitrophenyloxy)≈3-chloro≫2-chloromethyl>3-allyloxy>2-hydroxymethyl>2-chloro>2-allyl>3-(p-aminophenyloxy)

The strongest antifungal activity was shown by 3-(o-nitrophenyloxy) derivative(Ⅶ). This candidate compound was found to be more active (20 times) than 3-allyloxy derivative(Ⅱ) which has been known to be the effective ingredient against *Pyricularia oryzae*. And 3-(o-nitrophenyloxy) derivative(Ⅶ) was more effective than 3-(p-nitrophenyloxy) derivative(Ⅵ) for the antifungal activity to this fungus. But the activity of 3-(p-aminophenyloxy) derivative (Ⅷ) against this fungus was lower than (Ⅵ) and (Ⅶ). Among three chloro-substituted derivatives, MCS was shown the strongest antifungal activity against *Pyricularia oryzae*.

In general, 3-substituted derivatives, such as 3-chloro(Ⅲ) and 3-allyloxy (Ⅱ) were more effective than 2-substituted derivatives such as 2-chloro(Ⅳ) and 2-allyl(Ⅸ) derivatives.

Abstract

Some derivatives of 3-oxo-1, 2-benzisothiazole -1, 1-dioxide were synthesized, and their antifungal activities against *Pyricularia oryzae* was determined by the agar medium dilution method. I_{50} values of the candidate derivatives were shown to be as follows; 3-chloro(37.8ppm), 2-chloro(318.7ppm), MCS(20.1ppm), 2-allyl(946.2ppm), 3-(p-nitrophenyloxy) (35.4ppm), 3-(o-nitrophenyloxy) (11.8ppm), 3-(p-aminophenyloxy) (1643.2ppm), 2-chloromethyl(192.7ppm) and 2-hydroxymethyl derivative(248.4ppm).

Table 1. The antifungal activities(I_{50} values) against *Pyricularia oryzae* of the candidate compounds

Compounds	Substituents	I_{50}(ppm)
Ⅱ	3-allyloxy	212.7
Ⅲ	3-chloro	37.8
Ⅳ	2-chloro	318.7
Ⅵ	3-(p-nitrophenyloxy)	35.4
Ⅶ	3-(o-nitrophenyloxy)	11.8
Ⅷ	3-(p-aminophenyloxy)	1643.2
Ⅸ	2-allyl	946.2
Ⅹ	2-hydroxymethyl	248.4
Ⅺ	2-chloromethyl	192.7
Ⅻ	multichlorinated(MCS)	20.1

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