given by injection. 4-Ethyl-1,2,4-triazole, as a representative of the 4-alkyl-1,2,4-triazole series, was inactive.

1-(1,2,4-Triazolyl-1)-4-(4,1,2-triazolyl-4)-benzene (Compound A) showed weak anti-electroshock activity at 100 mg./kg.

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Derivatives of 8-Hydroxy-2-quinolineacrylic Acid. II[1,2]

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A series of halogenated derivatives of 8-hydroxy-2-quinolineacrylic acid and related compounds has been prepared as a part of a study of the structure-activity relationship of quinoline compounds having potential anti-infective properties.

As a part of a study of the structure activity relationships of anti-infective agents containing a quinoline nucleus a series of 2-quinolineacrylic acids with a hydroxyl or an alkoxyl group in the 8-position has been described.[2] This paper will report a series of halogenated derivatives of these compounds.

It was demonstrated by earlier workers that substitution of halogen atoms at the 5- and 7-positions of 8-quinolinol[5,6] and of 2-methyl-8-

(1) Presented before the Medical Chemistry Division of the American Chemical Society at the 140th Meeting at Chicago, Illinois, September 3–8, 1961.

(2) M. G. Vaidya and J. G. Cannon, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 10 (1959), should be considered as paper I of the series.

(3) Wisconsin Alumni Research Foundation Fellow 1957–1961. Abstracted from a thesis submitted by M. G. Vaidya in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Wisconsin, 1961.

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(5) K. A. Oster and M. J. Golden, *J. Am. Pharm. Assoc.*, **37**, 429 (1948).

(6) E. Schraufstätter, *Z. Naturforsch.*, **5b**, 190 (1950).

quinolinol[7-10] maintained the anti-infective potency and Mason[11] found that 5,7-dihalo-8-quinolinols were less toxic than 8-quinolinol. It was thought that if halogen were substituted in the 5- and 7-positions of 8-hydroxy- or alkoxy-2-quinolineacrylic acid, the biological potency of these structures might similarly be retained with a concomitant decrease in toxicity. Synthesis of 6-halo-8-hydroxy- or -alkoxy-2-quinolineacrylic acids was also planned since the literature contains no reports on the biological activities of 6-halo-8-quinolinols.

The general route for the preparation of halogenated 8-hydroxy- or -alkoxy-2-quinolineacrylic acids was the same as was reported earlier.[1] In the condensation of substituted quinaldines with chloral halogenated 8-alkoxyquinaldines generally gave good yields; halogenated 8-hydroxyquinaldines, 5-chloro-7-iodo-8-methoxyquinaldine, and 5-chloro-8-β-diethylaminoethoxyquinaldine produced only intractable tars. For the preparation of halogenated 8-hydroxy-2-quinolineacrylic acids the de-therification of halogenated 8-ethoxy-2-quinolineacrylic acids with hydrobromic acid was attempted. 5,7-Dichloro-8-hydroxy-2-quinolineacrylic acid was obtained by this method but 5-chloro-8-hydroxy-2-quinolineacrylic acid could not be isolated. This failure possibly was a result of the occurrence of a disproportionation similar to those observed during the reaction of hydrobromic acid with 5-bromo-8-methoxyquinaldine[12] and 5-chloro-7-iodo-8-quinolinol[13]; the former produced a mixture of 5,7-dibromo-8-hydroxyquinaldine, 5-bromo-8-hydroxyquinaldine, and 8-hydroxyquinaldine, and the latter gave a mixture of 5,7-dichloro-8-quinolinol and 5,7-diiodo-8-quinolinol. Such disproportionation was not possible in the case of 5,7-dichloro-8-ethoxy-2-quinolineacrylic acid because both the 5- and the 7-positions bear the same halogen atom.

Failure of some of the halogenated quinaldines mentioned above to condense with chloral necessitated an investigation into the use of the Perkin condensation and the Knoevenagel reaction in the preparation of 2-quinolineacrylic acids. Neither of these methods has been applied previously to the synthesis of 2-quinolineacrylic acids from the

(7) E. W. Elliot and R. S. Schuminard, U. S. Patent 2,695,881 (1954) [*Chem. Abstr.*, **49**, 2762 (1955)].
(8) E. Pfanner, British Patent 594,415 (1947) [*Chem. Abstr.*, **42**, 3437 (1948)].
(9) E. Senn, U. S. Patent 2,411,670 (1946) [*Chem. Abstr.*, **41**, 6024 (1947)].
(10) N. A. David, N. M. Phatak, and F. B. Zener, *Am. J. Trop. Med.*, **24**, 29 (1944).
(11) C. L. Mason, *Phytopathology*, **38**, 740 (1948).
(12) H. M. Irving and A. R. Pinnington, *J. Chem. Soc.*, 285 (1957).
(13) T. Nogradi, *Chem. Ber.*, **85**, 104 (1952).

