

5- and 7-Substituted 2-Methyl-8-quinolinols (I)

Herman Gershon and Maynard W. McNeil

Boyce Thompson Institute for Plant Research, Inc., Yonkers, New York 10701

Received December 13, 1971

The synthesis and characterization of the 5- and 7-monosubstituted 2-methyl-8-quinolinols where the substituents are fluorine, chlorine, bromine, iodine, nitro, amino, and sulfonic acid groups were carried out. The bischelates with copper(II) of those ligands containing hydrogen, fluorine, chlorine, bromine, iodine, and nitro are also reported.

Due to our interest in attempting to relate the anti-fungal activity of the copper(II) chelates of 8-quinolinol and its derivatives to the geometry and charge distribution of the molecules (2-4) and to their stability constants (5,6), the study was extended to a comparable series of 2-methyl-8-quinolinols. Thus it was decided to prepare and characterize the 5- and 7-monosubstituted 2-methyl-8-quinolinols and their respective copper(II) chelates, where the substituents included fluorine, chlorine, bromine, iodine, and nitro group.

Of the 5-substituted 2-methyl-8-quinolinols, the 5-chloro (7), 5-bromo (7), 5-iodo (7), 5-nitro (8), and 5-amino (8) derivatives were known. In the present study, 5-chloro and 5-bromo-2-methyl-8-quinolinols were prepared in good yield by electrophilic halogenation of the parent compound with the respective *N*-halosuccinimide in 90-93% sulfuric acid (9), and 5-fluoro-2-methyl-8-quinolinol was obtained by the Baltz-Schiemann reaction on 5-amino-2-methyl-8-quinolinol. The 7-chloro and 7-bromo-2-methyl-8-quinolinols were prepared by halogenation of 2-methyl-8-quinolinol-5-sulfonic acid followed by desulfonation (10). Iodination of 2-methyl-8-quinolinol with *N*-iodosuccinimide in 90% sulfuric acid yielded the 7-iodo derivative (9). 7-Fluoro-2-methyl-8-quinolinol was obtained by nitration of 2-methyl-8-quinolinol-5-sulfonic acid (11), desulfonation and hydrogenation followed by replacement of the amino group with fluorine under the conditions of the Baltz-Schiemann reaction (12). The bischelates of these ligands with copper(II) were subsequently prepared by mixing solutions containing stoichiometric quantities of copper(II) acetate monohydrate in 75% aqueous methanol with solutions of the ligand in methanol or methanol dimethyl formamide mixtures.

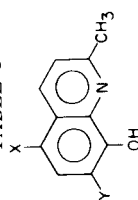
Since a number of 5-sulfonic acids were prepared as intermediates and a significant portion of the literature on 8-quinolinol-7-sulfonic acids has recently been correct-

ed (13), it was decided to make and characterize the additional members of the series of 5- and 7-2-methyl-8-quinolinol sulfonic acids, where the second substituent consisted of fluorine, chlorine, bromine, iodine, nitro, or sulfonic acid group. Although 2-methyl-8-quinolinol-5-sulfonic acid was reported, it was not fully characterized (14). This was accomplished by converting the sulfonic acid to 7-chloro-2-methyl-8-quinolinol, as indicated earlier in this work. The 7-chloro compound was shown to be different from the known 5-chloro derivative, and both yielded 5,7-dichloro-2-methyl-8-quinolinol on further chlorination. 7-Nitro-2-methyl-8-quinolinol was similarly reported but not fully characterized (11). The preparation of 7-chloro and 7-bromo-2-methyl-8-quinolinol-5-sulfonic acids was mentioned earlier, and although 7-bromo-2-methyl-8-quinolinol-5-sulfonic acid was previously reported, it was not fully characterized (11). 7-Fluoro-2-methyl-8-quinolinol-5-sulfonic acid was obtained by sulfonation of 7-fluoro-2-methyl-8-quinolinol. Iodination of 2-methyl-8-quinolinol-5-sulfonic acid to the 7-iodo derivative was achieved with *N*-iodosuccinimide.

Upon sulfonation of 5-fluoro, 5-chloro, and 5-bromo-2-methyl-8-quinolinols with 10% oleum, the respective 7-sulfonic acids were obtained. 2-Methyl-8-quinolinol-7-sulfonic acid was produced by hydrogenolysis of the 5-chloro derivative, and 5-iodo and 5-nitro-2-methyl-8-quinolinol-7-sulfonic acids were prepared by iodination with *N*-iodosuccinimide and nitration of the 7-sulfonic acid, respectively. For the preparation of 2-methyl-8-quinolinol-5,7-disulfonic acid, 2-methyl-8-quinolinol was dichloro-sulfonated with chlorosulfonic acid and subsequently hydrolyzed in water.

The data characterizing the compounds are contained in Table I, and the 60 MHz nmr spectral features of the compounds taken in d_6 -DMSO using tetramethyl silane as the internal standard are listed in Table II. Infrared spectra in potassium bromide are shown in Figures 1-6.

