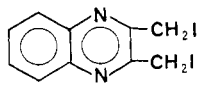
Fungicidal Activity of Halomethylquinoxalines

John J. Krajewski, Phillip J. Kotz, James T. Traxler, Samuel S. Ristich,[1] and Clarence W. Huffman*

Quinoxalines with one or more haloalkyl groups were prepared and evaluated as foliar fungicides. In greenhouse tests, some of these compounds were very active against tomato early and late blights, cucumber anthracnose, bean mildew, apple scab, and rice blast. The highest antifungal activity was contributed by 2,3-bis(iodomethyl) and 2,3-bis(bromomethyl) groups on the quinoxaline nucleus. This activity in some cases was eliminated by the presence of other groups on the carbocyclic portion of the quinoxaline molecule. Some 2-bromomethyl and 2-iodomethylquinoxalines also showed high activity.

Although many organic fungicides have come into use over the last 25 years (McCallan, 1967), there is a demand for more active and persistent materials which will control more than one disease. We have found that certain halomethylquinoxalines have activity against many fungi, including rice blast, early and late blights, mildew, anthracnose, and apple scab. Table I lists the antifungal activity of the various substituted quinoxalines in terms of an approximate ED_{90} for each fungus tested. These data indicated that two halomethyl groups in the 2,3 positions were necessary for the highest activity (**17**, **20**, **33**). Compound **33** is 2,3-bis(iodomethyl)quinoxaline.



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Additional substituents on the quinoxaline nucleus did not increase (**20** *vs.* **21**, **24**, **25**, **26**, and **33** *vs.* **36**) or eliminated (**23**, **27**, **31**) antifungal activity. Chlorine substituents in the carbocyclic ring reduced activity (**20** *vs.* **22**, **23**, and **33** *vs.* **34** and **35**), which follows the general pattern noted for other fungicides. Very specific types of halogen substitution were required for high activity. Either one or two monohalomethyl groups was essential. Dihalomethyl groups made the compounds inactive or only slightly active (**6**, **7**, **14**, **18**, **19**, **32**). The only secondary alkyl chloride listed (**38**) was inactive. Monohalomethyl compounds were very active if the halogen was bromine or iodine, but inactive if the halogen was 2-chloromethyl (**3**, **13**). These monohalomethyl quinoxalines also required a halogen substituent on the heterocyclic ring for high activity (**4** *vs.* **15**, **8** and **9** *vs.* **16**).

The residual activity of these compounds under greenhouse conditions generally was less than that for Maneb (manganous ethylene-1,2-bisdithiocarbamate) or Daconil (tetrachloroisophthalonitrile). At 100 ppm, compounds **20**, **21**, **26**, **28**, and **33** were approximately as effective as Maneb or Daconil against early blight initially. After 4 to 7 days of weathering, these quinoxalines did not protect plants from early blight as effectively as Maneb or Daconil. On infection 2 days after treatment, **33** was approximately as effective as Daconil and was slightly more effective than **20** after 4 days of weathering. These ratings were shown to be somewhat dependent upon method of application; *e.g.*, wettable powder (WP) formulations usually were more persistent than formulations made from acetone-surfactant dispersions. A number of the compounds tested were more active than Glyodin (2-heptadecylimidazoline acetate) against apple scab (**4**, **8**, **9**, **22**, **24**, **25**, **26**, **28**, and **29**). In subsequent apple scab tests **26** and **28** controlled this disease as well as Cyprex (*n*-dodecylguanidine acetate).

Less complete data are available for the residual activity of halomethylquinoxalines against other fungal diseases, but for rice blast residual activity of **20**, **21**, and **28** resembled that indicated above for early blights after 7 days of greenhouse weathering. Against late blights, after the seventh day of weathering, **20** WP and **33** WP were more effective than Daconil WP and Daconil EC (emulsifiable concentrate). The relatively poor residual activity may reflect photochemical degradation, as shown by preliminary experiments with **20** in the experimental section.

