Agricultural and Biological Chemistry

ISSN: 0002-1369 (Print) (Online) Journal homepage: http://www.tandfonline.com/loi/tbbb19

Fungicidal Activity of N-Benzoylanthranilates and Related Compounds

Osamu Kirino, Shigeo Yamamoto & Toshiro Kato

To cite this article: Osamu Kirino, Shigeo Yamamoto & Toshiro Kato (1980) Fungicidal Activity of N-Benzoylanthranilates and Related Compounds, Agricultural and Biological Chemistry, 44:9, 2143-2147, DOI: 10.1080/00021369.1980.10864289

To link to this article: http://dx.doi.org/10.1080/00021369.1980.10864289

Agric. Biol. Chem., **44** (9), 2143~2147, 1980

Fungicidal Activity of *N*-Benzoylanthranilates and Related Compounds*

Osamu KIRINO, Shigeo YAMAMOTO and Toshiro KATO

Research Department, Pesticides Division, Sumitomo Chemical Co., 4-2-1, Takatsukasa, Takarazuka, Hyogo 665, Japan

Received April 9, 1980

Methyl *N*-(substituted benzoyl)anthranilates were found to possess inhibitory activity against the powdery mildew of cucumber caused by *Sphaerotheca fuliginea*. Both the anthranilate and the *N*-benzoyl moieties were essential for this type of fungicidal activity. Substitution at the 2- and 4-positions of the *N*-benzoyl group was unfavorable to the activity except for the 4-methoxy group. Substitution at the 3-position varied the fungicidal activity to various extents. The variation in the activity of 3-substituted derivatives was analyzed quantitatively with substituent parameters and regression analysis indicating that the variation in the steric dimension of substituents was most responsible for the activity.

Benzanilide analogs such as 2-methylbenzanilide are known to possess fungicidal activity.[1] Anthranilic acid and its esters are reported as showing bactericidal[2] and fungicidal activities.[3] We have selected the *N*-benzoylanthranilic acid esters as a possible lead structure for a series of new fungicides.

As expected, some of the derivatives have been found to show the potent preventive effect against the powdery mildew of barley, apple and cucumber. Using a number of substituted derivatives and analogs, we have examined the substituent effect on the fungicidal activity. In this paper we describe the relationship between chemical structure of *N*-benzoylanthranilates and the preventive effect against the powdery mildew of cucumber in the pot tests.

MATERIALS AND METHODS

Synthesis of compounds. The structure of the compounds was confirmed by IR and NMR spectroscopy in addition to the elementary analyses for C, H, N, S and halogens. Most of the anilides were prepared by the reaction of appropriate acyl chlorides with respective anilines in the presence of a base. The acyl chlorides and anilines were either obtained commercially or synthesized by conventional methods. *N*-Benzoyl-2-methylsulfonylaniline (15) was prepared by oxidation of *N*-benzoyl-2-methylthioaniline (14) with 30% aq. hydrogen peroxide in acetic acid solution according to the method of Overberger *et al.*[4] A typical procedure is shown below.

Methyl N-(3-methoxybenzoyl)anthranilate (60). 3-Methoxybenzoyl chloride (8.5 g, 0.05 mol) was added to a mixture containing methyl anthranilate (7.6 g, 0.05 mol), triethylamine (6.1 g, 0.06 mol) and benzene (200 ml) with stirring at room temperature. After 4 hr, the reaction mixture was washed successively with water, dilute HCl and aq. $NaHCO_3$. The organic layer, after drying over anhydrous Na_2SO_4, was evaporated to dryness and the residue was recrystallized from ethanol to give 12.4 g of colorless needles, mp 86~87°C. *Anal.* Found: C, 67.42; H, 5.34; N, 4.85. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91%.

Biological test. Each test compound was formulated as the 20% emulsifiable concentrate including 32% *N*,*N*-dimethylformamide, 32% xylene and 16% Sorpol 1200 (a polyether type emulsifier, Toho Chemical Ind. Co., Tokyo) by weight. The resulting concentrate was diluted with water to desired concentrations. Cotyledonous plants of cucumber (cultivar; Sagamihanjiro) raised for 8 days in a greenhouse were sprayed with the test solution, 6 hr prior to the inoculation with conidia of *S. fuliginea*. The inoculated plants were maintained in an air-controlled room at 28°C under fluorescent lamps. The disease assessment was made by rating the disease severity 9 days after the inoculation. The preventive value was expressed as the percentage of inhibition of the disease development. The molar I_{50} value (concentration in the sprayed emulsion required for the 50% inhibition) was determined from the plot of the preventive value against the concentration with the logarithmic probability scale.[5]

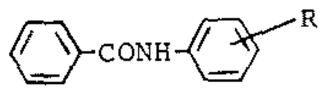
* Structure-Activity Study of Fungicidal *N*-Benzoylanthranilates. Part I.

