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Received for review January 25, 1989. Revised manuscript received June 23, 1989. Accepted September 5, 1989. Mention of a trademark or propietary product does not constitute a guarantee or warranty of the product by the USDA and does not imply its approval to the exclusion of other products that may also be suitable.

Registry No. Gossypol, 303-45-7.

Structure–Activity Relationships in (Haloalkyl)pyridazines: A New Class of Systemic Fungicides

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3,6-Dichloro-4-(2-chloro-1,1-dimethylethyl)pyridazine (1) is one of the most active members of a series of new fungicides active against *Oomycetes*. We report on 66 compounds representing modifications of structure 1 and showing that only very limited variation in this structure is possible without loss of activity. Activity is retained only when bromine or iodine is substituted for the chlorine on the *tert*-butyl function. A second chlorine may be added to an adjacent methyl group without large loss of activity. A bromine may be substituted for the 3-chlorine, and to a lesser extent, methyls may be substituted for the ring chlorines. All other changes we explored resulted in partial or complete loss of activity. The parent compound is mobile within plant tissue, moving through the root system to control the pathogen and also toward the tip of the leaf when applied to the middle of the leaf.

We have described the synthesis of 3,6-dichloro-4-(2-chloro-1,1-dimethylethyl)pyridazine (1) (Hackler et al., 1988). This compound is part of a series of compounds (Arnold et al., 1988) with very interesting systemic activity against *Phycomycetes* organisms in plants. We report on a study of the structure–activity relationships in this series of compounds, revealing a narrow set of structural parameters for retention of this activity.

EXPERIMENTAL SECTION

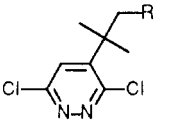
The primary test results reported in Tables I–V result from a foliar application of the test compounds to squash plants inoculated with *Pseudoperonospora cubensis*, the causative organism of downy mildew, 2–4 h after spraying. Formulation consisted of dissolving 48 mg of a selected compound in 1.2 mL of a solvent prepared by mixing 100 mL of Tween 20 (a nonionic surfactant) with 500 mL of acetone and 500 mL of ethanol. The solution of test compound was diluted to 120 mL with deionized water and further diluted to obtain the desired concentration.

The rating system used in the tables is based on a scale of 1–9, as follows: 1, 0–19% control; 2, 20–29%; 3, 30–39%; 4, 40–59%; 5, 60–74%; 6, 75–89%; 7, 90–96%; 8, 97–99%; 9, 100% control, no disease.

Soil and foliar local systemic activity were determined by using the formulation described above. The soil systemic test on squash consisted of using 50 mL of solution at the desired concentration to drench the soil in a 4-in. plastic pot containing 9-day-old Golden Crookneck squash plants. The plants were inoculated 24 h after treatment. The soil systemic test on tobacco was done by diluting the formulated sample to create a solution that would equal the desired concentration in pounds per acre when 20 mL was applied to a 4-in. square pot containing the tobacco plant var. NC2326. Twenty-four hours after application, the tobacco plant was inoculated by placing a 2-cm disk of tobacco black shank agar in a puncture wound in the tobacco stem. The wound was sealed with lanolin. Disease incidence was determined 9 days after inoculation.

The foliar local systemic test consisted of applying the solution to 14-day-old squash plants by spraying the lower leaf surface at right angles to midvein in a 5/8-in. band. Twenty-four hours after treatment, the plants were inoculated on the upper leaf surface with the sporangial suspension and incubated for 24 h in a moist chamber at 70 °F. The plants were then moved to the greenhouse for disease expression.

Table I. Activity of 3,6-Dichloro-4-(substituted *tert*-butyl)-pyridazines against Downy Mildew of Squash



no.	R	mp, °C	400 ppm	100 ppm	25 ppm	6.25 ppm
1	Cl	64–65	9	9	8.5	6
2	Br	86.5–88.5	9	9	8	5.5
3	I	106–108	9	9	8	2
4	F	36–38	9	9	3	
5	H	37–40	4			
6	OH	134–136	1	1	1	
7	CH_3	oil	9	2	1	
8	OAc	32–34	1	1	1	
9	OTos	111–113	1	1	1	
10	CN	80–82	5	2	1	
11	$OCOCH_2Cl$	74–75	1	1	1	
12	CH_2Cl	80–81	6	2	1	
13	CO_2Et	64–65	4	1	1	
14	$OCOC_6H_5$	62–64	3	2	1	
15	OCO_2CH_3	106–107	1	1	1	
16	$OCONHC_6H_5$	146–148	2	1	1	
17	$OCSNHC_6H_5$	135–136	6	4	3	

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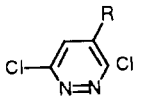
0021-8561/90/1438-0508$02.50/0

Table II. Effect of Multiple Halogens on Activity of 3,6-Dichloro-4-*tert*-butylpyridazines against Downy Mildew of Squash



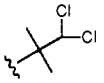
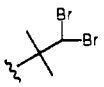
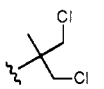
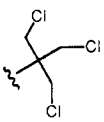
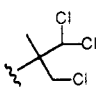
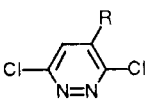
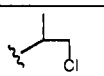
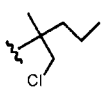
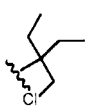
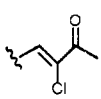
R	no.	mp, °C	400 ppm	100 ppm	25 ppm	6.25 ppm
	18	57–58	1	1	1	
	19	oil	1	1	1	
	20	92–94	9	8.5	8	1
	21	111–112	9	5	1	
	22	82–85	8	3	1	

Table III. Activity of Other 4-(Haloalkyl)-3,6-dichloropyridazines against Downy Mildew of Squash

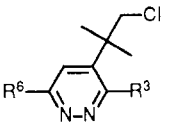


R	no.	mp, °C	400 ppm	100 ppm	25 ppm	6.25 ppm
	23	oil	9	8.5	2	1
	24	80–81	7	1	1	
	25	93–95	9	7	2	
	26	68–69	8	5	2	
	27	45–47	7	3	1	
	28	83–84	2	1	1	
	29	49–50	2	1	1	
	30	oil	5	1	1	
	31	oil	6	2	1	

The compounds were considered systemic only if they were mobile within the plant and demonstrated control of the pathogen beyond the band where they were applied.