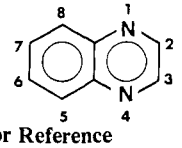
On a weight basis, the antifungal activity of the 2,3-bis(halomethyl) groups is about the same for Br and I, and much less for Cl. This factor is of importance for commercial use because bromine costs less than iodine. However, on a molar basis the iodo compounds rate best. Comparative molecular weights are: **33** iodo (MW 410), **20** bromo (MW 316), and **17** chloro (MW 228). It was quite surprising to find the chloro compound **17** much less active than the bromo **20** and iodo **33** compounds, because the present successful commercial fungicides often contain chlorine, while none have bromine or iodine substituents. A reviewer noted that the iodo (**33**) and bromo (**20**) compounds may have the optimum lipophilic solubility for toxicity to fungi, while the chloro (**17**) may have an undesirable hydrophobicity. A measurement of Hansch partition coefficients might corroborate this view (Fujita *et al.*, 1964).

If the halomethylquinoxalines were completely aromatic, one would expect the chloromethylquinoxalines to be too reactive to function as effective fungicides. The bromomethylquinoxalines and iodomethylquinoxalines would be even more reactive. Consequently, the unexpected stability and fungicidal activity must be explained.

The chemical reactivity of the halogens in 2-halomethylquinoxalines resembles that found by Baker (1932a) for the reaction of phenacyl halides with excess aniline in "90%" aqueous ethanol (*e.g.*, reaction rates for Cl:Br:I = 1.0:9.7:9.9). Very similar data have been obtained (Baker, 1932b) for the reaction of benzyl halides under the same conditions. We consider the 2-halomethylquinoxalines as electronic analogs of the phenacyl halides because of their structural similarity to 2-bromomethylquinoline, which has been shown by Brown *et al.* (1953) to be formed in a manner analogous to the acid-catalyzed α-bromination of methyl ketones in acetic acid

International Minerals & Chemical Corp., Growth Sciences Center, Libertyville, Ill. 60048
[1] Boyce Thompson Institute for Plant Research, 1086 N. Broadway, Yonkers, N.Y. 10701

