Registry No.—1, 607-66-9; **3a**, 21298-73-7; **3b**, 21298-74-8; **3c**, 21298-75-9; **3d**, 21298-76-0; **4a**, 21298-77-1; **4b**, 21298-78-2; **4c**, 21298-79-3; **5**, 21298-80-6; **6**, 21298-81-7; **12**, 21298-82-8; **13**, 12370-05-7; **14**, 21298-87-3; **15a**, 21298-83-9; **15b**, 21298-84-0; **16a**, 21298-86-2; **16b**, 21298-85-1.

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Reinvestigation of the Action of N-Halosuccinimides on Bis(8-quinolinolato)copper(II)[1]

HERMAN GERSHON, MAYNARD W. MCNEIL, AND A. T. GREFIG

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

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Halogenation of bis(8-quinolinolato)copper(II) with N-halosuccinimides revealed that on monochlorination a mixture of 5- and 7-chloro chelates was obtained, whereas, on monobromination, only the 5-bromo chelate and on monoiodination the 7-iodo chelate formed. Convenient syntheses of 7-chloro-, 7-bromo-, and 7-iodo-8-quinolinols from 8-quinolinol derivatives were also achieved.

As part of our studies on the mechanisms of antifungal action of 8-quinolinol and derivatives,[2-5] it was desired to prepare the copper(II) complex of tritiated 5-iodo-8-quinolinol. The method of Prasad, *et al.*,[6] appeared to offer a good approach to this compound. It was reported that on treatment of cobalt(III), aluminum(III), cobalt(II), and copper(II), chelates of 8-quinolinol with either N-chloro-, N-bromo-, or N-iodosuccinimide (1 mol/mol of 8-quinolinol in the chelate) in chloroform solution, monhalogenation took place, and that the halogen was found exclusively in the 5 position of the quinoline. This was reported to have been determined by comparison of the infrared and proton magnetic resonance spectra of the ligands prepared in this manner with the spectra obtained of authentic samples of the 5-halogeno-8-quinolinols.

Preliminary trials with the iodination of nontritiated 8-quinolinol copper(II) chelate by means of N-iodosuccinimide in chloroform[6] were carried out at 40–60° in order to reduce the volume of solvent employed. After completing several iodination reactions, the complex obtained always melted between five and ten degrees lower than authentic bis(5-iodo-8-quinolinolato)copper(II). Thin layer chromatography on silica gel revealed that the product obtained *via* N-iodosuccinimide had an R_f value different from those of authentic samples of bis(5-iodo-8-quinolinolato)copper(II). Differences in the infrared spectra of the respective ligands and copper(II) chelates also were found.

As a result of our inability to obtain the desired product by the method described[6] together with the incorrect characterization of the product reported,[6] it was deemed desirable to reinvestigate the halogenation of bis(8-quinolinolato)copper(II) with N-halosuccinimides. Several variations of the conditions of halogenation were carried out. All reactions were conducted in chloroform, and the molar ratios of N-halosuccinimide to chelate were 2:1, 4:1, and 6:1. Reaction temperatures were either ambient or in the range of 40–60°, and the reaction time was 3 hr in all cases. The different ratios of halogenating agent to chelate were employed to determine whether only monohalogenation could take place and, if not, what the orientation of second and possibly third substituents would be. Since it was reported that the rates of halogenation were too rapid for classical kinetic studies,[6] it was felt that kinetic effects might still be detected, on a gross scale, by identifying the formed products and determining their ratios. For this reason, two reaction temperatures were employed.

Upon completion of each halogenation, the reaction mixture was freed of solvent by evaporation, and the residue was dissolved in acid and treated with hydrogen sulfide to eliminate the copper(II). The filtrate was brought to pH 5 and extracted with chloroform in order to obtain all of the 8-quinolinols present. They were then converted into the trimethylsilyl derivatives and subjected to gas chromatography. The products were identified by retention times and infrared spectra. Quantitation was achieved by determining the area under the peaks in the gas chromatograms. Where only one product was detected or an overwhelming proportion of one component was present, infrared spectra of the chelates were taken and compared with spectra of authentic samples.

Retention data are listed in Table I, and the results of the halogenation reactions are compiled in Table II. Infrared spectra of the copper(II) chelates and their respective ligands have been obtained.[7]

The data of Table II indicate that chlorination of bis(8-quinolinolato)copper(II) with N-chlorosuccinimide yielded three halogenated derivatives, 5-chloro-, 7-chloro-, and 5,7-dichloro-8-quinolinol. It appears that the two monohalogeno quinolinols formed simultaneously, and that raising the temperature somewhat favored the formation of 5-chloro-8-quinolinol over the

(1) This work was supported in part by the U. S. Public Health Service, Grant AI-05808.

(2) H. Gershon and R. Parmegiani, *Appl. Microbiol.*, **11**, 62 (1963).

(3) H. Gershon, R. Parmegiani, A. Weiner, and R. D'Ascoli, *Contrib. Boyce Thompson Inst.*, **23**, 219 (1966).

(4) H. Gershon and R. Parmegiani, *ibid.*, **24**, 33 (1968).

(5) H. Gershon, *J. Med. Chem.*, **11**, 1094 (1968).

(6) R. Prasad, H. L. D. Coffer, Q. Fernando, and H. Freiser, *J. Org. Chem.*, **30**, 1251 (1965).

(7) For infrared spectra, order document NAPS-00498 from ASIS National Auxiliary Publications Service, % CCM Information Services, Inc., 22 West 34th Street, New York, N. Y. 10001, remitting $1.00 for microfiche or $3.00 for photocopies.