Chemicals. The syntheses of compounds **1**, **2**, **5**, **6**, **9**, **18**, **20–22**, and **35** were reported before (Hackler et al., 1988), and

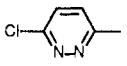
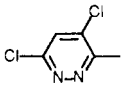
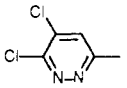
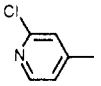
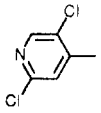
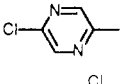
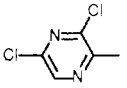
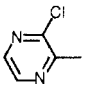
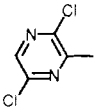
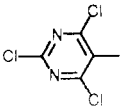
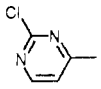
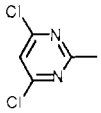
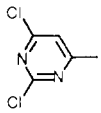
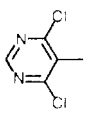
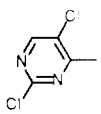
Table IV. Effect of Modification of 3- and/or 6-Positions of Pyridazines on Activity against Downy Mildew of Squash



no.	R^3	R^6	mp, °C	400 ppm	100 ppm	25 ppm	6.25 ppm
32	Br	Cl	79–81	9	9	8.5	4
33	F	F	oil	5	2	1	
34	Cl	H	oil	8	2	1	
35	OH	Cl	181–184	3	1	1	
36	H	H	oil	2	1	1	
37	Cl	OH	144–145	5	2	1	
38	Cl	CN	75–76	9	5	2	
39	Cl	Me	41–42	9	8.5	4	2
40	Cl	*t*-Bu	97–99	1	1	1	
41	Cl	EtS	63–64	7	3	1	
42	Cl	PhS	104–105	7	3	1	
43	Cl	$PhSO_2$	111–112	1	1	1	
44	Cl	Me_2N	oil	6	1	1	
45	Cl	EtNH	101–102	5	2	1	
46	Cl	PhNH	193–194	3	2	2	
47	Cl	MeO	oil	5	2	1	
48	Cl	4-ClPhO	102–103	2	1	1	
49	Me	Me	57–59	9	8	3	
50	OH	H	132–134	1	1	1	
51	OH	NO_2	163–164	1	1	1	

that paper illustrates some of the techniques used to synthesize additional molecules in this paper. The syntheses of compounds **3**, **4**, **23**, **25**, **32**, **38**, **39**, and **49** are described in a U.S. patent (Arnold et al., 1988). Compound **3** was made by treating **5** with *N*-iodosuccinimide with irradiation by a sunlamp. Compound **4** was made by treating **6** with (diethylamino)sulfur trifluoride (DAST) at 5 °C. Compounds **7**, **10**, **12**, **13**, and **28–30** were made by treatment of 3,6-dichloropyridazine with the respective alkyl radical derived from the carboxylic acid by silver-catalyzed oxidation. Compounds **8**, **11**, and **14–17** were made by treating alcohol **4** with the appropriate reagent. Compound **19** was isolated from the mixture obtained by treating **5** with *N*-bromosuccinimide, while compounds **23** and **24** were isolated from a mixture obtained by the photochemical chlorination of 3,6-dichloro-4-isopropylpyridazine with sulfuryl chloride. Compounds **25–27** were obtained by treating the corresponding alcohols with thionyl chloride. The alcohol for **25** came from a radical alkylation using cyclohexene with 3,6-dichloropyridazine. Compound **31** was obtained by sulfuryl chloride treatment at room temperature of the product derived from the silver-catalyzed oxidation of levulinic acid in the presence of 3,6-dichloropyridazine. Compound **32** was obtained when 3,6-dibromo-β,β-dimethyl-4-pyridazineethanol 4-methylbenzenesulfonate ester was treated with lithium chloride in dimethyl sulfoxide. Compound **33** was isolated from the treatment of **1** with potassium fluoride in DMF. Compound **34** was synthesized by the catalytic (5% Pd/C) reduction of **1** in a Paar shaker with triethylamine for 13 min, while a 50-min reduction under the same conditions yielded **36**. Compounds **37**, **41**, **42**, and **44–48** were made by treating **1** with the appropriate nucleophile. Compound **43** was made by oxidation of **42** with potassium hydrogen persulfate (Trost and Curran, 1981). Compound **50** was made by the catalytic reduction of **35**, and **51** resulted from the direct nitration of **50**. Compounds **52–54** were obtained from chlorination of 3-chloro-6-*tert*-butylpyridazine. Compounds **61** and **65** were derived by chlorination of the corresponding *tert*-butyl derivatives, which were made by cyclization reactions. Compounds **38**, **39**, **49**, **56–60**, **62–64**, and **66** were made by chlorination of products obtained from radical alkylations of appropriate substrates. Compound **40** was synthesized from the corresponding tosylate by displacement with lithium chloride in dimethyl sulfoxide at 110 °C for 3 h. Compound **55** was made by rearrangement of 4-(2-chloro-1,1-dimethylethyl)pyridine *N*-oxide with phosphorus oxychloride. The experimental details for selected compounds from the above

Table V. Other Chloro-*tert*-butyl Heterocycles and Their Activity against Downy Mildew of Squash

Het	no.	mp, °C	400 ppm	100 ppm	25 ppm
	**52**	66–68	1	1	
	**53**	46–47	2	1	1
	**54**	oil	2	1	1
	**55**	oil	1	1	1
	**56**	oil	3	1	1
	**57**	oil	1	1	1
	**58**	oil	1	1	1
	**59**	oil	4	2	1
	**60**	oil	1	1	1
	**61**	oil	9	4	1
	**62**	oil	1	1	1
	**63**	oil	2	1	1
	**64**	oil	1	1	1
	**65**	oil	5	2	1
	**66**	oil	1	1	1

lists are given, as well as details for intermediates for which the synthesis may not be obvious. In other cases, the elemental analysis and NMR data (ppm; coupling constants in hertz) are given.

3,6-Dichloro-4-(2-iodo-1,1-dimethylethyl)pyridazine (3). Anal. Found: C, 29.26; H, 2.80; N, 8.25. Calcd for $C_8H_9Cl_2IN_2$: C, 29.03; H, 2.74; N, 8.46. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.8 (2 H, s), 1.6 (6 H, s).

3,6-Dichloro-4-(2-fluoro-1,1-dimethylethyl)pyridazine (4). MS: m/z 222 (2 Cl). ^1H NMR ($CDCl_3$): 7.43 (1 H, s), 4.65 (2 H, d, J = 47), 1.53 (6 H, d, J = 2).

3,6-Dichloro-4-(1,1-dimethylpropyl)pyridazine (7). Anal. Found: C, 49.63; H, 5.33; N, 13.05. Calcd for $C_9H_{12}Cl_2N_2$: C, 49.33; H, 5.52; N, 12.79. ^1H NMR ($CDCl_3$): 7.44 (1 H, s), 2.01 (2 H, q), 1.44 (6 H, s), 0.69 (3 H, t).

3,6-Dichloro-β,β-dimethyl-4-pyridazineethanol Acetate (8). Anal. Found: C, 45.85; H, 4.36; N, 10.55. Calcd for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.65; H, 4.60; N, 10.65. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 4.4 (2 H, s), 2.0 (3 H, s), 1.6 (6 H, s).