Table I. Antifungal Activity of Substituted Quinoxalines



Compound	Substituents 2	3	other	ED_{90}[a] in ppm: Early Blight[b]	Late Blight[c]	Cucumber Anthracnose[d]	Bean Mildew[e]	Rice Blast[f]	Apple Scab[g]	Source or Reference
Maneb[h]	...	...	...	50	30	30	...	90		DuPont
Daconil[i]	...	...	...	80	40	20	...	30		Diamond Shamrock
Karathane[j]	...	...	...	...	...	...	10	...		Rohm & Haas
Glyodin[k]									20	
1	Cl	Cl	6Cl	I	N	I	N	N	100	Aldrich Chem.
2	CH_3	Cl	...	I	N	I	N	N	100	Aldrich Chem.
3	CH_2Cl	Cl	...	I		I	I			Table II
4	CH_2Br	Cl	...	100		30			4	Table II
5	CH_2Br	...	6Cl	I						Table II
6	$CHBr_2$	...	...	I			I			Elina (1959)
7	$CHBr_2$	Cl	...	250		130	I		100	Table II
8	CH_2I	Cl	...	60		50	I		4	Table II
9	CH_2I	...	6Cl	90		>100	I		4	Table II
10	CH_3	CH_3	...	I	N	I	N	N		Gabriel and Sonn (1907)
11	CH_3	CH_3	$6NO_2$	I	N	I	N	N		Landquist and Stacey (1953)
12	CH_3	CH_3	$5NO_2$, 7Cl	I	N	I	I	N		Gillespie *et al.* (1960)
13	CH_2Cl	CH_3	...	I	N	I	I	N		Arbuzov and Zoroastrova (1966)
14	$CHCl_2$	CH_3	...	I	N	I	N	N		Table II
15	CH_2Br	CH_3	...	I[l]	N	130	I	N		Simon *et al.* (1965)
16	CH_2I	CH_3	...	200	N	90	I	N	90	Table II
17	CH_2Cl	CH_2Cl	...	250	>100	I	N	N	I	Ahmad *et al.* (1966)
18	$CHCl_2$	CH_2Cl	...	I	N	250	250	N		Table II
19	$CHCl_2$	$CHCl_2$	...	I	N	I	250	N	90	Table II
20	CH_2Br	CH_2Br	...	70	50	30	>100	50		Aldrich Chem.
21	CH_2Br	CH_2Br	6Cl	70	40	20	N	20	10	Moriconi and Fritsch (1965)
22	CH_2Br	CH_2Br	6, $7Cl_2$	250	N	20	I	N	4	Moriconi and Fritsch (1965)
23	CH_2Br	CH_2Br	5, 6, 7, $8Cl_4$	I	N	N	I	N		Table II
24	CH_2Br	CH_2Br	$6NO_2$	200	N	I	I	N	4	Table II
25	CH_2Br	CH_2Br	$5NO_2$, 7Cl	200	N	I	I	N	4	Table II
26	CH_2Br	CH_2Br	$6OCH_3$	40	50	20	I	150	4	Table II
27	CH_2Br	CH_2Br	6, 7(OCH_2O)	I						Table II
28	CH_2Br	CH_2Br	$6CH_3$	50	40	20	250	80	4	Moriconi and Fritsch (1965)
29	CH_2Br	CH_2Br	$6CF_3$	I	N	250	I	N	4	Table II
30	CH_2Br	CH_2Br	6, 7(CH_3)$_2$	250	N	I	200	N	20	Moriconi and Fritsch (1965)
31	CH_2Br	CH_2Br	$6CO_2H$	I		I	I			Table II
32	$CHBr_2$	$CHBr_2$	...	I	N	I	N	N	90	Bennett and Willis (1928)
33	CH_2I	CH_2I	...	50	90	20	I	20	20	Wegmann and Dahn (1946)
34	CH_2I	CH_2I	6Cl	80	N	70	I	N	100	Moriconi and Fritsch (1965)
35	CH_2I	CH_2I	6, $7Cl_2$	I		>100	I		20	Moriconi and Fritsch (1965)
36	CH_2I	CH_2I	6OMe	I		>100	I		20	Table II
37	CH_2I	CH_2I	$6CF_3$	I		I	50			Table II
38	$CH(Br)C_2H_5$	CH_3	...[m]	I		I	I			Table II

[a] Approximate ED_{90} in ppm as the average of several tests. I = inactive (ED_{90} >250 ppm), N = not tested. [b] *Alternaria solani*. [c] *Phytophthora infestans*. [d] *Colletotrichum lagenarium*. [e] *Erysiphe polygone*. [f] *Piricularia oryzae*. [g] *Venturia inaequalis*. [h] Manganous ethylene-bis(dithiocarbamate). [i] Tetrachloroisophthalonitrile. [j] 2,4-Dinitro-6-(1-heptylmethyl)phenyl crotonate. [k] 2-Heptadecylimidazoline acetate. [l] Some activity, but phytotoxic at 250 ppm. [m] Submitted as HBr salt.

(Zucker and Hammett, 1939). Thus, we found that methylquinoxalines are halogenated successfully by iodine monochloride in acetic acid/sodium acetate (see methods C and E, Experimental), but not with NBS under a variety of experimental conditions.

Although the 2-halomethylquinoxalines appear to be electronic analogs of halomethyl ketones, the overall reactivity of the halogens, based on incidental comparisons of stability (*e.g.*, to hydrolyzing conditions), is much lower than that exhibited by the phenacyl halides. It is possible that the stability of the 2-halomethylquinoxalines is a result of a decrease in the electrophilicity of the halomethyl carbon atoms caused by the ring nitrogens. Thus, for example, quinaldine will not condense with benzaldehyde in the presence of piperidine, while quinaldine ethiodide does react (Mills and Raper, 1925), indicating the facilitated proton release from α-carbon as a result of the fixed positive charge on nitrogen. Similarly, lepidine cannot be ω-brominated, while lepidine methiodide brominates smoothly in aqueous sodium acetate (Brown *et al.*, 1951).

