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**Original Article**

# Quantitative Structure-Activity Relationships of Fungicidal *N*-(3,4-Diethoxyphenyl)carbamates*

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For 30 *N*-(3,4-diethoxyphenyl)carbamoyl esters with various alcoholic moiety substituents, their fungicidal activity against *Botrytis cinerea* resistant to benzimidazole fungicides was determined by the agar medium dilution method and the structure-activity relationships were analyzed by using the multiple regression technique. The hydrophobicity of the substituents was favorable to the activity. The activity was related parabolically to the maximum width of the substituents and the "$\beta$-branching" of the substituents was detrimental to the activity. The preventive activity of compounds against gray mold of cucumber caused by the resistant *B. cinerea* was determined by the foliar application in pot tests. The preventive activity was dependent on the magnitude of the fungicidal activity and the $\alpha$-branching of the substituents on analysis by the adaptive least-squares method.

## INTRODUCTION

*N*-Phenylcarbamates such as methyl *N*-(3,5-dichlorophenyl)carbamate (MDPC) and isopropyl *N*-(3,4-diethoxyphenyl)carbamate (diethofencarb) possess high fungicidal activity against various plant-pathogenic fungi resistant to benzimidazole fungicides. There is negatively correlated cross-resistance between these *N*-phenylcarbamates and benzimidazole fungicides.[1-3] In the preceding paper of this series,[4] we analyzed the structure-activity relationships of methyl *N*-phenylcarbamates with various benzene ring substituents in the fungicidal activity against the resistant strain of *Botrytis cinerea*. The 3,4-diethoxy substitution on the benzene ring of methyl *N*-phenylcarbamates was found to be one of the appropriate substitutions for high activity.[3,4]

In order to clarify the effect of the alcoholic moiety substituents of *N*-phenylcarbamoyl esters on the fungicidal activity, we have synthesized a number of *N*-(3,4-diethoxyphenyl)carbamoyl esters with various alcoholic moiety substituents and determined their fungicidal activity against the resistant *B. cinerea* by the agar medium dilution method. We have analyzed quantitatively the structure-activity relationships by the Hansch-Fujita method.[5] We have also determined their preventive activity against gray mold of cucumber, caused by the resistant *B. cinerea*, by the foliar application in pot tests, and examined the relationship with their agar medium fungicidal activity using the adaptive least-squares (ALS) method.[6] In this paper we discuss the physicochemical roles of the alcoholic moiety substituents of *N*-(3,4-diethoxyphenyl)carbamoyl esters in the fungicidal activity and the factors relating to the difference in bioassay system.

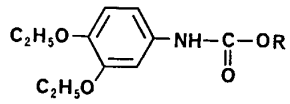
## MATERIALS AND METHODS

### 1. *Compounds*

All *N*-phenylcarbamates listed in Table 1

* Fungicidal Activity of *N*-Phenylcarbamates (Part 6). For Part 5, see Ref. 4).

Table 1 *N*-(3,4-Diethoxyphenyl) carbamates and their fungicidal and preventive activities against *Botrytis cinerea* resistant to benzimidazole fungicides.