3,6-Dichloro-β,β-dimethyl-4-pyridazinepropanenitrile (10). Anal. Found: C, 46.77; H, 4.13; N, 18.11. Calcd for $C_9H_9Cl_2N_3$: C, 46.98; H, 3.94; N, 18.26. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.0 (2 H, s), 1.6 (6 H, s).

Chloroacetic Acid, 2-(3,6-Dichloro-4-pyridazinyl)-2-methylpropyl Ester (11). Anal. Found: C, 40.47; H, 3.69; N, 9.37. Calcd for $C_{10}H_{11}Cl_3N_2O_2$: C, 40.36; H, 3.73; N, 9.41. ^1H NMR ($CDCl_3$): 7.35 (1 H, s), 4.5 (2 H, s), 3.9 (2 H, s), 1.5 (6 H, s).

3,6-Dichloro-4-(3-chloro-1,1-dimethylpropyl)pyridazine (12). Anal. Found: C, 42.76; H, 4.31; N, 10.86. Calcd for $C_9H_{11}Cl_3N_2$: C, 42.63; H, 4.37; N, 11.05. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.3 (2 H, t, J = 7), 2.5 (2 H, d, J = 7), 1.5 (6 H, s).

3,6-Dichloro-β,β-dimethyl-4-pyridazinepropionic Acid, Ethyl Ester (13). Anal. Found: C, 47.82; H, 5.37; N, 10.13. Calcd for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.67; H, 5.09; N, 10.11. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.9 (q, 2 H, J = 7), 3.1 (2 H, s), 1.5 (6 H, s), 1.1 (3 H, t, J = 7).

3,6-Dichloro-β,β-dimethyl-4-pyridazineethanol Benzoate (14). Anal. Found: C, 55.36; H, 4.19; N, 8.41. Calcd for $C_{15}H_{14}Cl_2N_2O_2$: C, 55.40; H, 4.34; N, 8.61. ^1H NMR ($CDCl_3$): 7.7 (2 H, m), 7.4 (1 H, s), 7.3 (3 H, m), 4.65 (2 H, s), 1.6 (6 H, s).

2-(3,6-Dichloro-4-pyridazinyl)-2-methylpropyl Methyl Carbonate (15). Anal. Found: C, 43.15; H, 4.36; N, 9.77. Calcd for $C_{10}H_{12}Cl_2N_2O_3$: C, 43.03; H, 4.33; N, 10.04. ^1H NMR ($CDCl_3$): 7.35 (1 H, s), 4.45 (2 H, s), 3.7 (3 H, s), 1.5 (6 H, s).

3,6-Dichloro-β,β-dimethyl-4-pyridazineethanol Phenylcarbamate (16). Anal. Found: C, 53.24; H, 4.55; N, 12.15. Calcd for $C_{15}H_{15}Cl_2N_3O_2$: C, 52.96; H, 4.44; N, 12.35. ^1H NMR ($CDCl_3$): 7.4 (1 H, s) 7.2 (5 H, m), 4.6 (2 H, s), 1.5 (6 H, s).

Phenylcarbamothioic Acid, *O*-2-(3,6-Dichloro-4-pyridazinyl)-2-methylpropyl Ester (17). Anal. Found: C, 50.33; H, 3.99; N, 11.54. Calcd for $C_{15}H_{15}Cl_2N_3OS$: C, 50.57; H, 4.24; N, 11.79. ^1H NMR ($CDCl_3$): 8.4 (NH), 7.2 (6 H, m), 4.85 (2 H, s), 1.45 (6 H, s).

3,6-Dichloro-4-[1-(dibromomethyl)-1-methylethyl]pyridazine (19). Anal. Found: C, 26.69; H, 2.16; N, 7.82. Calcd for $C_8H_8Br_2Cl_2N_2$: C, 26.48; H, 2.22; N, 7.72. ^1H NMR ($CDCl_3$): 7.45 (1 H, s), 6.85 (1 H, s), 1.8 (6 H, s).

3,6-Dichloro-4-(2-chloro-1-methylethyl)pyridazine (23). Anal. Found: C, 37.07; H, 3.04; N, 12.15. Calcd for $C_7H_7Cl_3N_2$: C, 37.28; H, 3.13; N, 12.42. ^1H NMR ($CDCl_3$): 7.45 (1 H, s), 3.7 (3 H, m), 1.45 (3 H, d, J = 7).

3,6-Dichloro-4-(1-chloro-1-methylethyl)pyridazine (24). Anal. Found: C, 37.09; H, 2.87; N, 12.14. Calcd for $C_7H_7Cl_3N_2$: C, 37.28; H, 3.13; N, 12.42. ^1H NMR ($CDCl_3$): 7.8 (1 H, s), 2.1 (6 H, s).

3,6-Dichloro-4-(2-chlorocyclohexyl)pyridazine (25). Anal. Found: C, 44.99; H, 3.93; N, 10.62. Calcd for $C_{10}H_{11}Cl_3N_2$: C, 45.23; H, 4.18; N, 10.55. ^1H NMR ($CDCl_3$): 7.3 (1 H, s), 4.6 (1 H, m), 3.3 (1 H, m), 2.2–1.4 (8 H, m).

3,6-Dichloro-4-[1-(chloromethyl)-1-methylbutyl]pyridazine (26). Anal. Found: C, 45.10; H, 4.66; N, 10.45. Calcd for $C_{10}H_{13}Cl_3N_2$: C, 44.89; H, 4.90; N, 10.47. ^1H NMR ($CDCl_3$): 7.35 (1 H, s), 4.35 (1 H, d, J = 14), 3.6 (1 H, d, J = 14), 1.55 (3 H, s), 2.4–0.8 (7 H, m).

3,6-Dichloro-4-[1-(chloromethyl)-1-ethylpropyl]pyridazine (27). Anal. Found: C, 44.86; H, 4.69; N, 10.48. Calcd for $C_{10}H_{13}Cl_3N_2$: C, 44.89; H, 4.90; N, 10.47. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 4.0 (2 H, s), 2.0 (4 H, q), 0.8 (6 H, t).

3,6-Dichloro-4-(3-chloro-2,2-dimethylpropyl)pyridazine (28). Anal. Found: C, 42.58; H, 4.17; N, 11.03. Calcd for C_9H_{11}-

Cl_3N_2: C, 42.63; H, 4.37; N, 11.05. ^1H NMR ($CDCl_3$) 7.45 (1 H, s), 3.4 (2 H, s), 2.8 (2 H, s), 1.1 (6 H, s).