corresponding quinaldaldehydes. Perkin reaction conditions produced only intractable tars, while the Knoevenagel reaction gave the desired product. 5-Chloro-8-hydroxyquinaldine could not be converted to 5-chloro-8-hydroxyquinaldaldehyde with selenium dioxide.

Evaluation of the antibacterial properties of 2-quinolineacrylic acids, their ethyl esters, and some intermediates in their preparation was accomplished by a serial dilution procedure. 8-Alkoxyquinaldines, their chloral condensation products, and all of the ethyl esters of 2-quinolineacrylic acids were inactive at concentrations of 500 mcg./ml. All of the 2-quinolineacrylic acids, including the parent 8-hydroxy compound, exhibited a low order of activity against *Staphylococcus aureus*, in approximately the same concentrations (200–400 mcg./ml). This suggested that the antibacterial moiety involved was the 2-quinolineacrylic acid itself, and that substituents on the benzene ring of the quinoline nucleus did not produce any change in activity. A 1% solution of 8-hydroxyquinoline was inactive against *S. aureus* over a 10-hr. incubation period.

The agar cup-plate method of Reddish[14] was employed for antifungal screening, using Sabouraud's agar as the culture medium. The antifungal potency was expressed by use of the fungistatic coefficient of Reddish,[14] which is the reciprocal of that concentration (in mg./ml.) of an agent which produces a zone of inhibition of 5 mm. The ethyl esters had pronounced activity against *Trichophyton mentagrophytes* (fungistatic coefficients of 80), as compared to the free acids which were inactive at concentrations of 500 mcg./ml. Antifungal potency was found to increase with an increase in halogen content; halogenated esters with an 8-alkoxy group and those with an 8-hydroxy group had fungistatic coefficients of 120–200. Alkyl ethers of 8-hydroxyquinaldines were inactive at concentrations of 500 mcg./ml., while all chloral condensation products exhibited some activity against *T. mentagrophytes* (fungistatic coefficients of 40 to 80). 8-Hydroxyquinoline demonstrated a fungistatic coefficient of 200.

8-Hydroxy- and 8-ethoxy-2-quinolineacrylic acids, 5,7-dichloro-8-hydroxy- and 8-ethoxy-2-quinolineacrylic acids, and 5-chloro-7-iodo-8-methoxy-2-quinolineacrylic acid were evaluated *in vitro* for

(14) G. F. Reddish, "Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization," 2nd Ed., Lea and Febiger, Philadelphia, Pa., 1958.

amebicidal (*Entameba histolytica*) potency concurrently with emetine as a standard, using the method of Cleveland and Sanders.[15] Microscopic examination of the cultures was made at 6, 24, 30, and 48 hr., for detection of viability of the organisms. At a concentration of 100 mcg./ml., 8-hydroxy- and 8-ethoxy-2-quinolineacrylic acids and 5,7-dichloro-8-hydroxy- and 8-ethoxy-2-quinolineacrylic acids possessed amebicidal activity comparable to that of emetine; 5-chloro-iodo-8-methoxy-2-quinolineacrylic acid was somewhat less potent. Because of the marked antiamebal potency of these compounds and their extremely weak antibacterial effects, it was concluded that they were exerting a direct toxic effect on the amebal organism under the conditions of the *in vitro* tests.

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Experimental

5,7-Dichloro-8-hydroxyquinaldine.—Chlorine was introduced at a moderate rate into a well-stirred solution of 32 g. (0.2 mole) of 8-hydroxyquinaldine in 400 ml. of 20% hydrochloric acid until 28.0 g. (0.4 mole) was absorbed; the reaction mixture then was stirred for 1 hr. The precipitated solid was collected on a filter and was dissolved in 2 l. of water. Sodium bisulfite (5 g.) was added to the solution and the mixture was neutralized with sodium bicarbonate. The yellow precipitate obtained was collected on a filter, washed with water, and recrystallized (see Table I).