| No. | R | Physical properties [mp °C or $n_D$ (°C)] | log $k'$[a] | log $P$ | $B_5$[b] | $I_\alpha$[c] | $I_\beta$[d] | $pI_{50}$[e] | | Activity ratings[f] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Obsd. | Calcd.[g] | Obsd. | Calcd.[h] |
| **1** | $CH_3$ | 120–121[i] | | 2.09[k] | 2.04 | 0 | 0 | 5.54 | 5.70 | 2 | 2 |
| **2** | $C_2H_5$ | 90–91[i] | | 2.50[k] | 3.17 | 0 | 0 | 6.36 | 6.61 | 3 | 2 |
| **3** | *n*-$C_3H_7$ | 79–80[i] | | 2.91[k] | 3.49 | 0 | 0 | 7.13 | 6.91 | 2 | 2 |
| **4** | *i*-$C_3H_7$ | 100–100.5[i] | | 2.82[k] | 3.17 | 1 | 0 | 6.82 | 6.75 | 3 | 3 |
| **5** | *n*-$C_4H_9$ | 78–80[i] | | 3.46[k] | 4.54 | 0 | 0 | 6.69 | 7.30 | 1 | 2 |
| **6** | *i*-$C_4H_9$ | 95.5–96[i] | | 3.36[k] | 4.45 | 0 | 1 | 5.34 | 5.82 | 1 | 1 |
| **7** | *s*-$C_4H_9$ | 97–98[i] | 0.48 | 3.31[l] | 3.49 | 1 | 0 | 6.85 | 7.08 | 3 | 3 |
| **8** | *t*-$C_4H_9$ | 106–107[i] | 0.48 | 3.31[l] | 3.17 | 1 | 0 | 4.87[m] | 6.97 | 1[m] | 2 |
| **9** | $CH(CH_3)$-*n*-$C_6H_{13}$ | 46.5–48 | 1.13 | 5.06[l] | 6.39 | 1 | 0 | 7.53 | 7.29 | 3 | 3 |
| **10** | $CH_2CH{=}CH_2$ | 86–87[i] | | 2.76[k] | 3.78 | 0 | 0 | 6.82 | 6.93 | 2 | 2 |
| **11** | $CH(C_2H_5)CH{=}CH_2$ | 98.5–99.5 | 0.52 | 3.42[l] | 3.78 | 1 | 0 | 7.47 | 7.21 | 3 | 3 |
| **12** | $CH(CH_3)CH_2CH{=}CH_2$ | 75–76 | 0.50 | 3.37[l] | 4.55 | 1 | 0 | 7.17 | 7.26 | 3 | 3 |
| **13** | $CH(CH_3)C{\equiv}CH$ | 116–117[i] | | 2.68[k] | 4.49 | 1 | 0 | 6.97 | 6.97 | 3 | 3 |
| **14** | $CH(C_2H_5)C{\equiv}CH$ | 118–119 | 0.39 | 3.07[l] | 4.49 | 1 | 0 | 6.74 | 7.14 | 3 | 3 |
| **15** | $CH_2CH_2C{\equiv}CH$ | 89–90 | 0.19 | 2.54[l] | 3.17 | 0 | 0 | 6.74 | 6.63 | 2 | 2 |
| **16** | $CH(CH_3)CH_2C{\equiv}CH$ | 99–100 | 0.31 | 2.86[l] | 3.17 | 1 | 0 | 6.86 | 6.77 | 3 | 3 |
| **17** | $CH_2CH_2C{\equiv}N$ | 85.5–86.5[j] | | 2.13[k] | 3.17 | 0 | 0 | 6.47 | 6.45 | 2 | 2 |
| **18** | $CH_2CH_2F$ | 101–102 | 0.09 | 2.27[l] | 3.17 | 0 | 0 | 6.59 | 6.51 | 3 | 2 |
| **19** | $CH(CH_3)CH_2F$ | 90–91 | 0.21 | 2.59[l] | 3.17 | 1 | 0 | 6.34 | 6.65 | 2 | 2 |
| **20** | $CH_2CH_2Cl$ | 89.5–90.5[i] | 0.22 | 2.62[l] | 3.25 | 0 | 0 | 7.12 | 6.70 | 2 | 2 |
| **21** | $CH_2CCl_3$ | 90–91 | 0.18 | 2.51[l] | 4.50 | 0 | 1 | 5.59 | 5.45 | 1 | 2 |
| **22** | $CH(CH_3)CH_2Cl$ | 82–83 | 0.35 | 2.97[l] | 3.25 | 1 | 0 | 6.88 | 6.85 | 3 | 3 |
| **23** | $CH(CH_3)CCl_3$ | 1.5316 (19.5) | 0.72 | 3.96[l] | 4.50 | 1 | 1 | 6.42 | 6.08 | 1 | 2 |
| **24** | $CH_2CH_2Br$ | 75–76 | 0.28 | 2.78[l] | 3.40 | 0 | 0 | 6.92 | 6.83 | 2 | 2 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **25** | $CH(CH_2Br)_2$ | 75–76[i] | | 3.50[k] | 3.40 | 1 | 0 | 7.15 | 7.13 | 3 | 3 |
| **26** | $CH_2CH_2OCH_3$ | 58–59.5[j] | | 2.31[k] | 4.44 | 0 | 0 | 7.15 | 6.81 | 1 | 2 |
| **27** | $CH(CH_3)CH_2OCH_3$ | 65–66.5 | 0.20 | 2.56[l] | 4.44 | 1 | 0 | 6.99 | 6.92 | 2 | 3 |
| **28** | $CH(CH_2Cl)CH_2OCH_3$ | 82–83[j] | | 2.82[k] | 4.44 | 1 | 0 | 7.34 | 7.03 | 2 | 3 |
| **29** | $CH_2C_6H_5$ | 109–110[i] | | 3.29[k] | 6.02 | 0 | 0 | 6.54 | 6.77 | 1 | 2 |
| **30** | $CH(CH_3)C_6H_5$ | 109–110[i] | 0.57 | 3.56[l] | 6.02 | 1 | 0 | 6.92 | 6.88 | 3 | 3 |