RESULTS AND DISCUSSION

Activity of N-benzoylanilines

Table I shows that only the 2-methoxycarbonyl derivative of *N*-benzoylaniline (compd. 9, *N*-benzoylanthranilic acid methyl ester) exhibits a strong preventive activity against the powdery mildew of cucumber. The 2-acetyl (5), 2-carbamoyl (7) and 2-carboxy (8) derivatives having the carbonyl function, and the 2-methoxymethyl derivative (13) having the methoxy group are inactive. The 3-methoxycarbonyl (10), and 4-methoxycarbonyl (11) derivatives are also inactive. Therefore, the methoxycarbonyl group at the 2-position of aniline seems essential for the high activity. Since the *N*-methylation (compd. 16) leads to the loss of activity, the hydrogen atom at the amide linkage seems also essential for the activity.

TABLE I. PREVENTIVE EFFECT OF *N*-BENZOYLANILINES AGAINST POWDERY MILDEW OF CUCUMBER



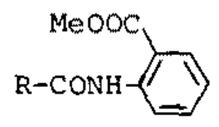
No.	R	mp (°C)[a] [li. value] or n_D^{25}	Preventive value (%) 500 ppm
1	H	163~164 [160~161[b]]	0
2	2-Me	142~143 [142~143[c]]	0
3	2-Cl	103~104 [99[c]]	0
4	2-NO_2	94~95 [94[c]]	0
5	2-COMe	98.5~100 [95~96[d]]	0
6	2-CN	158~159 [158[e]]	0
7	2-$CONH_2$	221~222 [237~238[f]]	0
8	2-COOH	175~176 [183~184[c]]	0
9	2-COOMe	101~102 [101[c]]	100
10	3-COOMe	126~127 [134[g]]	0
11	4-COOMe	172~173 [168[g]]	0
12	2-CH_2OH	93~94	0
13	2-CH_2OMe	75~76	21
14	2-SMe	95.5~97 [96[h]]	16
15	2-SO_2Me	119.5~120.5	59
16	2-COOMe[i] (*N*-Me)	1.5780	0

[a] Melting points are uncorrected.
[b] C. N. Webb, *Org. Syn. Coll. Vol. I*, 82 (1941).
[c] D. H. Hey and D. G. Turpin, *J. Chem. Soc.*, **1954**, 2471.
[d] G. W. Gribble and F. P. Bousquet, *Tetrahedron*, **27**, 3785 (1971).
[e] F. Piozzi *et al.*, *Gazz. chim. ital.*, **89**, 2342 (1959).
[f] D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, **1960**, 2157.
[g] P. Grammaticakis, *Bull. soc. chim. France*, **1951**, 220.
[h] F. Gialdi and A. Baruffini, *Farmaco (Pavia). Ed. Sci.*, **12**, 206 (1957).
[i] $C_6H_5CON(Me)C_6H_4$(2-COOMe).

Activity of methyl N-acylanthranilates

Methyl *N*-benzenesulfonylanthranilate (17) does not show the activity (Table II). Among the *N*-acylanthranilates, *N*-cyclohexanecarbonyl (18), -phenylacetyl (19), -cinnamoyl (20) and -naphthoyl (21, 22) derivatives are inactive as shown in Table II. The *N*-heterocyclic-acyl derivatives such as the furan-(23,24), thiophene-(25) and pyrazine-carbonyl (29) derivatives exhibit the potent activity. The 3- and 4-pyridinecarbonyl derivatives (27, 28) show the moderate activity but the 2-pyridinecarbonyl derivative (26) is inactive. Therefore, the benzoyl group at the nitrogen atom of methyl anthranilate seems replaceable with an appropriate heteroaromatic-acyl group without the loss of the activity.

TABLE II. PREVENTIVE EFFECT OF METHYL *N*-ACYLANTHRANILATES AGAINST POWDERY MILDEW OF CUCUMBER



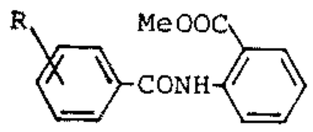
No.	R	mp (°C)[a] [lit. value]	Preventive value(%) 500 ppm
17	Benzenesulfonyl[b]	136~138	0
18	Cyclohexyl	98~99	0
19	Benzyl	58~59 [58[c]]	0
20	2-Phenylethenyl	98~99 [99[c]]	0
21	1-Naphthyl	121~122 [120[d]]	0
22	2-Naphthyl	134~135 [129[d]]	0
23	2-Furyl	114.5~115.5	100
24	3-Furyl	121~122	100
25	2-Thienyl	133~134	100
26	2-Pyridyl	64~66	0
27	3-Pyridyl	124~125	88
28	4-Pyridyl	123~124.5	82
29	Pyrazinyl	139~140	100

[a] Melting Points are uncorrected.
[b] $C_6H_5SO_2NHC_6H_4$(2-COOMe).
[c] H. Stephen and G. Wadge, *J. Chem. Soc.*, **1956**, 4420.
[d] L. Legrand, *Bull. soc. chim. France*, **1960**, 337.