6-Chloro-8-hydroxyquinaldine.—To a solution of 20 g. (0.14 mole) of 5-chloro-2-aminophenol[16] in 100 ml. of concentrated hydrochloric acid was added 20 g. of paraldehyde, and the mixture was heated on a water bath for 2 hr. The reaction mixture was diluted with about 600 ml. of water and filtered. The filtrate was neutralized and saturated with sodium carbonate and then was subjected to steam distillation. The solid obtained in the distillate was collected on a filter and recrystallized (see Table I).

(15) L. R. Cleveland and E. P. Sanders, *Arch. Protistenkunde*, **70** (2), 223 (1930).
(16) W. Theilacker, *Ber.*, **71**, 2065 (1938).

Halogenated 8-Alkoxyquinaldines.—A solution of 11.2 g. (0.28 mole) of sodium hydroxide in 15 ml. of water was added to 38.7 g. (0.2 mole) of 5-chloro-8-hydroxyquinaldine[17] in 500 ml. of ethanol. To the resulting mass 0.28 mole of alkyl halide (or dimethyl sulfate, for the preparation of the methyl ether) was added, and the mixture was refluxed on a steam bath for 12 hr. The solvent was evaporated on the steam bath under reduced pressure. The residue was suspended in about 500 ml. of water and the suspension was extracted several times with ether. The combined ethereal extracts were washed with a 2.5% solution of sodium hydroxide and then with water. The ether extract was dried over anhydrous sodium sulfate; solvent was removed on a steam bath and the residue was crystallized. For alkyl ethers of 5,7-dihalo-8-hydroxyquinaldines, an equimolecular portion of potassium hydroxide was substituted for sodium hydroxide (see Table I).

5-Chloro-8-β-diethylaminoethoxyquinaldine. (a) **4-Chloro-2-nitro-β-diethylaminoethoxybenzene.**—A mixture of 35 g. (0.2 mole) of 4-chloro-2-nitrophenol,[18] 34 g. (0.2 mole) of β-diethylaminoethyl chloride hydrochloride, 50 g. of anhydrous potassium carbonate, and 300 ml. of dry acetone was refluxed with vigorous stirring on a steam bath for 17 hr. The solvent was evaporated on the steam bath and the residue was suspended in about 700 ml. of water. The suspension was extracted with ether several times; the combined ethereal extracts were washed with 5% potassium hydroxide solution and then with water. The ether extract was dried over anhydrous sodium sulfate, the ether was evaporated and the oily residue was crystallized from Skelly B; yield 38.8 g. (72%); m.p. 60–61°.

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3$: C, 52.85; H, 6.28; N, 10.28; Cl, 13.00. Found: C, 52.76; H, 6.37; N, 10.31; Cl, 12.91.

The hydrochloride of the base was prepared from its ethereal solution and was recrystallized from ethanol–ether, m.p. 154–155°.[19]

Anal. Calcd. for $C_{12}H_{18}Cl_2N_2O_3$: C, 46.75; H, 5.88; N, 9.09; Cl, 23.00. Found: C, 46.77; H, 5.81; N, 9.29; Cl, 22.90.

2-Amino-4-chloro-β-diethylaminoethoxybenzene.—To 32 g. (0.117 mole) of 4-chloro-2-nitro-β-diethylaminoethoxybenzene and 20 g. of granular tin (20 mesh), heated in a water bath, was added 100 ml. of concentrated hydrochloric acid in 10-ml. portions from the top of the condenser; the vigorous reaction was allowed to subside before addition of a subsequent portion of acid. The reaction mixture then was heated gradually; at a bath temperature of 85–90° a vigorous but not violent reaction occurred. This was allowed to subside and the mixture was heated for 1 hr. and then allowed to cool to room temperature. A 50% aqueous solution of sodium hydroxide was added until the initially formed white precipitate dissolved; an oily layer separated at the top. The reaction mixture was extracted with ether; the ethereal extract was washed with water and then dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled; the fraction boiling at 135–140° (0.15 mm.) was collected (Bosshard[20]

(17) J. Büchi and P. Meier, *Acta Pharm. Intern.*, **2**, 149 (1951).

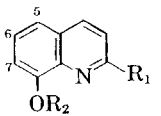
(18) M. Moittier, *Arch. Sci. Phys. Nat.*, **16**, 301 (1934) [*Chem. Abstr.*, **29**, 3322 (1935)].

(19) All melting points reported in the text of the experimental part of the article were taken on a block and are uncorrected.

(20) W. Bosshard, *Helv. Chim. Acta*, **27**, 1736 (1944).