3,6-Dichloro-4-(3-chloropropyl)pyridazine (29). Anal. Found: C, 37.28; H, 3.29; N, 12.40. Calcd for $C_7H_7Cl_3N_2$: C, 37.28; H, 3.13; N, 12.42. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.6 (2 H, t, J = 7), 2.9 (2 H, t, J = 7), 2.2 (2 H, m).

3,6-Dichloro-4-(4-chlorobutyl)pyridazine (30). Anal. Found: C, 39.89; H, 3.87; N, 11.61. Calcd for $C_8H_9Cl_3N_2$: C, 40.12; H, 3.79; N, 11.69. ^1H NMR ($CDCl_3$): 7.4 (1 H, s), 3.6 (2 H, t), 2.8 (2 H, t), 1.9 (4 H, m).

3-Chloro-4-(3,6-dichloro-4-pyridazinyl)-3-buten-2-one (31). Anal. Found: C, 37.99; H, 2.15; N, 10.86. Calcd for $C_8H_5Cl_3N_2O$: C, 38.21; H, 2.00; N, 11.14. ^1H NMR ($CDCl_3$): 7.9 (1 H, s), 7.6 (1 H, s), 2.6 (3 H, s).

3-Bromo-6-chloro-4-(2-chloro-1,1-dimethylethyl)pyridazine (32). Anal. Found: C, 34.06; H, 3.43; N, 9.99. Calcd for $C_8H_9BrCl_2N_2$: C, 33.84; H, 3.19; N, 9.86. ^1H NMR ($CDCl_3$): 7.45 (1 H, s), 4.1 (2 H, s), 1.6 (6 H, s), MS: m/z 282 (2 Cl). This was made as previously described from the tosylate; mp 119–121 °C. Anal. Found: C, 39.07; H, 3.28; N, 6.14. Calcd for $C_{15}H_{16}Br_2N_2O_3S$: C, 38.81; H, 3.47; N, 6.04. ^1H NMR ($CDCl_3$): 7.6 (2 H, d, J = 8), 7.45 (1 H, s), 7.3 (2 H, d, J = 8), 4.4 (2 H, s), 2.5 (3 H, s), 1.5 (6 H, s). The tosylate was made from the alcohol, which was obtained by the usual alkylation procedure, using 3,6-dibromopyridazine and 2,2-dimethyl-1,3-propanediol. The alcohol was recrystallized from toluene–hexane and obtained as white crystals, mp 140–141 °C. Anal. Found: C, 31.28; H, 3.02; N, 8.91. Calcd for $C_8H_{10}Br_2N_2O$: C, 31.00; H, 3.25; N, 9.04. ^1H NMR ($CDCl_3$): 7.7 (1 H, s), 4.0 (2 H, s), 1.5 (6 H, s).

4-(2-Chloro-1,1-dimethylethyl)-3,6-difluoropyridazine (33). Anal. Found: C, 46.73; H, 4.52; N, 13.42. Calcd for $C_8H_9ClF_2N_2$: C, 46.50; H, 4.39; N, 13.56. ^1H NMR ($CDCl_3$): 7.2 (1 H, dd, J_{6F} = 7, J_{3F} = 1), 3.8 (2 H, s), 1.5 (6 H, s). **33** was obtained in 10% yield by treatment of **1** with potassium fluoride in DMF under reflux for 80 h.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)pyridazine (34). Anal. Found: C, 46.54; H, 5.08; N, 13.82. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 8.9 (1 H, d, J = 6), 7.4 (1 H, d, J = 6), 4.0 (2 H, s), 1.6 (6 H, s).

4-(2-Chloro-1,1-dimethylethyl)pyridazine (36). Anal. Found: C, 56.10; H, 6.72; N, 16.28. Calcd for $C_8H_{11}ClN_2$: C, 56.31; H, 6.50; N, 16.42. ^1H NMR ($CDCl_3$): 9.1 (1 H, d, J = 1.5), 8.9 (1 H, dd, J_4 = 6, J_3 = 1), 7.3 (1 H, dd, J_3 = 1.5, J_6 = 6), 3.7 (2 H, s), 1.5 (6 H, s).

6-Chloro-5-(2-chloro-1,1-dimethylethyl)-3(2*H*)-pyridazinone (37). Anal. Found: C, 43.39; H, 4.32; N, 12.54. Calcd for $C_8H_{10}Cl_2N_2O$: C, 43.46; H, 4.56; N, 12.67. ^1H NMR ($CDCl_3$): 12.8 (1 H, br), 3.95 (1 H, s), 1.5 (6 H, s). **37** was obtained in 25% yield by treatment of **1** with sodium hydroxide in *tert*-butyl alcohol at 75 °C overnight.

6-Chloro-5-(2-chloro-1,1-dimethylethyl)-3-pyridazinecarbonitrile (38). Anal. Found: C, 47.07; H, 3.80; N, 18.00. Calcd for $C_9H_9Cl_2N_3$: C, 46.98; H, 3.94; N, 18.26. ^1H NMR ($CDCl_3$):7.7 (1 H, s), 4.0 (2 H, s), 1.6 (6 H, s). The starting material for this compound was made by the usual oxidative decarboxylation of pivalic acid in the presence of 3-chloro-6-pyridazinecarbonitrile and was obtained as the major component of a 70:30 mixture of isomers, eluting first from a silica gel column with 6:1 heptane/ethyl acetate; mp 118–119 °C. Anal. Found: C, 55.53; H, 4.95; N, 21.18. Calcd for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48. ^1H NMR ($CDCl_3$): 7.7 (1 H, s), 1.5 (9 H, s). We were unable to chlorinate the isomer, 6-chloro-4-(1,1-dimethylethyl)-3-pyridazinecarbonitrile, mp 121–123 °C. Anal. Found: C, 56.23; H, 5.48; N, 21.16. ^1H NMR ($CDCl_3$): 7.5 (1 H, s), 1.5 (9 H, s).

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-methylpyridazine (39). Anal. Found: C, 49.55; H, 5.79; N, 12.56. Calcd for $C_9H_{12}Cl_2N_2$: C, 49.33; H, 5.62; N, 12.78. ^1H NMR ($CDCl_3$): 7.2 (1 H, s), 4.0 (1 H, s), 2.7 (3 H, s), 1.55 (6 H, s). The starting material for this compound was the tosylate derived from the alcohol obtained by the radical alkylation of 3,6-dichloropyridazine with 2,2-dimethyl-1,3-propanediol. The position of the hydroxy-*tert*-butyl group in the alcohol was confirmed by an X-ray.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-(1,1-dimethylethyl)pyridazine (40). Anal. Found: C, 55.03; H, 6.67; N, 10.60; Cl, 27.37. Calcd for $C_{12}H_{18}Cl_2N_2$: C, 55.18; H, 6.95; N, 10.60; Cl, 27.37. ^1H NMR ($CDCl_3$): 7.47 (1 H, s), 6.27 (2 H, s), 1.58 (6 H, s), 1.45 (9 H, s).