[a] Capacity factor in HPLC.
[b] Calculated by the STERIMOL program.
[c] An indicator variable for $\alpha$-branching derivatives.
[d] An indicator variable for $\beta$-branching derivatives.
[e] Determined by the agar medium dilution method.
[f] Determined by the foliar application method in pot tests.
The activity was rated from 1 to 3, 1: below 70% prevention relative to the untreated control at the rate of 50 ppm, 2: above or equal to 70% at 50 ppm, 3: above or equal to 70% at the rate of 12.5 ppm.
[g] Calculated by Eq. (5).
[h] Calculated by Eq. (6).
[i] Reported in Ref. 3).
[j] Reported in Ref. 7).
[k] Determined by the shake-flask method in Ref. 7).
[l] Estimated from log $k'$ values using Eq. (2).
[m] Not included in the correlation.

were reported previously[3,7] or prepared by the reaction of 3,4-diethoxyaniline with chloroformates in the presence of a base or by the reaction of 3,4-diethoxyphenyl isocyanate with alcohols.[8] The structure of the compounds was confirmed by PMR and IR spectra. All melting points are uncorrected.

*2. Fungicidal and Preventive Activities*

The fungicidal activity against *B. cinerea* resistant to benzimidazole fungicides was determined by the agar medium dilution method as described in our previous paper[1] and expressed as $pI_{50}$ value, the negative logarithm of the molar concentration required for 50% inhibition of mycelial growth. The preventive activity by the foliar application in pot tests was evaluated according to the method reported previously[1] and rated by visual observation from 1 to 3: 1, below 70% prevention relative to the untreated control at the rate of 50 ppm; 2, above or equal to 70% at 50 ppm; 3, above or equal to 70% at 12.5 ppm.

*3. Quantitative Correlation Analyses*

The structure-activity relationships were analyzed quantitatively by the Hansch-Fujita method[5] according to Eq. (1),

$$pI_{50} = a \log P + \sum b_i E_i + c \qquad (1)$$

where $P$ is a partition coefficient in 1-octanol/water system and $E_i$ denotes a free-energy related substituent parameter concerning physicochemical effects such as steric and electronic. $a$, $b_i$ and $c$ are susceptibility constants and an intercept determined by means of regression analysis.

In the preceding paper we examined the relationship between $\log P$ and $\log k'$ values for *N*-(3,4-diethoxyphenyl)carbamoyl esters with various alcoholic moiety substituents, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclo-pentyl, allyl, 1-methyl-2-propynyl, 1,3-dibromo-2-propyl, 2-methoxyethyl, 1-chloro-3-methoxy-2-propyl, 2-cyanoethyl and benzyl. We obtained Eq. (2).[7]

$$\log P = 2.680 \log k' + 2.028 \qquad (2)$$

In Eq. (2), $k'$ is the capacity factor in high-performance liquid chromatography (HPLC) defined according to Eq. (3),