TABLE I

HALOGENATED DERIVATIVES OF 8-HYDROXYQUINALDINE



No.	R_1	R_2	Halogen substituent	M.p.,[a] °C.	Yield, %	Formula	Analyses, [b,c] %: Carbon[b,c] Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
1	CH_3	CH_3	5-Cl	102–103[d,e]	55	$C_{11}H_{10}ClNO$	...	...	...	...	12.84	12.70	8.12	8.21
	Picrate			230–232[f] dec.		$C_{17}H_{13}ClN_4O_8$								
2	CH_2CHCCl_3 | OH	CH_3	5-Cl	147–148[f]	63	$C_{13}H_{11}Cl_4NO_2$	43.94	43.49	3.09	3.25	3.94	3.87	40.00	40.25
3	CH_3	C_2H_5	5-Cl	77–78[e]	70	$C_{12}H_{12}ClNO$	65.10	65.44	5.42	5.78	6.35	6.14	16.03	16.17
	Picrate			203–204[f] dec.	..	$C_{18}H_{15}ClN_4O_8$	...	...	...	..	12.40	11.94	7.87	7.71
4	CH_2CHCCl_3 | OH	C_2H_5	5-Cl	130–131[f]	60	$C_{14}H_{13}Cl_4NO_2$	45.50	45.31	3.53	3.55	3.80	3.78	38.50	38.32
	Hydrochloride			155–156[g]	..	$C_{14}H_{14}Cl_5NO_2$	41.50	41.39	3.46	3.46	3.46	3.53	43.30	43.24
5	$CH{=}CHCOOH$	C_2H_5	5-Cl	204–206[f] dec.	17	$C_{14}H_{12}ClNO_3$	60.63	60.77	4.33	4.36	5.05	4.76	12.80	12.92
6	$CH{=}CHCOOC_2H_5$	C_2H_5	5-Cl	78–79[e]	50	$C_{16}H_{16}ClNO_3$	62.80	62.41	5.24	5.33	4.58	5.00	11.60	11.78
7	CH_3	n-C_3H_7	5-Cl	59–60[e]	56	$C_{13}H_{14}ClNO$	66.30	66.63	5.95	5.92	5.95	5.86	15.10	15.32
	Picrate			197–199 dec.	..	$C_{19}H_{17}ClN_4O_8$	...	...	...	...	12.45	12.37	7.65	7.87
8	CH_2CHCCl_3 | OH	n-C_3H_7	5-Cl	106–107	66	$C_{15}H_{15}Cl_4NO_2$	46.98	46.96	3.92	4.24	3.66	3.73	37.08	36.94
9	CH_3	H	6-Cl	114–115[h]	5	$C_{10}H_8ClNO$	62.08	62.35	4.17	4.41	7.24	7.05	18.31	18.25
	Picrate			203–204[f]	..	$C_{16}H_{11}ClN_4O_8$	...	...	...	...	13.25	13.41	8.38	8.31

TABLE I (*Continued*)