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-(ethylthio)pyridazine (41). Anal. Found: C, 45.45; H, 5.45; N, 10.65. Calcd for $C_{10}H_{14}Cl_2N_2S$: C, 45.29; H, 5.32; N, 10.56. ^1H NMR ($CDCl_3$): 7.1 (1 H, s), 3.9 (2 H, s), 3.3 (2 H, q, J = 7), 1.5 (6 H, s), 1.4 (3 H, t, J = 7). **41** was obtained in 35% yield by treatment of **1** with the sodium salt of ethanethiol in ethanol at room temperature for 15 h.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-(phenylthio)pyridazine (42). Anal. Found: C, 53.87; H, 4.47; N, 8.68. Calcd for $C_{14}H_{14}Cl_2N_2S$: C, 53.68; H, 4.50; N, 8.94. ^1H NMR ($CDCl_3$): 7.4 (5 H, m), 6.9 (1 H, s), 3.8 (2 H, s), 1.4 (6 H, s). **42** was obtained in 50% yield by treatment of **1** with the sodium salt of thiophenol in ethanol at 40 °C for 1 h.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-(phenylsulfonyl)pyridazine (43). Anal. Found: C, 48.75; H, 4.23; N, 7.83. Calcd for $C_{14}H_{14}Cl_2N_2O_2S$: C, 48.71; H, 4.09; N, 8.11. ^1H NMR ($CDCl_3$): 8.1 (1 H, s), 8.0 (2 H, m), 7.5 (3 H, m), 4.0 (2 H, s), 1.6 (6 H, s).

6-Chloro-5-(2-chloro-1,1-dimethylethyl)-*N*,*N*-dimethyl-3-pyridazinamine (44). Anal. Found: C, 48.59; H, 6.19; N, 16.97. Calcd for $C_{10}H_{15}Cl_2N_3$: C, 48.40; H, 6.09; N, 16.93. ^1H NMR ($CDCl_3$): 6.65 (1 H, s), 3.95 (2 H, s), 3.1 (6 H, s), 1.5 (6 H, s). **44** was obtained in 40% yield by treatment of **1** with dimethylamine in DMF for 2 h at 55 °C.

6-Chloro-5-(2-chloro-1,1-dimethylethyl)-*N*-ethyl-3-pyridazinamine (45). Anal. Found: C, 48.59; H, 6.36; N, 16.69. Calcd for $C_{10}H_{15}Cl_2N_3$: C, 48.40; H, 6.09; N, 16.93. ^1H NMR ($CDCl_3$): 6.6 (1 H, s), 5.0 (1 H, br), 4.0 (2 H, s), 3.4 (2 H, q, J = 7), 1.5 (6 H, s), 1.3 (3 H, t, J = 7). **45** was obtained in 25% yield by treatment of **1** with ethylamine in DMF for 16 h at 55 °C.

6-Chloro-5-(2-chloro-1,1-dimethylethyl)-*N*-phenyl-3-pyridazinamine (46). Anal. Found: C, 57.04; H, 5.12; N, 13.91. Calcd for $C_{14}H_{15}Cl_2N_3$: C, 56.77; H, 5.10; N, 14.19. ^1H NMR ($CDCl_3$–DMSO-d_6): 7.6 (2 H, m), 7.1 (3 H, m), 7.1 (1 H, s), 4.0 (2 H, s), 1.5 (6 H, s). **46** was obtained in 45% yield by treatment of **1** with aniline in DMF for 72 h at reflux.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-methoxypyridazine (47). Anal. Found: C, 46.22; H, 5.23; N, 11.90. Calcd for $C_9H_{12}Cl_2N_2O$: C, 45.98; H, 5.14; N, 11.90. ^1H NMR ($CDCl_3$): 6.9 (1 H, s), 4.1 (3 H, s), 4.0 (2 H, s), 1.5 (6 H, s). **47** was obtained in 30% yield by treatment of **1** with sodium methoxide in methanol for 16 h at 25 °C.

3-Chloro-4-(2-chloro-1,1-dimethylethyl)-6-(4-chlorophenoxy)pyridazine (48). Anal. Found: C, 50.57; H, 4.18; N, 8.69. Calcd for $C_{14}H_{13}Cl_3N_2O$: C, 50.71; H, 3.95; N, 8.45. ^1H NMR ($CDCl_3$): 7.2 (2 H, d, J = 6), 7.05 (1 H, s), 7.0 (2 H, d, J = 6), 3.95 (2 H, s), 1.6 (6 H, s). **48** was obtained in 50% yield by treatment of **1** with the sodium salt of 4-chlorophenol in DMF for 1.5 h at reflux.

4-(2-Chloro-1,1-dimethylethyl)-3,6-dimethylpyridazine (49). Anal. Found: C, 60.74; H, 7.40; N, 14.02. Calcd for $C_{10}H_{15}ClN_2$: C, 60.45; H, 7.61; N, 14.10. ^1H NMR ($CDCl_3$): 7.1 (1 H, s), 3.8 (2 H, s), 2.8 (3 H, s), 2.6 (3 H, s), 1.5 (6 H, s). **49** was obtained by lithium chloride displacement of the tosylate. The tosylate was characterized by the following analysis. Anal. Found: C, 60.66; H, 6.53; N, 8.32. Calcd for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38.

4-(2-Chloro-1,1-dimethylethyl)-3(2*H*)-pyridazinone (50). Anal. Found: C, 51.34; H, 5.87; N, 15.25. Calcd for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01. ^1H NMR ($CDCl_3$): 12.7 (1 H, br), 7.7 (1 H, d, J = 4), 7.1 (1 H, d, J = 4), 4.1 (2 H, s), 1.4 (6 H, s).

4-(2-Chloro-1,1-dimethylethyl)-6-nitro-3(2*H*)-pyridazinone (51). Anal. Found: C, 41.78; H, 4.47; N, 17.91. Calcd for $C_8H_{10}ClN_3O_3$: C, 41.48; H, 4.35; N, 18.14. ^1H NMR ($CDCl_3$): 12.7 (1 H, br), 8.1 (1 H, s), 4.1 (2 H, s), 1.5 (6 H, s). **51** was obtained in 20% yield by treatment of **50** with 90% fuming nitric acid in concentrated sulfuric acid at 80–90 °C for 4 h.

3-Chloro-6-(2-chloro-1,1-dimethylethyl)pyridazine (52). Anal. Found: C, 46.78; H, 4.73; N, 13.40. Calcd for C_8H_{10}-

Cl_2N_2: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 7.5 (2 H, s), 3.9 (2 H, s), 1.5 (6 H, s). **52** was made by photochemical chlorination of the known 3-chloro-6-(1,1-dimethylethyl)pyridazine (Abdulla, 1983).