TABLE I



X	Y	M.p., °C	Yield, %	Formula	Calcd.			Found			
					H	N	C	H	N	C	
F	H	57-58 (a)	37	C ₁₀ H ₈ FNO	67.79	4.55	7.90	67.98	4.58	7.94	F 10.92
NH ₂	H	305-310 dec. (b)	76	C ₁₀ H ₁₁ ClN ₂ O	57.01	5.26	13.30	57.19	5.24	12.98	Cl 16.59
H	F	82-83 (c)	1.7	C ₁₀ H ₈ FNO	67.79	4.55	7.90	68.03	4.66	7.85	F 10.98
H	Cl	116-118 (a)	42	C ₁₀ H ₈ ClNO	62.02	4.16	7.23	62.06	4.12	7.33	Cl 18.41
H	Br	134-136 (a)	57	C ₁₀ H ₈ BrNO	50.45	3.39	5.88	50.70	3.56	5.82	Br 33.72
H	I	88-89 (a)	56	C ₁₀ H ₈ I NO	42.13	2.83	4.91	42.19	2.72	4.75	I 44.36
H	NO ₂	182 (d)	70	C ₁₀ H ₈ N ₂ O ₃	58.82	3.94	13.71	58.97	3.83	13.47	Cl 16.75
H	NH ₂	(b,c)	90	C ₁₀ H ₁₁ ClN ₂ O	57.01	5.26	13.30	57.08	5.05	13.38	5.61
SO ₃ H	H	298-299 dec. (f)	81	C ₁₀ H ₁₁ NO ₅ S(i)	46.69	4.31	5.44	46.85	4.01	5.61	F 6.79
SO ₃ H	F	318 dec. (f)	64	C ₁₀ H ₁₀ FNO ₅ S(k)	43.63	3.66	5.09	43.36	3.83	4.97	Cl 12.86
SO ₃ H	Cl	308-309 dec. (f)	91	C ₁₀ H ₈ ClNO ₄ S(l)	43.88	2.95	5.12	43.60	2.98	5.33	Br 25.24
SO ₃ H	Br	274 dec. (f)	85	C ₁₀ H ₈ BrNO ₄ S(m)	37.75	2.53	4.40	37.61	2.56	4.48	I 33.05
SO ₃ H	I	(e,f)	52	C ₁₀ H ₁₀ INO ₅ S(n)	31.35	2.63	3.66	31.78	2.94	3.28	F 6.60
SO ₃ H	NO ₂	283 dec. (f)	88	C ₁₀ H ₈ N ₂ O ₆ S	42.26	2.84	9.86	42.01	2.99	9.68	Cl 12.09
H	SO ₃ H	312 dec. (d)	83	C ₁₀ H ₉ NO ₄ S(o)	50.20	3.79	5.85	49.92	3.74	5.83	Br 25.29
F	SO ₃ H	316 dec. (f)	75	C ₁₀ H ₁₀ FNO ₅ S(p)	43.63	3.66	5.09	43.46	3.69	5.16	I 34.49
Cl	SO ₃ H	328 dec. (f)	84	C ₁₀ H ₁₀ ClNO ₅ S(q)	41.17	3.46	4.80	41.32	3.47	4.78	F 9.45
Br	SO ₃ H	305-306 dec. (f)	78	C ₁₀ H ₈ BrNO ₄ S(t)	37.75	2.53	4.40	37.84	2.53	4.43	Cl 15.48
I	SO ₃ H	(e,g)	95	C ₁₀ H ₈ INO ₄ S(s)	32.89	2.21	3.84	32.64	2.24	3.71	Br 29.47
NO ₂	SO ₃ H	(e,g)	97	C ₁₀ H ₈ N ₂ O ₆ S	42.26	2.84	9.86	42.02	2.94	9.68	I 40.52
SO ₃ H	SO ₃ H	304-305 dec. (h)	80	C ₁₀ H ₁₃ NO ₉ S ₂ (t)	33.80	3.69	3.94	33.66	3.78	3.77	F 9.24
Bis(2-methyl-8-quinolinolato)copper(II) Complexes											
F	H	286 dec. (d)	95	C ₂₀ H ₁₄ F ₂ N ₂ O ₂ Cu	57.76	3.39	6.74	57.90	3.34	6.85	Cl 15.48
Cl	H	278-280 dec. (d)	97	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₂ Cu	53.52	3.14	6.24	53.81	3.23	6.24	Br 29.47
Br	H	238 dec. (d)	98	C ₂₀ H ₁₄ Br ₂ N ₂ O ₂ Cu	44.67	2.62	5.21	44.42	2.59	5.14	I 40.52
I	H	210 dec. (i)	94	C ₂₀ H ₁₄ I ₂ N ₂ O ₂ Cu	38.02	2.23	4.43	38.37	2.36	4.30	F 9.24
NO ₂	H	> 320 (i)	98	C ₂₀ H ₁₄ N ₄ O ₆ Cu	51.12	3.00	11.92	50.96	3.00	12.15	
H	F	239-240 dec. (d)	96	C ₂₀ H ₁₄ F ₂ N ₂ O ₂ Cu	57.76	3.39	6.74	58.04	3.55	6.60	

TABLE I (continued)

X	Y	M.p., °C	Yield, %	Formula	Calcd.			Found		
					C	H	N	C	H	N
H	Cl	>320 (d)	95	C ₂₀ H ₁₄ Cl ₂ N ₂ O ₂ Cu	53.52	3.14	6.24	53.59	3.13	6.27
H	Br	>320 (d)	94	C ₂₀ H ₁₄ Br ₂ N ₂ O ₂ Cu	44.67	2.62	5.21	44.79	2.62	5.05
H	I	223-224 dec. (i)	98	C ₂₀ H ₁₄ I ₂ N ₂ O ₂ Cu	38.02	2.23	4.43	38.32	2.42	4.27
H	NO ₂	354 dec. (i)	94	C ₂₀ H ₁₄ N ₄ O ₄ Cu	51.12	3.00	11.92	50.90	3.16	11.92

(a) Crystallized from methanol. (b) Crystallized as hydrochloride from water-acetone mixture. (c) Crystallized from hexane. (d) Crystallized from methanol-dimethyl formamide mixture. (e) Decomposes slowly above 270°. (f) Crystallized from water. (g) Crystallized from dilute sulfuric acid. (h) Crystallized from water-acetone mixture. (i) Crystallized from dimethyl formamide. (j) Crystallized as monohydrate. *Anal.* Calcd.: O, 31.10. Found: O, 30.85. (k) Crystallized as monohydrate. *Anal.* Calcd.: O, 29.06. Found: 28.80. (l) *Anal.* Calcd.: O, 27.42. Found: O, 27.40. (m) *Anal.* Calcd.: O, 20.12. Found: O, 19.80. (n) Crystallized as monohydrate. *Anal.* Calcd.: O, 20.88. Found: O, 20.46. (o) *Anal.* Calcd.: O, 26.75. Found: 26.69. (p) Crystallized as monohydrate. *Anal.* Calcd.: O, 29.06. Found: 28.92. (q) Crystallized as monohydrate. *Anal.* Calcd.: O, 27.42. Found: O, 27.14. (r) *Anal.* Calcd.: O, 17.25. Found: O, 17.53. (s) *Anal.* Calcd.: O, 17.25. Found: O, 17.25. (t) Crystallized as dihydrate. *Anal.* Calcd.: O, 40.52. Found: O, 40.25.