$$k' = (t_R - t_0)/t_0 \qquad (3)$$

where $t_R$ and $t_0$ are respectively the retention time of the test compound and potassium iodide as the unretained reference. HPLC was carried out using octadecylsilane column, Zorbax ODS (250 mm×4.6 mm, Du Pont), kept at 50°C by column oven with water–acetonitrile (4: 7, v/v) as the mobile phase. The standard deviation of the $\log k'$ obtained from three replicate measurements was within 0.01. The $\log P$ values of the compounds (**1**–**6**, **10**, **13**, **17**, **25**, **26**, **28** and **29**) were determined by the shake flask method[7] and those of others were estimated from their $\log k'$ values by using Eq. (2). The $\log k'$ values used for the estimation of $\log P$ values are listed in Table 1 together with the $\log P$ values.

The STERIMOL $B_5$ values were calculated by the STERIMOL program and used as the steric parameter. The STERIMOL parameters are the set of values developed by Verloop *et al.*[9] and the $B_5$ represents the maximum width of the substituent in the direction perpendicular to the axis connecting the $\alpha$-atom of substituents with the rest of the molecule. The $B_5$ values used in the correlation are also listed in Table 1.

Since the preventive activity in pot tests was represented as rating scores, we analyzed the relationship between the preventive activity and fungicidal activity by using the ALS method,[6] which can be represented by Eq. (4),

$$PA = w_0 + w_1 x_1 + w_2 x_2 + \ldots + w_p x_p \qquad (4)$$

where $PA$ is the discriminant score for classification, $x_k$ ($k=0, 1, \ldots, p$) is the $k$th descriptor for the structure, and $w_k$ ($k=0, 1, \ldots, p$) is the $k$th weight coefficient. Classification was performed using the value of $PA$ as follows: if $PA \leqq 1.5$, then the compound was assigned to class 1; if $1.5 < PA \leqq 2.5$, then it was assigned to class 2; if $PA > 2.5$, then it was assigned to class 3. The accuracy of the correlation was confirmed by the leave-one-out prediction.

## RESULTS AND DISCUSSION

*1. Relationship between Structure and Fungicidal Activity*

The fungicidal activity on agar medium, $pI_{50}$, of *N*-(3,4-diethoxyphenyl)carbamoyl

esters was varied with the variation of the alcoholic moiety substituents (Table 1). The activity of the derivatives, **6**, **21** and **23**, possessing alkyl groups whose $\beta$-carbon atom is linked with more-than-one alkyl or halo substituents was considerably lower than that of the structurally related compounds without "$\beta$-branching." The *tert*-butyl derivative (**8**) having tertiary branching at the $\alpha$-position also showed reduced activity. Therefore, we first examined the structure-activity correlation for compounds, excluding the derivatives **6**, **8**, **21** and **23**.

The fungicidal activity was not well correlated with $\log P$ alone ($r=0.563$). The addition of $(B_5)^2$ and $B_5$ terms to the equation with only $\log P$ term significantly improved the correlation to give Eq. (5) ($F_{2,22}=10.5$, $F_{2,22,0.01}=5.7$).

$$\begin{aligned} pI_{50} = {} & \underset{(0.246)}{0.411}\log P - \underset{(0.083)}{0.179}(B_5)^2 + \underset{(0.721)}{1.588}B_5 \\ & + \underset{(1.645)}{2.354} \end{aligned} \quad (5)$$

$$n=26,\ s=0.257,\ r=0.806,\ F_{3,22}=13.6$$

In this and the following equations, $n$ is the number of compounds included in the correlation, $s$ is the standard deviation, $r$ is the correlation coefficient, and $F_{\nu_1,\nu_2}$ is the $F$ value of the correlation, where $\nu_1=m$ and $\nu_2=n-m-1$: $m$ is the number of independent variables. The figures in parentheses are the 95% confidence limits of the corresponding coefficients. All terms were justified above 99.5% level by $t$-test. The use of other steric parameters such as STERIMOL $L$ and $B_1$,[9] Hancock's corrected steric $E_S^C$,[10] molar refractivity $MR$,[11] molecular weight $MW$ and van der Waals volume $V_W$[12] instead of $B_5$ did not afford any significant correlation. The addition of the hydrophobic $(\log P)^2$ and electronic $\sigma^*$[13] terms to Eq. (5) did not produce any significant result either.