EXPERIMENTAL

Synthesis. The procedures A–F given below outline the techniques used to make the compounds listed in Table II. The reagents were purchased from Aldrich Chemical Company, Matheson, Coleman and Bell, or Distillation Products Industries (Eastman), and were used as received. All melting points are uncorrected. Analyses were by the Analytical Group of International Minerals & Chemical Corp., Libertyville, Ill. Care should be exercised in the use of these compounds, some of which have been found to exhibit lacrimatory and/or vesicant activity.

(A) 2 - IODOMETHYL - 3 - METHYLQUINOXALINE (No. **16**). 2-Bromomethyl-3-methylquinoxaline (**15**, 10.0 g, 0.04 mole) was added to a solution of sodium iodide, 6.3 g (0.04 mole), in

Table II. Physical and Analytical Data for New Haloalkylquinoxalines

Compound No.	Yield %	Method[a]	m.p. °C	Analyses: Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Nitrogen Calcd	Nitrogen Found
3	93.4	F	145.5–147.5	50.74	50.46	2.84	2.84	13.14	13.04
4	42	B	150–152	40.56	40.84	2.66	2.38	10.51	10.34
5	62.7	D	102.5–106 dec	41.98	41.72	2.35	2.20	10.88	10.80
7	29.3	B	121.5–122.5	32.13	32.25	1.50	1.71	8.33	8.13
8	30.4	E	153–155	35.99	36.03	2.01	2.14	9.21	9.24
9	32.7	E	118.5–120.5 dec	35.50	35.05	1.99	1.99	9.20	9.03
14	88	C	142–144	57.80	57.94	3.52	3.35	12.35	12.42
16	47.5	A	126–127	42.32	42.32	3.19	2.91	9.86	9.91
18	23	C	125–127	46.00	46.29	2.68	2.70	10.74	10.82
19	4	C	175–177	40.50	40.17	2.03	1.98	9.45	9.45
23	68	D	188–190	26.47	26.69	0.89	0.83	6.17	6.10
24	28	D	108–109	33.36	33.32	1.68	2.05	11.67	11.53
25	92	D	155–156 dec	30.40	30.11	1.52	1.61	10.64	10.54
26	93	D	132–133	38.20	38.36	2.89	2.83	8.08	8.04
27	94	D	183.5–184	36.70	36.43	2.24	2.21	7.78	7.50
29	39.5	D	61–62	34.41	34.80	1.83	1.78	7.30	7.21
31	74	D	194 dec	36.70	36.80	2.22	2.16	7.77	7.81
36	89	A	159.5–160	30.02	30.09	2.29	2.24	6.32	6.17
37	53.4	A	113–114	27.64	27.37	1.48	1.48	5.86	5.63
38[b]	71	B	176–178 dec	41.64	41.79	4.08	4.05	8.00	7.90

[a] See Experimental section for specific examples of each procedure. [b] Hydrobromide salt.

acetone, 80 ml. The resultant thick yellow mixture was filtered and the solids washed with water to yield crude product, m.p. 123–124° C. Recrystallization from acetone and water afforded 5.4 g (47%) pale yellow product, m.p. 126–7° C.

(B) 2-α-Bromopropyl-3-methylquinoxaline Hydrobromide (No. **38**). Bromine, 16.0 g (0.10 mole), dissolved in acetic acid, 50 ml, was added at 25–83° C in 1 hr to a solution of 2-methyl-3-propylquinoxaline (Heilbron *et al.*, 1946), 18.6 g (0.10 mole), in acetic acid, 200 ml. The resulting mixture was stirred at 80–82° C for 1 hr, cooled to 25° C, and stirred an additional 2.5 hr. The reddish brown mixture was filtered by vacuum and washed with water, 500 ml. The crude product was purified by recrystallization from acetonitrile to afford (71%) buff product, m.p. 176–178° C dec.