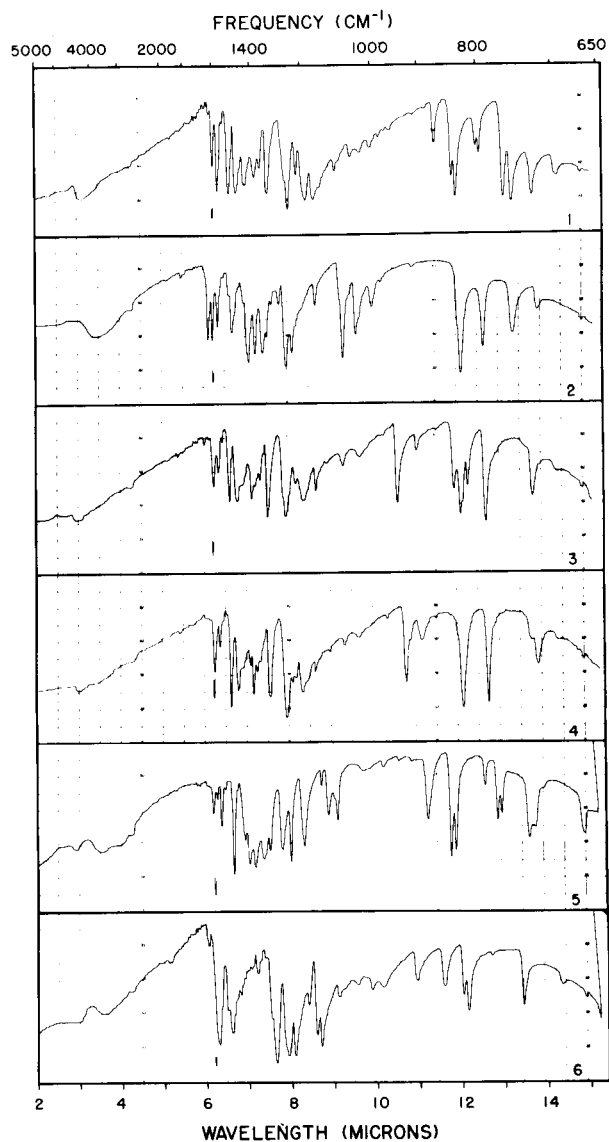


Figure 1. Ir spectra in potassium bromide of 1: 2-methyl-8-quinolinol, 2: 5-fluoro-2-methyl-8-quinolinol, 3: 5-chloro-2-methyl-8-quinolinol, 4: 5-bromo-2-methyl-8-quinolinol, 5: 5-iodo-2-methyl-8-quinolinol, 6: 2-methyl-5-nitro-8-quinolinol.

EXPERIMENTAL (15)

5-Amino-2-methyl-8-quinolinol Hydrochloride.

A suspension of 37.6 g. (0.2 mole) of 2-methyl-5-nitroso-8-quinolinol (8) and 100 mg. of platinum oxide in 150 ml. of dimethyl formamide was shaken under 5 atmospheres of hydrogen in a Parr hydrogenator. After 0.4 mole of hydrogen had been taken up, the catalyst was removed by filtration, and the filtrate was acidified with 17.5 ml. of concentrated hydrochloric acid and diluted with 3 volumes of acetone. The mixture was stirred overnight at room temperature, and the product was filtered off and washed with acetone until the washings were nearly colorless.

TABLE II
Proton Chemical Shifts for 5- and 7-Substituted 2-Methyl-8-quinolins (a)
(tms internal standard)

Substituents on 2-Methyl-8- quinolinol	2-Methyl	Proton Chemical Shift ppm (τ)				
		3	4	5	6	7
None	7.28	2.30-2.90 (un- resolved multi- plet)	1.62 (doublet $J_{43} = 9$)	2.30-2.90	(unresolved multiplet)	
5-F	7.28	2.35 (doublet $J_{34} = 9$)	1.53 (doublet $J_{43} = 9$)		2.30-3.05 (unresolved)	
5-Cl	7.26	2.28 (doublet $J_{34} = 9$)	1.47 (doublet $J_{43} = 9$)		2.34 (doublet $J_{67} = 9$)	2.82 (doublet $J_{76} = 9$)
5-Br	7.26	2.30 (doublet $J_{34} = 9$)	1.54 (doublet $J_{43} = 9$)		2.17 (doublet $J_{67} = 9$)	2.86 (doublet $J_{76} = 9$)
5-I	7.26	2.38 (doublet $J_{34} = 9$)	1.58 (doublet $J_{43} = 9$)		2.09 (doublet $J_{67} = 9$)	2.68 (doublet $J_{76} = 9$)
5-NO ₂	7.26	2.30 (doublet $J_{34} = 9$)	0.96 (doublet $J_{43} = 9$)		1.51 (doublet $J_{67} = 9$)	2.84 (doublet $J_{76} = 9$)
5-SO ₃ H	6.99	1.83 (doublet $J_{34} = 9$)	0.20 (doublet $J_{43} = 9$)		1.86 (doublet $J_{67} = 9$)	2.56 (doublet $J_{76} = 9$)
7-F	7.27	2.35-2.60 (un- resolved multi- plet)	1.60 (doublet $J_{43} = 9$)	2.35-2.60 (unresolved multiplet)		
7-Cl	7.25	2.41 (doublet $J_{34} = 9$)	1.56 (doublet $J_{43} = 9$)	2.25-2.60 (unresolved multiplet)		
7-Br	7.23	2.37 (doublet $J_{34} = 9$)	1.54 (doublet $J_{43} = 9$)	2.53 (doublet $J_{56} = 9$)	2.27 (doublet $J_{65} = 9$)	
7-I	7.27	2.37 (doublet $J_{34} = 9$)	1.71 (doublet $J_{43} = 9$)	2.97 (doublet $J_{56} = 9$)	1.95 (doublet $J_{65} = 9$)	
7-NO ₂	7.20	2.20 (doublet $J_{34} = 9$)	1.46 (doublet $J_{43} = 9$)	2.48 (doublet $J_{56} = 9$)	1.88 (doublet $J_{65} = 9$)	
7-SO ₃ H	6.98	1.83 (doublet $J_{34} = 9$)	0.79 (doublet $J_{43} = 9$)	2.14 (doublet $J_{56} = 9$)	1.90 (doublet $J_{65} = 9$)	
5-F, 7-SO ₃ H	7.01	1.86 (doublet $J_{34} = 9$)	0.89 (doublet $J_{43} = 9$)		2.25 (doublet $J_{HF} = 9$)	
5-Cl, 7-SO ₃ H	7.02	1.86 (doublet $J_{34} = 9$)	0.93 (doublet $J_{43} = 9$)		2.01 (singlet)	