4,6-Dichloro-3-(2-chloro-1,1-dimethylethyl)pyridazine (53). Anal. Found: C, 40.13; H, 3.98; N, 11.58. Calcd for $C_8H_9Cl_3N_2$: C, 40.12; H, 3.79; N, 11.69. ^1H NMR ($CDCl_3$): 7.6 (1 H, s), 3.9 (2 H, s), 1.5 (6 H, s). The starting materials for **53** and **54** were obtained as a mixture upon chlorination of 3-chloro-6-(1,1-dimethylethyl)pyridazine with sulfuryl chloride. Elution from a silica gel column with hexane/methylene chloride gave first 3,4-dichloro-6-(1,1-dimethylethyl)pyridazine as an oil. Anal. Found: C, 46.80; H, 4.77; N, 13.71. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 7.52 (1 H, s), 1.57 (9 H, s). The isomer, 4,6-dichloro-3-(1,1-dimethylethyl)pyridazine, was then obtained as white crystals from hexane; mp 70–71 °C. Anal. Found: C, 46.97; H, 4.75; N, 13.45. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 7.60 (1 H, s), 1.45 (9 H, s). NOE studies where the *tert*-butyl peak was irradiated resulted in a much greater effect for the 3,4-dichloro isomer.

3,4-Dichloro-6-(2-chloro-1,1-dimethylethyl)pyridazine (54). Anal. Found: C, 39.91; H, 3.92; N, 11.75. Calcd for $C_8H_9Cl_3N_2$: C, 40.12; H, 3.79; N, 11.69. ^1H NMR ($CDCl_3$): 7.5 (1 H, s), 4.1 (2 H, s), 1.7 (6 H, s).

2-Chloro-4-(2-chloro-1,1-dimethylethyl)pyridine (55). Anal. Found: C, 52.75; H, 5.65; N, 6.98; Cl, 35.01. Calcd for $C_9H_{11}Cl_2N$: C, 52.96; H, 5.43; N, 6.98; Cl, 34.74. ^1H NMR ($CDCl_3$): 8.4 (1 H, d, J = 6), 7.4 (1 H, s), 7.3 (1 H, d, J = 6), 3.6 (2 H, s), 1.4 (6 H, s). The *N*-oxide from which **55** was made was obtained by treating 4-(2-chloro-1,1-dimethylethyl)pyridine (6.79 g, 0.04 mol) in acetic acid (24 mL) with hydrogen peroxide (6 mL of 30%) for 7 h at 65–75 °C. The product was taken into chloroform and chromatographed over silica gel, eluting with methanol to obtain white crystals: 2.0 g, 25%; mp 147–149 °C. Anal. Found: C, 57.99; H, 6.33; N, 7.43. Calcd for $C_9H_{12}ClNO$: C, 58.23; H, 6.52; N, 7.54. ^1H NMR (DMSO-d_6): 8.2 (2 H, d, J = 6), 7.46 (2 H, d, J = 6), 3.87 (2 H, s), 1.4 (6 H, s).

2,5-Dichloro-4-(2-chloro-1,1-dimethylethyl)pyridine (56). Anal. Found: C, 45.56; H, 4.29; N, 5.86. Calcd for $C_9H_{10}Cl_3N$: C, 45.32; H, 4.23; N, 5.87. ^1H NMR ($CDCl_3$): 8.3 (1 H, s), 7.3 (1 H, s), 3.9 (2 H, s), 1.5 (6 H, s). **56** was obtained by chlorination with trichloroisocyanuric acid (benzoyl peroxide catalyst) of 2,5-dichloro-4-(1,1-dimethylethyl)pyridine. Anal. Found: C, 52.82; H, 5.57; N, 6.68. Calcd for $C_9H_{11}Cl_2N$: C, 52.96; H, 5.43; N, 6.86. Mp: 43–44 °C. ^1H NMR ($CDCl_3$): 8.25 (1 H, s), 7.3 (1 H, s), 1.5 (9 H, s). This dichloropyridine was made by cuprous chloride treatment of the diazonium salt of 5-chloro-4-(1,1-dimethylethyl)-2-pyridinamine: Anal. Found: C, 58.77; H, 7.14; N, 14.89. Calcd for $C_9H_{13}ClN_2$: C, 58.54; H, 7.10; N, 15.17. Mp: 123–5 °C. ^1H NMR ($CDCl_3$): 7.9 (1 H, s), 6.5 (1 H, s), 4.4 (2 H, br), 1.35 (9 H, s). This amine was the major product of chlorination in sulfuric acid (Kress et al., 1976) of 4-(1,1-dimethylethyl)-2-pyridinamine (Reilly Chemical).

2-Chloro-5-(2-chloro-1,1-dimethylethyl)pyrazine (57). Anal. Found: C, 46.55; H, 4.88; N, 13.71. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 8.57 (1 H, d, J = 1.47), 8.39 (1 H, d, J = 1.47), 3.8 (2 H, s), 1.5 (6 H, s). Irradiation of the peak at 8.57 ppm resulted in a strong NOE response on the peak at 1.5 ppm.

3,5-Dichloro-2-(2-chloro-1,1-dimethylethyl)pyrazine (58). Anal. Found: C, 40.29; H, 3.81; N, 11.52. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70. ^1H NMR ($CDCl_3$): 8.45 (1 H, s), 4.05 (2 H, s), 1.6 (6 H, s).

2-Chloro-3-(2-chloro-1,1-dimethylethyl)pyrazine (59). Anal. Found: C, 46.90; H, 5.18; N, 13.81. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 8.45 (1 H, d, J = 2.21), 8.24 (1 H, d, J = 2.21), 4.1 (2 H, s), 1.6 (6 H, s).

2,5-Dichloro-3-(2-chloro-1,1-dimethylethyl)pyrazine (60). Anal. Found: C, 40.13; H, 4.05; N, 11.55. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70. ^1H NMR ($CDCl_3$): 8.48 (1 H, s), 4.06 (1 H, s), 1.59 (6 H, s).

2,4,6-Trichloro-5-(2-chloro-1,1-dimethylethyl)pyrimidine (61). Anal. Found: C, 34.88; H, 3.06; N, 10.45. Calcd for $C_8H_8Cl_4N_2$: C, 35.07; H, 2.94; N, 10.22. ^1H NMR ($CDCl_3$): 4.2 (2 H, s), 1.8 (6 H, s). **61** was obtained by the photochemical chlorination with *N*-chlorosuccinimide of 2,4,6-trichloro-5-(1,1-dimethylethyl)pyrimidine. Anal. Found: C, 40.32; H, 3.63; N, 11.52. Calcd for $C_8H_9Cl_3N_2$: C, 40.12; H, 3.79; N, 11.69. Mp: 48–50 °C. ^1H NMR ($CDCl_3$): 1.67. ^{13}C NMR ($CDCl_3$): 162.3, 154.9, 137.4, 77.5, 77.0, 76.5, 36.7, 30.9. This pyrimidine was obtained in 65% yield from 5-(1,1-dimethylethyl)barbituric acid by treatment with phosphorus oxychloride in the presence of *N*,*N*-diethylaniline.