Activity of methyl N-(substituted benzoyl) anthranilates

Table III shows that the substitution at the 2- or 4-position of the benzoyl group of methyl *N*-benzoylanthranilate with the chlorine (32, 55), bromine (33, 56), iodine (34, 57) or methyl substituent (30, 51) greatly reduces the activity. The substitution at the 2-position with fluorine (31) or methoxy (36) only slightly reduces the activity. While the methoxy substitution (60) maintains the activity, the fluorine substitution (54) considerably reduces the activity. The substitution at the 3-position with the substituent as mentioned above maintains the activity. In the alkoxybenzoyl derivatives, the activity decreases with increasing the carbon number in the alkoxy group.

TABLE III. PREVENTIVE EFFECT OF METHYL *N*-(SUBSTITUTED BENZOYL)ANTHRANILATES AGAINST POWDERY MILDEW OF CUCUMBER



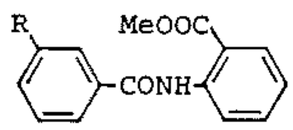
No.	R[a]	mp (°C)[b] [lit. value] or n_D^{25}	Preventive value(%) 500 ppm
9	H	101~102	100
30	2-Me	97~98 [98[c]]	0
31	2-F	87~88	90
32	2-Cl	81.5~82.5	0
33	2-Br	80~81 [86~87[c]]	30
34	2-I	102~103	14
35	2-NO_2	158~160 [158[c]]	0
36	2-OMe	1.6112	90
37	2-OEt	84~85	65
38	3-Me	67~68 [74[d]]	100
39	3-Et	49~50	95
40	3-F	104~105.5	100
41	3-Cl	98~99	100
42	3-Br	90~91 [83[c]]	100
43	3-I	86~87	100
44	3-CF_3	91~92	100
45	3-CN	142~143.5	100
46	3-CH_2OMe	62~63.5	98
47	3-OMe	86~87	100
48	3-OEt	77~78	100
49	3-POr(*n*)	72~73	20
50	3-OPr(*i*)	71~72	86
51	4-Me	111~112 [114[c]]	0
52	4-Pr(*i*)	1.5938	0
53	4-Bu(*t*)	1.5796	0
54	4-F	138~139	48
55	4-Cl	138.5~139.5 [138[c]]	0
56	4-Br	149~150	0
57	4-I	167~168.5	0
58	4-CN	165~167	6
59	4-NO_2	199~200	0
60	4-OMe	113.5~114.5[113[d]]	100
61	4-OEt	121~122	35
62	4-OPr(*n*)	106~107	0
63	4-OPr(*i*)	84~85	0

[a] *n*, *i* and *t* denote normal, iso and tertiary.
[b] Melting points are uncorrected.
[c] L. Legrand, *Bull. soc. chim. Franc*, **1960**, 337.
[d] H. Stephen and G. Wadge, *J. Chem. Soc.*, **1956**, 4420.

Structure-activity correlation of methyl N-(3-substituted benzoyl)anthranilates

(3-Substituted benzoyl)anthranilates were generally more active than their 2- and 4-isomers. Since the activity was modified by substitution at this position more remarkably than by those at the 2 and 4 positions, we followed the dose-response relationship for each compound and determined the pI_{50} value

TABLE IV. PREVENTIVE ACTIVITY AGAINST POWDERY MILDEW OF CUCUMBER AND STERIC PROPERTIES OF METHYL *N*-(3-SUBSTITUTED BENZOYL)-ANTHRANILATES



No.	R[a]	B_4[b]	L[b]	Activity (pI_{50}) Obsvd	Calcd[c]
9	H	1.00	2.06	4.42	4.38
38	Me	2.04	3.00	3.89	4.11
39	Et	2.97	4.11	3.59	3.75
40	F	1.35	2.65	4.55	4.45
41	Cl	1.80	3.52	4.32	4.46
42	Br	1.95	3.83	4.60	4.43
43	I	2.15	4.23	4.66	4.35
44	CF_3	2.61	3.30	3.68	3.81
45	CN	1.60	4.23	4.55	4.74
46	CH_2Me	2.88	4.91	3.62	3.85
47	OMe	2.87	3.98	4.22	3.80
48	OEt	3.36	4.92	3.55	3.51
49	OPr(*n*)	4.30	6.05	2.68	2.64
50	OPr(*i*)	3.61	4.59	3.27	3.33

[a] *n* and *i* denote normal and iso.
[b] STERIMOL parameter, taken from ref. 12.
[c] Calculated by eq. 2.