5-Br, 7-SO ₃ H	7.03	1.86 (doublet J ₃₄ = 9)	1.00 (doublet J ₄₃ = 9)	1.85 (singlet)
5-I, 7-SO ₃ H	7.02	1.90 (doublet J ₃₄ = 9)	1.10 (doublet J ₄₃ = 9)	1.62 (singlet)
5-NO ₂ , 7-SO ₃ H	7.13	1.92 (doublet J ₃₄ = 9)	0.65 (doublet J ₄₃ = 9)	1.21 (singlet)
7-F, 5-SO ₃ H	7.01	1.87 or 1.91 (doublet J ₃₄ = 9)	0.25 (doublet J ₄₃ = 9)	1.87 or 1.91 (doublet J _{HF} = 9)
7-Cl, 5-SO ₃ H	7.08	1.98 (doublet J ₃₄ = 9)	0.42 (doublet J ₄₃ = 9)	1.90 (singlet)
7-Br, 5-SO ₃ H	7.09	2.00 (doublet J ₃₄ = 9)	0.45 (doublet J ₄₃ = 9)	1.76 (singlet)
7-I, 5-SO ₃ H	7.03	1.90 (doublet J ₃₄ = 9)	1.12 (doublet J ₄₃ = 9)	1.60 (singlet)
7-NO ₂ , 5-SO ₃ H	7.09	1.94 (doublet J ₃₄ = 9)	0.52 (doublet J ₄₃ = 9)	1.41 (singlet)
5,7-(SO ₃ H) ₂	6.99	1.77 (doublet J ₃₄ = 9)	0.14 (doublet J ₄₃ = 9)	1.58 (singlet)

(a) Spectra taken on 3% solutions of sulfonic acids in d₆-DMSO and 5% solutions of other compounds.

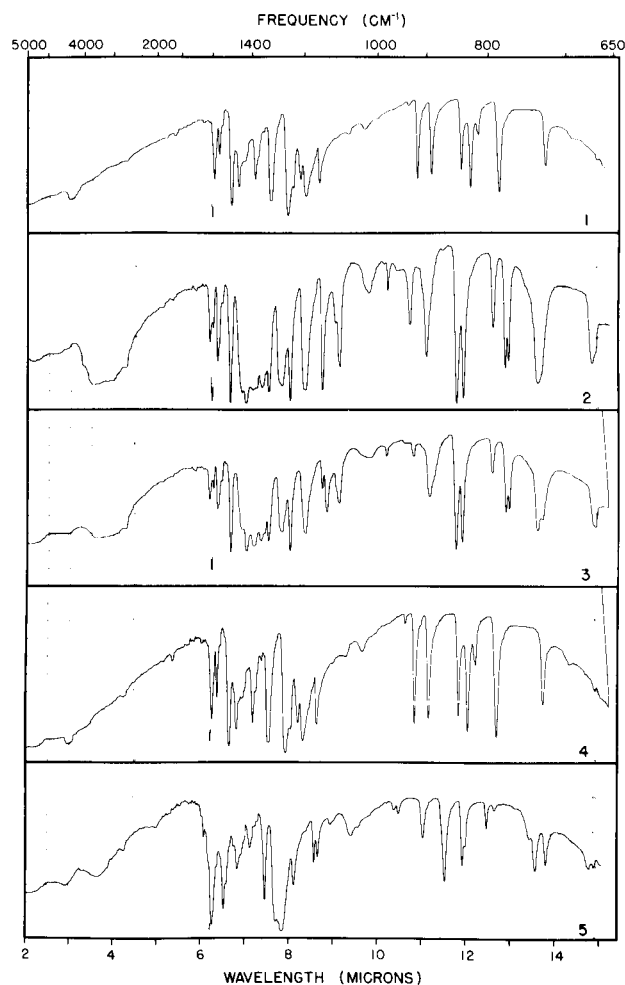


Figure 2. Ir spectra in potassium bromide of 1: 7-fluoro-2-methyl-8-quinolinol, 2: 7-chloro-2-methyl-8-quinolinol, 3: 7-bromo-2-methyl-8-quinolinol, 4: 7-iodo-2-methyl-8-quinolinol, 5: 2-methyl-7-nitro-8-quinolinol.

The compound which was dried under vacuum at room temperature was obtained in 76% yield.

5-Fluoro-2-methyl-8-quinolinol.

Method 1.

5-Amino-2-methyl-8-quinolinol hydrochloride (26.2 g., 0.125 mole) was suspended in 250 ml. of tetrahydrofuran with stirring. Fluoroboric acid (48-50%, 113 ml.) was added, and the temperature was maintained at 0-5°. Solid sodium nitrite (9.0 g., 0.13 mole) was added in small portions over 0.5 hour and stirring was continued for an additional 2 hours. The precipitate was removed by filtration on a coarse sintered glass funnel, slurried twice with 35 ml. portions of cold 1:1 ether-ethanol mixture (v/v) and twice with 65 ml. portions of cold ether, and dried under vacuum at 30-35° overnight. The yield of product was 42 g., m.p. 179° dec. The compound was combusted in 2 portions of 21 g. spread over the bottom of Fernbach flasks fitted with air condensers. Each product was boiled in 100 ml. of 5% sulfuric acid, and the com-