The $pI_{50}$ values of the "$\beta$-branching" derivatives, which were not used in Eq. (5), were found to be 1.1 to 1.9 lower than those calculated by Eq. (5). The detrimental effect of the "$\beta$-branching" was found to be best represented by an indicator variable, $I_\beta$, which takes 1 for the "$\beta$-branching" derivatives or 0 for the others. Equation (6) shows that the indicator variable, $I_\beta$, is highly significant in correlating the activity value of the whole series of compounds, except for the *tert*-butyl derivative (**8**).

$$\begin{aligned} pI_{50} = {} & \underset{(0.237)}{0.428}\log P - \underset{(0.088)}{0.180}(B_5)^2 + \underset{(0.768)}{1.592}B_5 \\ & - \underset{(0.371)}{1.441}I_\beta + \underset{(1.731)}{2.307} \end{aligned} \quad (6)$$

$$n=29,\ s=0.275,\ r=0.876,\ F_{4,24}=19.9$$

The positive sign of the $\log P$ term in Eq. (6) means that the greater the hydrophobicity of the substituents, the higher the activity. When the hydrophobic terms are significant in a QSAR equation, three cases are possible with respect to the hydrophobic effect of substituents or compounds: the effect is attributed to a hydrophobic interaction with the receptor site, the membrane transport, or both. In the previous structure-activity study for methyl *N*-(substituted phenyl)carbamates, we reported that the greater the hydrophobicity of the benzene ring substituents, the higher the activity against the resistant strain of *B. cinerea*, where the coefficient of the $\pi$ term for the *o*- and *m*-substituents was 1.075 and that for the *p*-substituents was 0.632.[4] Compared with these two values, the coefficient of the $\log P$ term in Eq. (6) is somewhat small. Such a position-specific hydrophobic effect of substituents may indicate the existence of a hydrophobic interaction with the receptor site at the critical step. It can be said that the receptor region corresponding to the alcoholic moiety substituents may be less hydrophobic than those corresponding to the benzene ring substituents. There is the possibility, however, that a certain part of each hydrophobic term of the benzene ring and alcoholic moiety substituents may be attributed to the membrane transport stated. A direct experiment on the transport of the compounds through the membrane of fungi would clarify this issue.

Equation (6) shows that the activity is related parabolically to the maximum width, $B_5$, of the alcoholic moiety substituents reaching maximum when $B_5$ is 4.42Å. The suitable steric fit of the molecule around the substituents with the receptor site may be important for high fungicidal activity. The

fact that the coefficient of the $I_\beta$ term in Eq. (6) is −1.44 means that the "$\beta$-branching" lowers the activity down to about 1/30 that expected for the compounds without "$\beta$-branching," other things being equal. The "$\beta$-branching" of the substituents may interfere with the interaction between the molecule and the receptor site. The activity of the *tert*-butyl derivative (**8**) is about 1/130 that calculated by Eq. (6) as shown in Table 1. This suggests that the tertiary branching at the $\alpha$-position also causes unfavorable effect on the activity. The lack of the electronic term in Eq. (6) is due to the fact that the electronic property of the substituents does not vary much within the set of compounds.

Although having a structural feature similar to the "$\beta$-branching," the benzyl (**29**) and 1-phenylethyl derivatives (**30**) were well included in Eq. (6). Here, the $\beta$-carbon atoms of these derivatives are $sp^2$ ones. This result may indicate that the planarity at the $\beta$-position does not interfere with the interaction with the receptor site.