as shown in Table IV. In order to understand the factors governing the activity variation, the regression analysis was made for the pI_{50} value with the physicochemical substituent parameters.[6] We examined various combinations of substituent parameters. No significant correlation was derived with the hydrophobic π[7] and electronic σ[8,9] parameters. The use of the steric parameters such E_s[10], V_u[11], and MR[8,9] singly or together with π and σ values did not also yield significant correlation. Finally, we found that the STERIMOL parameters[12] are best in correlating the activity variation. The STERIMOL parameters are the set of values developed by Verloop *et al.* representing the directional character of the steric effect. With the L and B_4 values, we derived eqs. 1 and 2.

$$pI_{50} = -0.568B_4 + 5.371 \quad (1)$$
$$(\pm 0.188) \quad (\pm 0.493)$$
$$n=14,\ S=0.289,\ r=0.885,\ F=43.30$$

$$pI_{50} = -0.114L^2 + 1.082L - 0.715B_4 + 3.349 \quad (2)$$
$$(\pm 0.104) \quad (\pm 0.839) \quad (\pm 0.291) \quad (\pm 1.640)$$
$$n=14,\ s=0.229,\ r=0.942,\ F=26.02$$

The L parameter expresses the length of substituents (in Å) along the axis connecting the aromatic carbon where the substituents are located with the α-atom of substituents. The B_4 value is the largest one among the four width values perpendicular to each other as well as the L-axis. In eqs. 1 and 2, n is the number of compounds included in the correlation and figures in parentheses are the 95% confidence intervals of the corresponding constants. s is the standard deviation, r is the correlation coefficient and F is the F-value of the correlation. The collinearity between variables is shown in Table V. The B_4 term in eqs. 1 and 2 is justified by the t-test at better than the 99.5% level of significance. The L^2 and L terms in eq. 2 are justified respectively at levels more than 95% and 97.5%. The single parameter eq. 1 with the B_4 term shows a fairly good correlation indicating that the width of the substituent plays the most important role in determining the activity variation. Both the L and L^2 terms are significant in eq. 2 ($F_{2,10}=4.55$, $F_{2,10,0.05}=4.10$), but the B_4 and L terms may not be entirely separated from each other because of a relatively high collinearity between B_4 and L values. Addition of any other parameters to eq. 2 does not afford a significant reduction in the standard deviation.

TABLE V. THE SEQUEARED CORRELATION MATRIX OF VARIABLES USED IN EQS. 1 AND 2

	B_4	L	L^2
B_4	1.000	0.719	0.721
L		1.000	0.972
L^2			1.000

In eqs. 1 and 2, the negative sign of the B_4 term means that the preventive activity decreases with increasing the width of the 3-substituent. According to eq. 2, the activity is also related parabolically to the L value, the length of substituents, the optimum L value being 4.74 Å. These relationships indicate that the suitable fit of the substituent with the critical site of the fungicidal action may be important for the high activity.

Acknowledgments. We wish to express our thanks to Prof. K. Yamashita, Tohoku University, for his continuing guidance, and to Prof. T. Fujita, Kyoto University, for his invaluable suggestions. We also thank Dr. C. Takayama for his fruitful discussions, and Mr. M. Ishiwatari for his skilled technical assistance. Thanks are also due to Drs. Y. Nishizawa and A. Fujinami for their continuing encouragement.

REFERENCES

1) G. A. White and G. D. Thorn, *Pest. Biochem. Physiol.*, **5**, 380 (1975).
2) B. E. Voleani, S. Sicher, E. D. Bergmann and H. Bendas, *J. Biol. Chem.*, **207**, 411 (1954).
3) N. D. Heindel, T. F. Lemke, S. M. Lemke and V. B. Fish, *J. Med. Chem.*, **11**, 369 (1968).
4) C. G. Overberger, S. P. Ligthelm and E. A. Swire, *J. Am. Chem. Soc.*, **72**, 2856 (1950).
5) T. Kono, *Botyu-Kagaku*, **16**, 62 (1951).
6) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
7) T. Fujita, J. Iwasa and C. Hansch, *ibid.*, **86**, 5175 (1964).

8) C. Hansch, A. Leo, S. H. Unger, K.-H. Kim, D. Nikaitani and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
9) C. Hansch, S. D. Rockwell, P. Y. C. Jow, A. Leo and E. E. Steller, *ibid.*, **20**, 304 (1977).
10) S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, **12**, 91 (1976).
11) I. Moriguchi and T. Kanada, *Chem. Pharm. Bull.*, **24**, 1799 (1976).
12) A. Verloop, W. Hoogenstraaten and J. Tipker, "Drug Design, Vol. VII," ed. by E. J. Ariens, Academic Press, New York, 1976, p. 165.