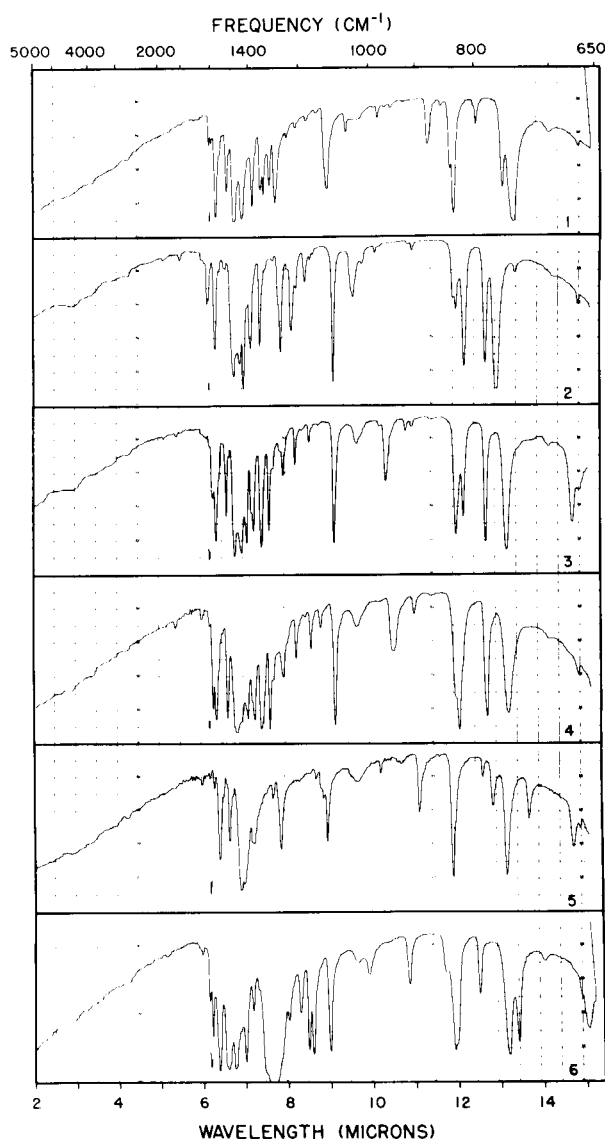


Figure 3. Ir spectra in potassium bromide of 1: bis(2-methyl-8-quinolinolato)copper(II), 2: bis(5-fluoro-2-methyl-8-quinolinolato)copper(II), 3: bis(5-chloro-2-methyl-8-quinolinolato)copper(II), 4: bis(5-bromo-2-methyl-8-quinolinolato)copper(II), 5: bis(5-iodo-2-methyl-8-quinolinolato)copper(II), 6: bis(2-methyl-5-nitro-8-quinolinolato)copper(II).

bined liquids were brought to pH 5-6 with dilute sodium hydroxide solution and steam distilled. A yield of 6 g. of compound was obtained by filtration of the distillate, m.p. 57-58°. Upon adjusting the filtrate to pH 7 with sodium bicarbonate, 2.1 g. of additional compound, m.p. 53-54.5° was obtained. The combined yield of product was 37%, and crystallization of the first yield of compound from methanol did not alter the melting point.

Method II.

To 20 g. (0.122 mole) of 5-fluoro-8-quinolinol (17) dissolved in 800 ml. of anhydrous ether was added 200 ml. (2.3 N, 0.46

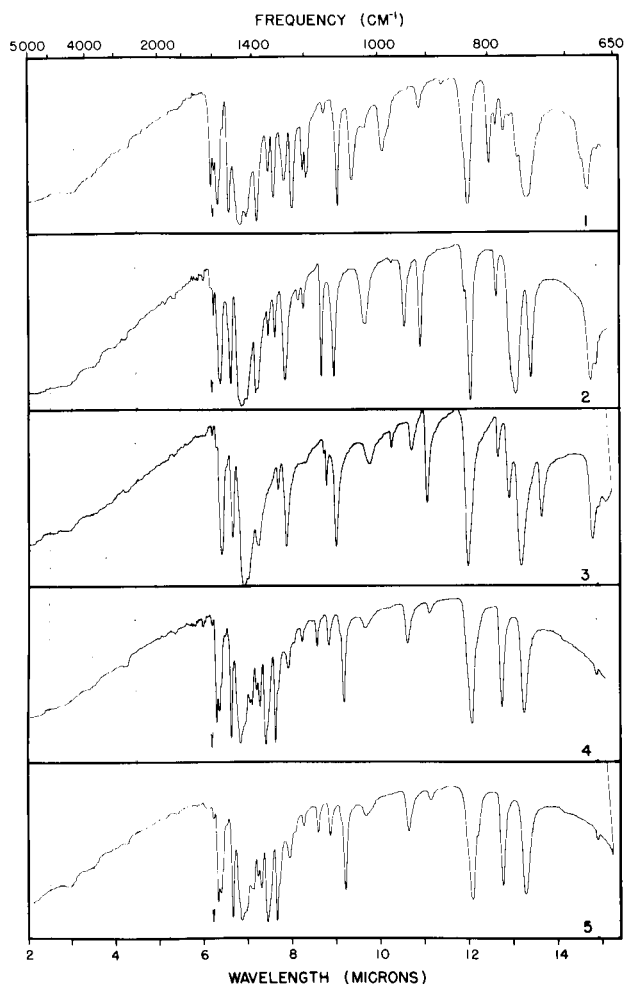


Figure 4. Ir spectra in potassium bromide of 1: bis(7-fluoro-2-methyl-8-quinolinolato)copper(II), 2: bis(7-chloro-2-methyl-8-quinolinolato)copper(II), 3: bis(7-bromo-2-methyl-8-quinolinolato)copper(II), 4: bis(7-iodo-2-methyl-8-quinolinolato)copper(II), 5: bis(2-methyl-7-nitro-8-quinolinolato)copper(II).

mole) of methyl lithium dropwise with stirring at 0°. Stirring was continued for 2 hours, after which 50 ml. of water was added dropwise with continued stirring. The mixture was brought to pH 5-6 by addition of acetic acid. The ether layer was separated and the aqueous layer was extracted twice again with ether. The combined ether solutions were freed of ether by flash evaporation and the residue was steam distilled. The crude product was obtained in 70% yield, after filtration and drying under vacuum at room temperature, m.p. 50-51°.

5-Chloro-2-methyl-8-quinolinol.