2-Chloro-4-(2-chloro-1,1-dimethylethyl)pyrimidine (62). Anal. Found: C, 46.61; H, 4.79; N, 13.67. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 8.57 (1 H, d, J = 5), 7.27 (1 H, d, J = 5), 3.81 (2 H, s), 1.45 (6 H, s).

4,6-Dichloro-2-(2-chloro-1,1-dimethylethyl)pyrimidine (63). Anal. Found: C, 40.18; H, 3.78; N, 11.79. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70. ^1H NMR ($CDCl_3$): 7.25 (1 H, s), 3.90 (2 H, s), 1.47 (6 H, s).

2,4-Dichloro-6-(2-chloro-1,1-dimethylethyl)pyrimidine (64). Anal. Found: C, 39.90; H, 3.61; N, 11.49. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70. ^1H NMR ($CDCl_3$): 7.29 (1 H, s), 3.80 (2 H, s), 1.44 (6 H, s).

4,6-Dichloro-5-(2-chloro-1,1-dimethylethyl)pyrimidine (65). Anal. Found: C, 40.02; H, 3.85; N, 11.44. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70. ^1H NMR ($CDCl_3$): 8.56 (1 H, s), 4.17 (2 H, s), 1.79 (6 H, s). This compound was derived from 4,6-dichloro-5-(1,1-dimethylethyl)pyrimidine; mp 42–43 °C. Anal. Found: C, 46.72; H, 4.70; N, 13.44. Calcd for $C_8H_{10}Cl_2N_2$: C, 46.85; H, 4.91; N, 13.66. ^1H NMR ($CDCl_3$): 8.5 (1 H, s), 1.7 (9 H, s). This dichloropyrimidine was derived from phosphorus oxychloride treatment of 4,6-dihydroxy-5-(1,1-dimethylethyl)pyrimidine; mp 299–300 °C dec. Anal. Found: C, 56.86; H, 7.14; N, 16.37. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. ^1H NMR (DMSO-d_6): 11.35 (2 H, br), 7.8 (1 H, s), 1.3 (9 H, s). This dihydroxypyrimidine was made by the condensation of *tert*-butylmalonic ester with formamidine in ethanol with 4 equiv of sodium ethoxide by heating under reflux for 5 h.

2,5-Dichloro-4-(2-chloro-1,1-dimethylethyl)pyrimidine (66). Anal. Found: C, 40.40; H, 3.60; N, 11.45; Cl, 44.66. Calcd for $C_8H_9Cl_3N_2$: C, 40.11; H, 3.79; N, 11.70; Cl, 44.40. ^1H NMR ($CDCl_3$): 8.49 (1 H, s), 4.04 (2 H, s), 1.57 (6 H, s).

RESULTS AND DISCUSSION

It is evident from the screening data in Table I that a halogen is the only group resulting in significant activity when used to substitute the *tert*-butyl function in the 4-position of the pyridazine ring. Compounds **1** and **2** were of approximately equal activity in all the tests run. This limited potential for variation of substituents while retaining activity would seem to be due to a combination of several factors. Compound **7** suggests it is more than a steric effect, since a methyl group should approximate the chlorine. One might expect compound **10** to approximate both the electronic and the steric influences of compound **1**, yet it is nearly inactive. Compounds **8**, **9**, **11**, **14**, and **15** suggest that the biological activity is not dependent upon having a leaving group as a substituent.

The substitution of another chlorine on the same carbon (**18**) causes a loss of activity as shown in Table II, but placing the second chlorine on another carbon (**20**) causes only a slight decrease of activity. The effect of adding a third chlorine also depends on whether the addition is to a carbon that already bears a chlorine or not, as seen with **21** and **22**.

Table III shows that activity is associated with the chlorine two carbons removed from the pyridazine ring, and also that the chloro-*tert*-butyl group is the optimal size. Compound **24** with the chlorine one carbon removed from the ring is nearly inactive, while compounds **23** and **25–27** with the chlorine two carbons removed from the ring are active at a reduced level. Removing the chlorine one carbon further from the pyridazine as in **12** and **28–30** virtually eliminates activity.

Table VI. Foliar Systemic Activity of Substituted Pyridazines against Downy Mildew of Squash

no.	rate, ppm	control rating[a] A	B	C[b]
1	400	9	9	2
	100	9	9	1
2	400	9	9	5
	100	8	9	2
18	400	1	1	1
	100	1	1	1
20	400	7	9	1
	100	2	6	1
21	400	2	7	1
	100	1	1	1
22	400	2	3	1
	100	1	1	1
38	400	1	2	1
39	400	8	9	1
49	400	9	9	1
67	400	1	5	1
	100	1	1	1
68	400	1	2	1
	100	1	1	1

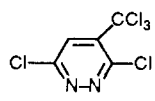
[a] Control rating on a 1–9 scale as for previous tables. [b] A–C are leaf locations on band-sprayed plant. A = area toward the tip portion of the leaf. B = band area sprayed. C = area toward the stem or basal portion of the leaf.

It may be seen in Table IV that changes in the 3- and/or 6-positions almost invariably reduce activity. Changes were made most readily in the 6-position, and most of the new substituents caused a near-complete loss of activity, with the exceptions of cyano (**38**) and methyl (**39** and **49**). The activity of even these three compounds was greatly reduced over that of **1**. We cannot fully evaluate the effect of replacing the chlorine in the 3-position, since only two such compounds were made (**32** and **35**).

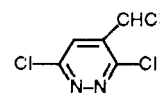
The specificity of the ring system and the arrangement of groups relative to the ring nitrogens may be observed in Table V. Exchanging the alkyl group with a chlorine as in **53** results in an inactive compound. Removal of one nitrogen to give the pyridine **56** also gives an inactive compound. The isomer where the chloro-*tert*-butyl would be on the 3-position of the pyridine was not made. The other dichlorodiazine isomers **58**, **60**, and **63–66** are all inactive. Only trichloropyrimidine **61** showed a significant measure of activity at 400 ppm. Removing the 2-chlorine to give **65** reduced even this activity.