The designated structure was consistent with the nmr spectrum.

(C) 2-Dichloromethyl-3-methylquinoxaline (**14**). Chlorine, in excess, was bubbled at room temperature into a stirred solution of 2,3-dimethylquinoxaline, 35.2 g (0.2 mole), and sodium acetate, 32.8 g (0.4 mole), in glacial acetic acid, 200 ml. The resultant mixture was filtered and the solids washed with 150 ml acetone. The acetone washings and acetic acid mother liquor were combined and treated with three volumes of water to yield crude product, 40 g (88%), m.p. 104–143° C. Recrystallization from methanol afforded 30 g (66%) white solid, m.p. 143° C.

The designated structure was consistent with the nmr spectrum.

(D) 2,3-Bis(bromomethyl)-5-nitro-7-chloroquinoxaline (**25**). 3-Nitro-5-chloro-*o*-phenylenediamine, 20.2 g (0.0925 mole), and 1,4-dibromo-2,3-butanedione, 22.4 g (0.0925 mole), in 300 ml ethanol was refluxed for 10 min and diluted with water, 600 ml. The resulting brick red solid was filtered and dried to yield 36.5 g (100%) crude product. Recrystallization from acetone and water gave 28.5 g yellow product, m.p. 155–156.5° C dec.

(E) 6-Chloro-2-iodomethylquinoxaline (No. **9**). 6-Chloro-2-methylquinoxaline (14.4 g, 0.08 mole) and 6.6 g (0.08 mole) sodium acetate in 180 ml acetic acid were added in a slow stream at room temperature to 13.0 g (0.08 mole) of ICl in 100 ml acetic acid. After the addition the solution was warmed to 50° C and stirred magnetically for 5 hr. The reaction mixture was cooled to *ca.* 20° C and added slowly to a well stirred solution of 8.6 g (0.08 mole) sodium bisulfite in 2 l. ice-water. After stirring 15 min, the brown precipitate was filtered, washed with cold water, and dried overnight at 30° C in vacuum to give 17.3 g of black solid. This material was extracted with pet ether (Soxhlet) for 6 hr to give a red-brown solid, 8.0 g (32.7%), m.p. 74–94° C dec. This material was recrystallized several times to give 4.24 g, m.p. 106–112° C dec. Continued recrystallization of a sample of this material gave a red-brown analytical sample, m.p. 118.5–120.5° C dec.

(F) 2-Chloromethyl-3-chloroquinoxaline (No. **3**). This compound was prepared in 93% yield by treatment of 2-bromomethyl-3-chloroquinoxaline (**4**) in DMF with HCl, according to the procedure of Kheifets and Khromov-Borisov (1964).

PHOTOLYTIC DECOMPOSITION

A dilute (0.4%) solution of 2,3-bis(bromomethyl)quinoxaline (**20**) in MEOH was allowed to stand in a Vicor flask in direct sunlight. Aliquots were taken periodically and analyzed by glc. Only traces of **20** remained after 4 days. Therefore, sunlight may be causing decomposition of the halomethylquinoxalines after application to plants.

FUNGICIDAL TESTING

Greenhouse tests were carried out at Boyce Thompson Institute, Yonkers, N.Y. Tomato plants of the Bonny Best variety (4 to 5 weeks old) were placed on a revolving turntable and sprayed with a formulation of 4 to 500 ppm of the test chemical. When the spray deposit dried, the plants were inoculated with a spore suspension of the early blight fungus (*Alternaria solani*) and placed in an incubation chamber for 24 hr, after which they were removed and held until lesions developed. Comprehensive and broader spectrum tests were made with: tomato late blight (*Phytophthora infestans*), bean

powdery mildew (*Erysiphe polygoni*), bean rust (*Uromyces phaseoli*), cucumber anthracnose (*Colletotrichum lagenarium*), and rice blast (*Piricularia oryzae*).

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