To a solution of 32 g. (0.2 mole) of 2-methyl-8-quinolinol in 1000 ml. of 90% sulfuric acid, kept at 25° by means of external cooling, was added 27 g. (0.2 mole) of *N*-chlorosuccinimide in small portions, with stirring. The mixture was allowed to stir for 3 hours, after which it was poured onto ice and adjusted to pH 6-7 with sodium hydroxide. The precipitate was removed by filtration,

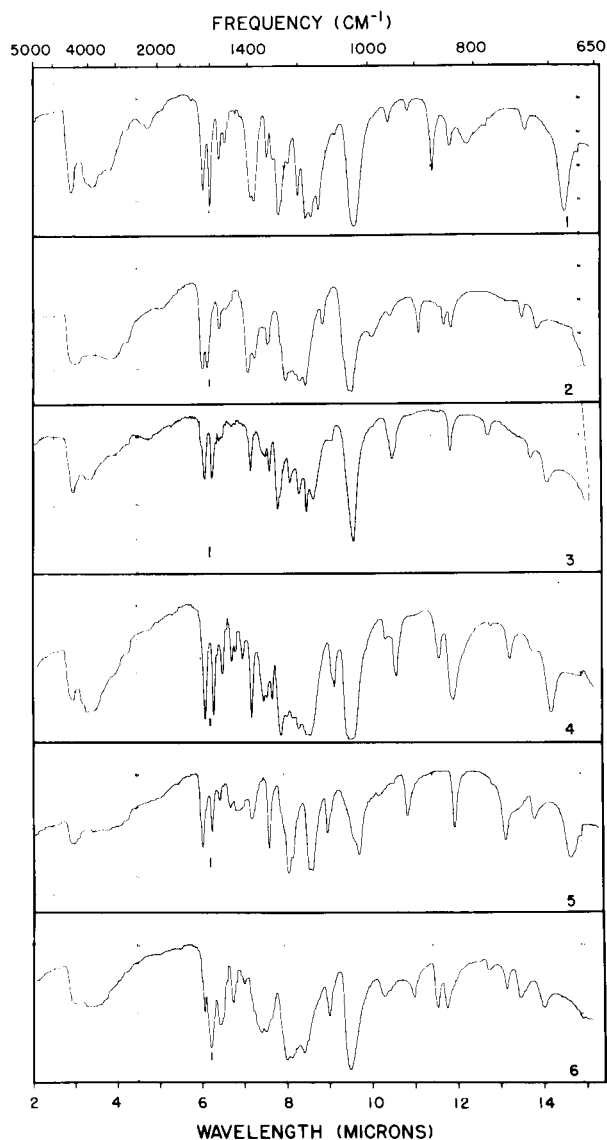


Figure 5. Ir spectra in potassium bromide of 1: 2-methyl-8-quinolinol-5-sulfonic acid, 2: 7-fluoro-2-methyl-8-quinolinol-5-sulfonic acid, 3: 7-chloro-2-methyl-8-quinolinol-5-sulfonic acid, 4: 7-bromo-2-methyl-8-quinolinol-5-sulfonic acid, 5: 7-iodo-2-methyl-8-quinolinol-5-sulfonic acid, 6: 2-methyl-7-nitro-8-quinolinol-5-sulfonic acid.

washed with water, and dried at 35° in a vacuum desiccator overnight. The yield of product was 33 g. (85%), m.p. 55-58°. After several recrystallizations from methanol, the compound melted at 63-64° [Lit. (7) m.p. 60-61°; lit. (18) m.p. 68°; lit. (19) m.p. 64°] and was shown to be over 99% pure by gas chromatography.

5-Bromo-2-methyl-8-quinolinol.

The title compound was prepared in a manner similar to that of the chloro analog by using *N*-bromosuccinimide in place of *N*-chlorosuccinimide. The yield of product was nearly quantitative,

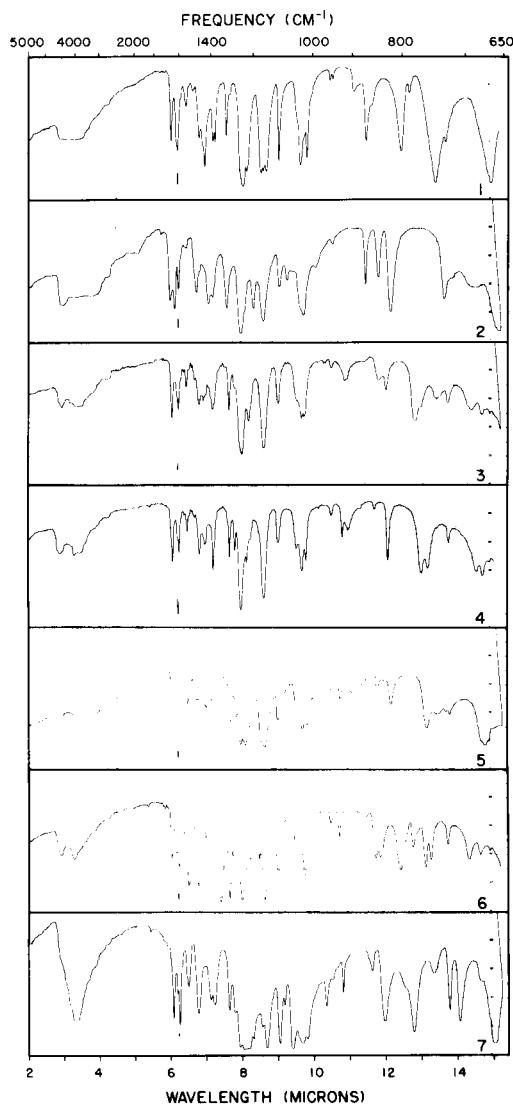


Figure 6. Ir spectra in potassium bromide of 1: 2-methyl-8-quinolinol-7-sulfonic acid, 2: 5-fluoro-2-methyl-8-quinolinol-7-sulfonic acid, 3: 5-chloro-2-methyl-8-quinolinol-7-sulfonic acid, 4: 5-bromo-2-methyl-8-quinolinol-7-sulfonic acid, 5: 5-iodo-2-methyl-8-quinolinol-7-sulfonic acid, 6: 2-methyl-7-nitro-8-quinolinol-7-sulfonic acid, 7: 2-methyl-8-quinolinol-5,7-disulfonic acid.

m.p. 63-67°. Upon crystallization from methanol, a gas chromatographically pure compound was obtained which melted at 67-68° [Lit. (7) m.p. 63-64°; Lit. (20) m.p. 68°].

5-Iodo-2-methyl-8-quinolinol.

A solution of 120 g. (0.47 mole) of iodine and 90 g. (0.54 mole) of potassium iodide in 250 ml. of water was added over 4 hours to a suspension of 80 g. (0.5 mole) of 2-methyl-8-quinolinol in a solution of 98 g. (1.0 mole) of potassium acetate in 600 ml. of water at room temperature. After stirring overnight, sufficient

sodium bisulfite was added to reduce any unreacted iodine, and the product was removed by filtration, washed with water, and dried at 70° overnight. The dried product was extracted with 300 ml. of boiling ethanol, which on refrigeration overnight, yielded 102 g. (71%) of material, m.p. 126-148°. After several additional recrystallizations from ethanol the compound melted at 151-152° [lit. (7) m.p. 151-153°] and was over 99% pure by gas chromatographic assay.