10	CH_3	C_2H_5	6-Cl	95–96[i]	53	$C_{12}H_{12}ClNO$	65.10	65.33	5.42	5.45	6.35	6.24	16.03	16.14
	Picrate			190–191[f]	..	$C_{18}H_{15}ClN_4O_8$	...	...	...	...	12.45	12.65	7.90	8.05
11	CH_3	H	5-Cl 7-Cl	112–114[f,j]	45	$C_{10}H_7Cl_2NO$	...	...	...	...	...	...	...	...
12	CH=CHCOOH	H	5-Cl 7-Cl	270–272 dec.[k]	35	$C_{12}H_7Cl_2NO_3$	50.70	50.43	2.46	2.49	4.93	4.75	25.00	24.06
13	$CH=CHCOOC_2H_5$	H	5-Cl	132–133[e]	70	$C_{14}H_{11}Cl_2NO_3$	53.9	53.77	3.53	3.55	4.49	4.22	22.80	22.40
14	CH_3	C_2H_5	5-Cl 7-Cl	60–61[e]	90	$C_{12}H_{11}Cl_2NO$	56.38	56.55	4.30	4.67	5.47	5.47	27.75	28.05
	Picrate			158–160[f]	..	$C_{18}H_{14}Cl_2N_4O_8$	...	...	...	...	11.55	11.65	14.65	14.95
15	$CH_2C(OH)HCCl_3$	C_2H_5	5-Cl 7-Cl	132–133[f]	50	$C_{14}H_{12}Cl_5NO_2$	41.64	41.97	2.97	3.05	3.47	3.38	43.99	43.70
16	CH=CHCOOH	C_2H_5	5-Cl 7-Cl	240–242 dec.[f]	76	$C_{14}H_{11}Cl_2NO_3$	53.84	54.12	3.53	3.60	4.49	3.77	22.76	23.91
17	$CH=CHCOOC_2H_5$	C_2H_5	5-Cl 7-Cl	110–111[e]	66	$C_{16}H_{15}Cl_2NO_3$	56.47	56.55	4.31	4.25	4.12	4.09	20.87	20.95
18	CH_3	CH_3	5-Cl 7-I	105–106[f]	63	$C_{11}H_9ClINO$	39.68	40.01	2.71	2.52	4.22	4.34	10.65	10.24
													I, 38.13	37.87
19	CHO	CH_3	5-Cl 7-I	129–131[h]	46	$C_{11}H_7ClINO_2$	37.98	37.00	2.15	2.18	4.03	3.82	...	...
	Oxime			211–213[f]	..	$C_{11}H_8ClIN_2O_2$	36.24	35.78	2.21	2.27	7.73	7.44	...	...
20	CH=CHCOOH	CH_3	5-Cl 7-I	256–258 dec.[l]	57	$C_{12}H_9ClINO_3$	40.01	39.50	2.31	2.37	3.59	3.49	...	...
21	CH_3	C_2H_5	5-Cl 7-I	60–61[f]	25	$C_{12}H_{11}ClINO$	41.50	41.77	3.17	3.34	4.03	4.16	10.2	9.87
													I, 36.62	36.24
22	CH_2CHCCl_3 (OH)	C_2H_5	5-Cl 7-I	131–132[j]	35	$C_{14}H_{12}Cl_4INO_2$	33.92	33.79	2.43	2.49	2.83	2.24	28.7	28.00
													I, 25.76	26.13

[a] All melting points were taken on a block and are uncorrected. [b] Analyses by Huffman Microanalytical Laboratories, Wheatridge, Colorado, and by Drs. Weiler and Strauss, Oxford, England. [c] Compounds for which an analysis is not listed are known compounds but prepared by a different procedure. [d] M. Weizmann and E. Bograchov, *J. Am. Chem. Soc.*, **69**, 1222 (1947). [e] Recrystallized from Skelly B. [f] Recrystallized from 95% ethanol. [g] Recrystallized from ethanol–ether. [h] Recrystallized from Skelly C. [i] Recrystallized from Skelly A. [j] Pfanner, ref. 8. [k] Recrystallized from glacial acetic acid. [l] Recrystallized from 1-butanol.

reported b.p. 195–198° (at 10 mm.)). **5-Chloro-8-β-diethylaminoethoxyquinaldine** was prepared by the method of Bosshard.[20]

6-Chloro-8-ethoxyquinaldine.—To a solution of 4 g. (0.0206 mole) of 6-chloro-8-hydroxyquinaldine in 50 ml. of absolute ethanol was added a solution of 1.2 g. (0.03 mole) of sodium hydroxide in 10 ml. of 95% ethanol. To the resulting mass 3.3 g. (0.03 mole) of ethyl bromide was added, and the mixture was refluxed on a steam bath for 12 hr. The product was isolated and purified by the procedure previously described for halogenated 8-alkoxyquinaldines (see Table I).

Condensation of Halogenated 8-Alkoxyquinaldines with Chloral.—A mixture of 0.05 mole of halogenated 8-alkoxyquinaldine, 4.0 g. (0.05 mole) of pyridine (dried over potassium hydroxide), and 0.05 mole of chloral was heated on a steam bath for 5 hr. in the case of monohalogenated 8-alkoxyquinaldines and for 12 hr. in the case of dihalogenated 8-alkoxyquinaldines. The reaction mixture was poured into about 300 ml. of ether; the ethereal solution was filtered and the ether was removed from the filtrate on a steam bath; the oily residue was crystallized (see Table I).

Hydrolysis of Chloral Condensation Products.—To a stirred refluxing solution of 25 g. (0.45 mole) of potassium hydroxide in 250 ml. of 95% ethanol was added 0.075 mole of chloral condensation products over a period of 1 hr. The mixture was further stirred and refluxed on the steam bath for 3 hr., cooled, the precipitate obtained was collected on a filter and dissolved in about 500 ml. of water. The solution was acidified with glacial acetic acid; the resulting precipitate was collected on a filter and recrystallized (see Table I).