The active members of this series of compounds demonstrate selective toxicity between higher plants and fungi but are very specific for controlling the taxonomic groups of fungi known as *Oomycetes*. Thus, compound **1** shows good control of downy mildew on grapes, late-blight complex in potatoes and tomatoes, tobacco blue mold, and tobacco black shank.

Not all members of this series of compounds are systemic in the plant. Table VI demonstrates some of the structural changes affecting mobility within plants and presents challenges to our understanding of this process. Compounds **67** and **68** are compounds previously patented (Bublitz, 1975). These compounds have a broader fungicidal spectrum than our compounds and seem to be fumigants.



67



68

Compounds **38**, **67**, and **68**, although they show good control when the innoculation is on the same side of the leaf to which the compounds are applied, do not show translaminar movement. The results for **67** and **68** may reflect volatilization from the leaf since inoculation was 24 h after treatment. Compounds **1**, **2**, **39**, and **49** show both translaminar movement and good mobility toward the tip of the leaf. Concentrations of **1** or **2** of 1000 ppm also show control in the C portion of the leaf.

This systemic activity also extends to soil drench studies. When **1** and **2** are applied as a soil drench at 20 ppm, 100% control of squash downy mildew is observed. Compounds **67** and **68** show no control in the same test. When these same compounds are applied at 0.5 lb/acre in the tobacco black shank soil drench test, 100% control is observed.

ACKNOWLEDGMENT

We gratefully acknowledge G. E. Babbitt for spectral data, and especially for NOE studies to enable structural assignments. We acknowledge Dr. Noel Jones and John Swartzendruber for X-ray data.

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Received for review July 17, 1989. Accepted October 9, 1989.

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dimethylethyl)-2-diazopyridine, 124420-76-4; 5-(1,1-dimethylethyl)-2,4,6-trichloropyrimidine, 124420-77-5; 4,6-dichloro-5-(1,1-dimethylethyl)pyrimidine, 124420-78-6; 4,6-dihydroxy-5-(1,1-dimethylethyl)pyrimidine, 124420-79-7.

Development of N,O-Disubstituted Hydroxylamines and N,N-Disubstituted Amines as Insect Juvenile Hormone Mimetics and the Role of the Nitrogenous Function for Activity

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Insect juvenile hormone (JH) active N,O-disubstituted hydroxylamines were developed to examine the role of the nitrogenous function for high activity. They are *O*-alkyl-*N*-[(4-phenoxyphenoxy) and (4-benzylphenoxy)alkyl]hydroxylamines and reversely substituted *N*-alkyl-*O*-[(4-phenoxyphenoxy)-alkyl]hydroxylamines. The activity against *Culex pipiens* of the most potent member of each class was as high as that of the compounds known so far as the most active of JH mimics. When the overall length of the molecules is kept at the optimum, about 21 Å, suggested in our earlier works, the compounds having a hydroxylamino nitrogen atom, rather than the oxygen atom, at the δ-position from the central phenoxy oxygen atom or at the 4-position (about 4.6 Å) from the alkyl end showed about 10 times higher activity than those having the nitrogen atom at the position one atom missed the point. The corresponding amine compounds also prepared showed this more clearly, but their activity was considerably lower than that of the hydroxylamines. The lower potency of the amines with $pK_a \approx 10$ was attributed to their quarternization at physiological pH, preventing going to or binding with the action site.

In our developmental studies on a series of insect juvenile hormone (JH) mimetic compounds, (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkanaldoximes (Niwa et al., 1988), (4-alkoxyphenoxy)- and (4-alkylphenoxy)alkanaldoximes (Hayashi et al., 1989), and (4-phenoxyphenoxy)- and (4-benzylphenoxy)alkyl alkyl ethers (Niwa et al., 1989), we found that the positions of the oxime and ether functions in a molecule are important for high activity. The positional effect has been clearly specified in the ether series of compounds to be at the δ-position from the common phenoxy oxygen atom; the activity against *Culex pipiens* of (phenoxyphenoxy)- and (benzylphenoxy)propyl propyl ethers was more than 10 times higher than that of the corresponding ethyl butyl and butyl ethyl ethers. This is illustrated in Figure 1, where the shadowing on the structure shows the pertinent δ-position. Comparison of the oximes with these ethers suggests that the activity is highest when a nitrogen atom, rather than oxygen atom, is located at the δ-position in the oxime molecules; in other words, the point of interaction with the receptor is more favorable with nitrogen. This situation is also shown in Figure 1; 3-(4-benzylphenoxy)propionaldoxime *O*-isopropyl ether, a δ-nitrogen compound for example, is about 10 times more active than the corresponding δ-oxygen compound.

This study was done to examine this in more detail, and the first thing done was to change the sp^2 nitrogen atom in the oximes to the sp^3 type. This led us to develop a new class of highly active JH mimics, *O*-alkyl-*N*-[(4-phenoxyphenoxy) and (4-benzylphenoxy)alkyl]hydroxylamines. The optimization of the structure gave *O*-isopropyl-*N*-[3-[4-(3-methylphenoxy)phenoxy]propyl]hydroxylamine (**9**); the activity against *C. pipiens* was as high as that of our previous propionaldoxime (Niwa et al., 1988; Hayashi et al., 1989) and propyl ether (Niwa et al., 1989) types of compounds. Again in this series of compounds, those with a nitrogen atom at the δ-position were found to be more potent than the corresponding δ-oxygen compounds. The situation was the same when the hydroxylamine function was built in a molecule in the reverse way, and the optimized member, *N*-isobutyl-*O*-[2-[4-(3-methylphenoxy)phenoxy]ethyl]hydroxylamine (**16**), had activity as high as that of above-mentioned oximes and ethers, constituting another new class of highly active JH mimics.

To examine the nitrogen effect more simply and straightforwardly, we finally prepared *N*-alkyl-*N*-(4-phenoxyphenoxy)alkylamines. Their activity was, against expectation, far poorer than that of the corresponding hydroxylamines and also ethers, and this was found to be attributable to the quarternization of the amine function at physiological pH. The generic formulaes of the sets of compounds studied here are shown in Figure 2.

EXPERIMENTAL SECTION

^1H NMR spectra were obtained in $CDCl_3$ on a JEOL 60 spectrometer with tetramethylsilane as the internal reference.

4-Methoxy-3′-methylbenzophenone. A solution of 3-methylbenzoyl chloride (5.6 g, 36.2 mmol) in carbon tetrachloride (10 mL) was added dropwise to 15 mL of carbon tetrachloride containing 3.0 g (27.8 mmol) of anisole and 5.0 g (37.5 mmol) of $AlCl_3$ at ice bath temperature. The mixture was stirred for 3 h at room temperature, poured into water, and treated with *n*-hexane. The organic layer was washed with 2 N NaOH and water, dried over $MgSO_4$, and concentrated under reduced pres-

0021-8561/90/1438-0514$02.50/0