5-Fluoro-2-methyl-8-quinolinol-7-sulfonic Acid.

5-Fluoro-2-methyl-8-quinolinol (1.8 g., 0.01 mole) was heated to 200° in 30 ml. of 10% oleum. The solution was allowed to cool to room temperature and was poured onto ice. The crystalline sulfonic acid was filtered off, washed with water followed by acetone, and dried at 70° overnight. The yield of product was 2.1 g. (75%) as the monohydrate.

5-Chloro-2-methyl-8-quinolinol-7-sulfonic Acid.

The title compound was prepared from 5-chloro-2-methyl-8-quinolinol (5.0 g., 0.026 mole) by heating in 50 ml. of 10% oleum to 160°. The isolation procedure was similar to that for the 5-fluoro compound. The yield of product was 6.3 g. (84%) as the monohydrate.

5-Bromo-2-methyl-8-quinolinol-7-sulfonic Acid.

This compound was obtained in 78% yield by the same method as employed for the preparation of the 5-chloro derivative.

2-Methyl-8-quinolinol-7-sulfonic Acid.

A suspension of 9.5 g. (0.033 mole) of 5-chloro-2-methyl-8-quinolinol-7-sulfonic acid and 1.0 g. of 10% palladium on charcoal in 250 ml. of hot water was shaken in a Parr hydrogenator until 0.033 mole of hydrogen was taken up. The mixture was heated and filtered, and the insoluble residue was extracted twice with 100 ml. volumes of hot water. After refrigerating overnight, the product was obtained by filtration, washed with water and acetone, and dried at 70° overnight. A yield of 8.5 g. (83%) of compound was obtained, m.p. 305-306° dec.

5-Iodo-2-methyl-8-quinolinol-7-sulfonic Acid.

2-Methyl-8-quinolinol-7-sulfonic acid (2.05 g., 0.0086 mole) and *N*-iodosuccinimide (2.25 g., 0.01 mole) were stirred overnight in a mixture of 20 ml. of methanol and 5 ml. of water. The product was removed by filtration, washed with water and acetone, and dried at 70° overnight, and the yield was 95% of the theoretical.

2-Methyl-5-nitro-8-quinolinol-7-sulfonic Acid.

2-Methyl-8-quinolinol-7-sulfonic acid (2.05 g., 0.008 mole) was dissolved in 11 ml. of 2% oleum. Nitric acid (0.75 ml.) was added with stirring during 30 minutes keeping the temperature at 0°. Stirring was continued for an additional 30 minutes at 0°, and the solution was then poured onto ice. The product was obtained in 97% yield by filtration, washing with water and acetone, and drying at 70° overnight.

2-Methyl-8-quinolinol-5-sulfonic Acid.

2-Methyl-8-quinolinol (500 g., 3.14 moles) was dissolved in 2000 ml. of sulfuric acid with heating and stirring. The solution was allowed to cool to 65° and 1000 ml. of 20% oleum was added. Stirring was continued for an additional 2 hours after which the solution was poured onto ice. Acetone (3000 ml.) was added to the mixture and the crystalline product was removed by filtration, washed with acetone and dried at 70° overnight. The product was obtained in 81% yield as the monohydrate.

7-Chloro-2-methyl-8-quinolinol-5-sulfonic Acid.

To a solution of 25.7 g. (0.1 mole) of 2-methyl-8-quinolinol-5-sulfonic acid monohydrate and 16 g. (0.28 mole) of potassium hydroxide in 250 ml. of water was added 250 ml. of sodium hypochlorite (5.25% active chlorine). After stirring for 1.5 hours at ambient temperature, the solution was passed through a column of Amberlite IR-120 (H⁺) to remove cations, and the effluent was flash evaporated to a small volume, which was doubled by addition of acetone. The product was obtained by filtration, washing with acetone, and drying at 70° overnight. The yield of compound was 91%, m.p. 306-307° dec.

7-Bromo-2-methyl-8-quinolinol-5-sulfonic Acid.

To a slurry of 25.7 g. (0.1 mole) of 2-methyl-8-quinolinol-5-sulfonic acid monohydrate in 80 ml. of water adjusted to pH 6 with potassium hydroxide was added dropwise with stirring a solution of potassium hypobromite composed of 14 g. (0.25 mole) of potassium hydroxide and 20 g. (0.125 mole) of bromine in 60 ml. of water. After completion of addition of the hypobromite solution, stirring was continued for an additional hour. The mixture was brought to pH 1 with 48% hydrobromic acid and cooled to 5°, after which the product was removed by filtration and washed with water and acetone. The yield of compound was 85%, m.p. 271° dec.

7-Iodo-2-methyl-8-quinolinol-5-sulfonic Acid.

The title compound was obtained as the monohydrate in 52% yield by reacting 2-methyl-8-quinolinol-5-sulfonic acid monohydrate with *N*-iodosuccinimide in the same manner as for the preparation of 5-iodo-2-methyl-8-quinolinol-7-sulfonic acid.

2-Methyl-7-nitro-8-quinolinol-5-sulfonic Acid.

2-Methyl-8-quinolinol-5-sulfonic acid monohydrate (486 g., 2.0 moles) was dissolved in 2500 ml. of sulfuric acid and cooled to -30° in a dry ice acetone bath. Nitric acid (70%, 200 g., 3.0 moles) was added dropwise with agitation during the course of 2 hours. After all of the nitric acid had been added, the temperature was allowed to rise to 0°, and the solution was poured onto ice. The product was removed by filtration, washed with acetone, and air dried. The yield of compound was 88%, m.p. 283°.

2-Methyl-7-nitro-8-quinolinol.

2-Methyl-7-nitro-8-quinolinol-5-sulfonic acid (135 g., 0.46 mole) was heated with stirring under reflux in a mixture of 750 ml. of acetic acid and 75 ml. of sulfuric acid for 48 hours. The solution was diluted with an equal volume of water and filtered to remove a small quantity of 5,7-dinitro-2-methyl-8-quinolinol. The filtrate was then adjusted to pH 5 with aqueous ammonia, and the product was obtained by filtration, washed with water, and dried at 70° overnight. The yield of product was 65 g. (70%), m.p. 179-181°.

7-Amino-2-methyl-8-quinolinol Hydrochloride.