## 2. *Correlation between Fungicidal and Preventive Activities*

The above mentioned examination was for *in vitro* fungicidal activity on the agar medium. From the viewpoint of practical use as a fungicide, *in vivo* fungicidal activity is also to be considered. The relationship of preventive activity by the foliar application in pot tests with fungicidal activity on the agar medium was hence analyzed for the compounds in Table 1, excluding for the *tert*-butyl derivative (**8**), by using the ALS method to clarify the factors relating to the difference in bioassay system. The direct relationship between the two types of activities was not significant ($R_s=0.504$), and the correlation was not improved by the addition of $\log P$, $(B_5)^2$ and $B_5$, singly or together. The best discriminant function for the preventive activity formulated within 20 iterative calculations was Eq. (7) with $pI_{50}$ and an indicator variable, $I_\alpha$, which takes 1 for the $\alpha$-branching derivatives or 0 for the others, as an independent variable.

$$PA=0.285pI_{50}+0.693I_\alpha-0.060 \quad (7)$$
$$n=29 \text{ (three grades)}, R_s=0.773,$$

Table 2 The squared correlation matrix ($r^2$) for the variables of Eqs. (5) and (6).

| | $\log P$ | $(B_5)^2$ | $B_5$ | $I_\alpha$ | $I_\beta$ |
|---|---|---|---|---|---|
| $\log P$ | 1.000 | 0.450 | 0.437 | 0.211 | 0.030 |
| $(B_5)^2$ | | 1.000 | 0.978 | 0.041 | 0.018 |
| $B_5$ | | | 1.000 | 0.048 | 0.031 |
| $I_\alpha$ | | | | 1.000 | 0.016 |
| $I_\beta$ | | | | | 1.000 |

$$n_{mis}=9(0),\ n_{mis}(\text{after leave-one-out})=11(0)$$

In this equation, $PA$ is the discriminant score of the preventive activity for the classification. $R_s$ is the Spearman's rank correlation coefficient and $n_{mis}$ is the number of misclassified compounds. The figure in parentheses after the value of $n_{mis}$ is the number of compounds misclassified into the next class by one. The squared correlation matrix for variables used in Eqs. (6) and (7) is listed in Table 2. The correlation was not improved by the addition of $\log P$, $(B_5)^2$ and $B_5$ to Eq. (7), singly or together.

The $pI_{50}$ term in Eq. (7) indicates that the preventive activity by the foliar application in pot tests is related to the fungicidal activity on the agar medium. The positive coefficient of the $pI_{50}$ term means that the greater the fungicidal activity, the greater the preventive activity. The positive sign of the $I_\alpha$ term indicates that the $\alpha$-branching of the substituents increases the activity. Generally, the stability of a compound is one of the factors affecting the activity variation in pot tests. In substituents possessing $\alpha$-branching, metabolic degradation of the molecule in the plant body at the carbamate moiety may be supressed. Therefore, the positive sign of the $I_\alpha$ term may indicate that the stability of the compounds is important for high preventive activity. According to Eq. (7), the high preventive activity of the isopropyl analog (**4**), diethofencarb, is due to its large $pI_{50}$ value and the $\alpha$-branching. The QSAR analysis on the *in vitro* fungicidal activity could serve to estimate the *in vivo* preventive activity when the branching pattern of the compound is taken into account.

Our conclusion is that *N*-(3,4-diethoxy-

phenyl)carbamoyl esters having alcoholic moiety substituents with great hydrophobicity and appropriate maximum width and without "$\beta$-branching" show the high fungicidal activity on the agar medium. The compounds with high fungicidal activity, which have $\alpha$-branched substituents, show high preventive activity by the foliar application in pot tests.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## 要　　約

### 殺菌活性を有する *N*-(3,4-diethoxyphenyl)-carbamate 類の定量的構造活性相関*

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アルコール部位に種々の置換基を有する30個の *N*-(3,4-diethoxyphenyl)carbamate 類の，benzimidazole 系殺菌剤耐性の *Botrytis cinerea* に対する殺菌活性を，寒天培地希釈法で測定した．構造と活性との関係を重回帰分析により，定量的に解析した．その結果，殺菌活性は，置換基の疎水性が増大するほど大きくなることが判明した．また活性は置換基の最大幅に対して放物線的な関係にあり，置換基の $\beta$-位の枝分れは活性を低下させることが明らかとなった．さらに，茎葉処理ポット試験で測定した殺菌剤耐性の *B. cinerea* によるキュウリ灰色かび病に対する防除効果は，適応最小二乗法により，殺菌活性と $\alpha$-位の枝分れとに関係することが判明した．

* *N*-Phenylcarbamates の殺菌活性（第6報）