5,7-Dichloro-8-hydroxy-2-quinolineacrylic Acid.—A mixture of 3.12 g. (0.01 mole) of 5,7-dichloro-8-ethoxy-2-quinolineacrylic acid, 25 ml. of glacial acetic acid, and 25 ml. of 47% hydrobromic acid was refluxed for 5 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was extracted with 5% aqueous potassium hydroxide solution. The extract was neutralized with glacial acetic acid; the precipitated 5,7-dichloro-8-hydroxy-2-quinolineacrylic acid was collected on a filter, washed with copious amounts of water, dried, and recrystallized (see Table I).

Quinaldaldehyde was prepared by oxidation of quinaldine with selenium dioxide as described by Ramsey[21] and by this sequence of reactions: ω-tribromoquinaldine[22] was converted to ω-dibromoquinaldine by the method of Sharp,[23] which was hydrolyzed to quinaldaldehyde by the method of Hammick.[24]

2-Quinolineacrylic Acid.—(a) By the Doebner modification of the Knoevenagel reaction: a mixture of 3.14 g. (0.02 mole) of quinaldaldehyde, 20 ml. of pyridine (dried over potassium hydroxide pellets), 4.5 g. (0.0432 mole) of malonic acid (dried at 80° for 3 hr.), and 0.5 ml. of piperidine was heated on a steam bath until the evolution of gas stopped (approximately 2 hr.); it was then refluxed for 5 min. using a heating mantle. The resulting mass was poured into about 400 ml. of water; the precipitate obtained was collected on a filter, washed with water, dried, and recrystallized from 95% ethanol; yield 1.1 g. (25%); m.p. 198–199°

(21) V. Ramsey, *J. Am. Pharm. Assoc.*, **40**, 564 (1951).
(22) D. L. Hammick, *J. Chem. Soc.*, 2882 (1923).
(23) L. K. Sharp, *J. Pharm. Pharmacol.*, **1**, 395 (1949).
(24) D. L. Hammick, *J. Chem. Soc.*, **1303** (1926).

dec. (b) It was prepared by the method of Alberts and Bachman.[25]

A mixture melting point determination of the products obtained in (a) and (b) showed no depression. Infrared spectra of 2-quinolineacrylic acids obtained by the two methods were superimposable.

5-Chloro-7-iodo-8-methoxyquinaldaldehyde.—To a mixture of 16.65 g. (0.05 mole) of 5-chloro-7-iodo-8-methoxyquinaldine[16] and 125 ml. of sodium dried dioxane maintained at 90°, 5.5 g. (0.05 mole) of freshly prepared and sublimed selenium dioxide was added with vigorous stirring over a period of 30 min.; stirring was continued for 1 hr. The precipitated selenium was removed with the aid of Filter-Cel and the filtrate was evaporated to dryness under reduced pressure on a steam bath. The residue was suspended in about 500 ml. of water; solid sodium bicarbonate was added to the well stirred mixture until it was distinctly alkaline. Stirring was continued for 30 min. in order to neutralize the selenious acid completely. The suspension was extracted several times with chloroform and the combined chloroform extracts were washed with water. The solvent was evaporated on a steam bath and the solid residue was recrystallized (see Table I).

5-Chloro-7-iodo-8-methoxy-2-quinolineacrylic Acid.—A mixture of 6 g. (0.0173 mole) of 5-chloro-7-iodo-8-methoxyquinaldaldehyde, 5.0 g. (0.048 mole) of malonic acid, 30 ml. of pyridine (dried over potassium hydroxide pellets), and 1 ml. of piperidine was heated on a steam bath until evolution of gas ceased (approximately 5 hr.). The resulting solution then was refluxed for 5 min., and poured into about 600 ml. of water; 5-chloro-7-iodo-8-methoxy-2-quinolineacrylic acid separated as a solid and was collected on a filter, washed with water, and recrystallized (see Table I).

Ethyl 2-Quinolineacrylate Esters.—Substituted 2-quinolineacrylic acid (0.05 mole) was dissolved in 50 ml. of absolute ethanol saturated with hydrogen chloride gas and the solution was refluxed on a steam bath for 3 hr.; the solvent was removed under reduced pressure, and the residue was suspended in about 100 ml. of water. The mixture was neutralized with solid sodium bicarbonate. The resulting suspension was extracted with ether; the ethereal extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed on a steam-bath and the oily residue was crystallized (see Table I).

(25) A. A. Alberts and G. B. Bachman, *J. Am. Chem. Soc.*, **57**, 1284 (1935).