The title compound was prepared in 90% yield from the corresponding nitro derivative by the same method as employed for the preparation of 5-amino-2-methyl-8-quinolinol hydrochloride.

7-Fluoro-2-methyl-8-quinolinol.

The title compound was prepared in 1.7% yield from the amino derivative by the method employed for the preparation of 5-fluoro-2-methyl-8-quinolinol.

7-Fluoro-2-methyl-8-quinolinol-5-sulfonic Acid.

7-Fluoro-2-methyl-8-quinolinol (0.8 g., 0.0049 mole) was dissolved in 10 ml. of 20% oleum and heated to 150°. The solution

was cooled to room temperature and poured onto ice. An equal volume of acetone was added to the solution, and it was stirred for 2 hours. The product (0.8 g., 64%) which was removed by filtration, washed with acetone, and dried at 70° overnight, melted at 310° dec.

7-Chloro-2-methyl-8-quinolinol.

7-Chloro-2-methyl-8-quinolinol-5-sulfonic acid was desulfonated by the method employed for the preparation of 2-methyl-7-nitro-8-quinolinol. The yield of product was 42% of the theoretical, m.p. 112-115° and was nearly pure by gas chromatographic assay.

7-Bromo-2-methyl-8-quinolinol.

The title compound was prepared from 7-bromo-2-methyl-8-quinolinol-5-sulfonic acid in 57% yield in the same manner as the 7-chloro derivative, and it melted at 126-128° and was nearly pure by gas chromatographic assay.

7-Iodo-2-methyl-8-quinolinol.

To 100 g. of sulfuric acid diluted with 8 ml. of water was added 8.5 g. (0.05 mole) of 2-methyl-8-quinolinol. The temperature was kept at 5-10° by external cooling, and 11.3 g. (0.05 mole) of *N*-iodosuccinimide was added in small portions during 0.5 hour. After stirring overnight, 500 g. of ice was added to the solution which was subsequently decolorized by addition of sodium bisulfite. The solution was adjusted to pH 5 with aqueous ammonia and further diluted with 1000 ml. of ice water. After filtration, washing with water, and drying at 70° overnight, the product weighed 8.3 g. (56%), m.p. 83-84°. A gas chromatographic assay indicated the presence of only a trace of starting material as the impurity.

2-Methyl-8-quinolinol-5,7-dichlorosulfonate.

2-Methyl-8-quinolinol (10 g., 0.063 mole) was heated to 160° in 100 ml. of chlorosulfonic acid. After cooling the solution to 5°, it was poured onto ice, and the precipitate was removed by filtration, washed with water and dried at room temperature under vacuum. The yield of product was 11.2 g. (50%), m.p. 140-175°. An analytical sample which charred slowly above 225° was prepared by recrystallizing twice from benzene.

Anal. Calcd. for C₁₀H₇Cl₂NO₅S₂: C, 33.72; H, 1.98; Cl, 19.91; N, 3.93. Found: C, 33.98; H, 2.19; Cl, 19.73; N, 3.89.

2-Methyl-8-quinolinol-5,7-disulfonic Acid.

2-Methyl-8-quinolinol-5,7-dichlorosulfonate (10 g., 0.028 mole) was hydrolyzed by stirring with 25 ml. of water overnight. Upon flash evaporation of the liquid, 8.0 g. (80%) of the dihydrate of the disulfonic acid was obtained, m.p. 295-300° dec.

REFERENCES

- (1) This work was supported in part by the U. S. Public Health Service, Grant AI-05808.
- (2) H. Gershon, R. Parmegiani, A. Weiner, and R. D'Ascoli, *Contrib. Boyce Thompson Inst.*, **23**, 219 (1966).
- (3) H. Gershon, *J. Med. Chem.*, **11**, 1094 (1968).
- (4) H. Gershon, M. W. McNeil, and Y. Hinds, *ibid.*, **12**, 1115 (1969).
- (5) H. Gershon, S. G. Schulman, and D. Olney, *Contrib. Boyce Thompson Inst.*, **24**, 167 (1969).
- (6) H. Gershon, W. P. Kilroy, and S. G. Schulman, *ibid.*, **24**, 351 (1971).
- (7) R. G. Beimer and Q. Fernando, *Anal. Chem.*, **41**, 1003 (1969).
- (8) V. Petrow and B. Sturgeon, *J. Chem. Soc.*, 570 (1954).
- (9) H. Gershon, M. W. McNeil, and S. G. Schulman, *J. Org. Chem.*, **36**, 1616 (1971).
- (10) H. Gershon, M. W. McNeil, and A. T. Grefig, *ibid.*, **34**, 3268 (1969).
- (11) J. Fresco and H. Freiser, *Inorg. Chem.*, **2**, 82 (1963).
- (12) H. Gershon and M. W. McNeil, *J. Heterocyclic Chem.*, **8**, 821 (1971).
- (13) H. Gershon and M. W. McNeil, *J. Org. Chem.*, **36**, 3494 (1971).
- (14) J. P. Phillips and L. L. Merritt, *J. Am. Chem. Soc.*, **70**, 410 (1948).
- (15) Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector. The purity of all the monohalogeno 2-methyl-8-quinolinols was established by gas chromatographing the trimethyl silyl derivatives (16). The chloro derivatives were separated using a column packed with 10% QF-1 on acid-washed chromosorb W (80/100 mesh), bromo derivatives were separated by means of a column packed with 5% OV-225 on high performance chromosorb W (80/100 mesh), and iodo derivatives were separated by a column containing 1% Apiezon L on acid washed chromosorb W (80/100 mesh), previously treated with dimethyldichlorosilane. Nmr spectra were taken with a Jeolco JNM-C-60HL spectrometer.
- (16) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Am. Chem. Soc.*, **88**, 3390 (1966).
- (17) A. F. Helin and C. A. Vanderwerf, *J. Org. Chem.*, **17**, 229 (1952).
- (18) M. Weizmann and E. Bograchov, *ibid.*, **69**, 1222 (1947).
- (19) E. Pfanner, Swiss Patent, 253,474 (1948); *Chem. Abstr.*, **44**, 669 (1950).
- (20) A. R. Pinnington, Ph.D. Thesis, Oxford (1954), in "Oxine and Its Derivatives," Vol. 3, R. G. W. Hollingshead, Butterworths, London, 1956, p. 779.