TABLE I

RETENTION DATA OF TRIMETHYLSILYLATED 5-, 7-, AND 5,7-DISUBSTITUTED 8-QUINOLINOLS

Substituent on 8-quinolinol	Retention time,[a] min
None	1.5
5-Chloro	2.1
7-Chloro	2.4
5,7-Dichloro	3.0
5-Bromo	2.6
7-Bromo	2.8
5,7-Dibromo	4.0
5-Iodo	3.3
7-Iodo	3.5
5,7-Diiodo	5.5

[a] Gas chromatographic conditions are described in footnote 12.

concentration of iodinating agent. Nearly pure bis-(5,7-diiodo-8-quinolinolato)copper(II) was obtained with 6 equiv of N-iodosuccinimide per mol of bis(8-quinolinolato)copper(II).

On comparing the formation of dihalogeno compounds, it seems that the rates of halogenation of the monohalogenated chelates decrease in the following order of halogenating agent, N-bromosuccinimide > N-iodosuccinimide > N-chlorosuccinimide. The rate of monochlorination obviously is slower than either the rates of monobromination or monoiodination.

No attempt will be made to present mechanisms for these reactions, or explain the orientation of the substituents, but it is apparent that the results of Prasad, *et al.*,[6] are in error.

TABLE II

ACTION OF N-HALOSUCCINIMIDE ON BIS(8-QUINOLINOLATO)COPPER(II) IN CHLOROFORM

Halogenating agent	Molecular ratio of N-halosuccinimide to bis(8-quinolinolato)copper(II)	Temp, °C	Products, % (as free ligands)			
			Ox	5-ClOx	7-ClOx	5,7-Cl_2Ox
NCS[a]	2	Ambient	22	38	34	6
	4	Ambient	3	41	51	5
	6	Ambient	4	33	52	11
	2	40–60	16	61	18	5
	4	40–60	10	47	38	5
	6	40–60	0	59	38	3
			Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
NBS	2	Ambient	10	80	0	10
	4	Ambient	0	tr[c]	0	99
	6	Ambient	0	0	0	100
	2	40–60	0	72	0	28
	4	40–60	0	tr	0	99
	6	40–60	0	0	0	100
			Ox	5-IOx	7-IOx	5,7-I_2Ox
NIS	2	Ambient	tr	0	99	tr
	4	Ambient	0	0	62	38
	6	Ambient	0	0	tr	99
	2	40–60	5	0	92	3
	4	40–60	0	0	33	67
	6	40–60	0	0	tr	99

[a] NCS = N-chlorosuccinimide; NBS = N-bromosuccinimide; NIS = N-iodosuccinimide. [b] Ox = 8-quinolinol. [c] tr = trace.

7 isomer. Addition of the second chlorine seemed to be a slow step which would explain the nearly constant yield of dichloro product in all six runs.

N-Bromosuccinimide afforded only 5-bromo-8-quinolinol as a monohalogenated product, which was further brominated to 5,7-dibromo-8-quinolinol. Under none of these reaction conditions was it possible to form 5-bromo-8-quinolinol free of 5,7-dibromo-8-quinolinol. Addition of the second bromine atom to the 7 position of 5-bromo-8-quinolinol is undoubtedly slower than the first monobromination step, but its rate is favored by increased temperature and increased concentration of N-bromosuccinimide. Only 5,7-dibromo-8-quinolinol was obtained when an excess of brominating agent was employed. Nearly pure bis(5,7-dibromo-8-quinolinolato)copper(II) was obtained with 4 equiv of brominating agent.

Iodination with N-iodosuccinimide yielded only one iodination product, 7-iodo-8-quinolinol, and at ambient temperatures the chelate, bis(7-iodo-8-quinolinolato)-copper(II), was nearly pure. An increased reaction temperature caused an increase in the rate of formation of the 5,7-diiodo compound, as did increasing the

8-Quinolinol, the 5-chloro, 5-bromo, 5,7-dichloro, 5,7-dibromo, 5,7-diiodo, and 5-sulfonic acid analogs, as well as the N-halosuccinimides, were commercially available. 5-Iodo-8-quinolinol was prepared according to the method of Coll and Coll.[8] The 7-chloro and 7-bromo derivatives of 8-quinolinol were obtained in high yield and purity by modifications of the procedure of Claus and Giwartovsky.[9] The preparation of 7-bromo-8-quinolinol was recently reported by Pearson, Wysong, and Breder[10] by two methods. The first depended on the action of bromine in the presence of *t*-butylamine on 8-quinolinol in toluene at −70°. It was claimed that 92% pure 7-bromo-8-quinolinol was obtained. In our hands, this procedure yielded mixtures of which a typical analysis was as follows: 8-quinolinol, 30%; 5-bromo-8-quinolinol, 9%; 7-bromo-8-quinolinol, 46%; 5,7-dibromo-8-quinolinol, 15%. The second method that was suggested depended on the action of N-bromosuccinimide on 8-quinolinol in

(8) A. L. Coll and G. P. Coll, *Afinidad*, **28**, 101 (1951).
(9) A. Claus and R. Giwartovsky, *J. Prakt. Chem.*, **54**, 377 (1896).
(10) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

toluene, also at −70°. Although 7-bromo-8-quinolinol was obtained in good yield, it was accompanied by small quantities of 8-quinolinol and the 5,7-dibromo derivative. Copper(II) chelates of all of the ligands were prepared by methods compiled by Hollingshead.[11]

Experimental Section[12]

Halogenation of Bis(8-quinolinolato)copper(II) with N-Halosuccinimides.—To a suspension of 352 mg (1 mmol) of bis(8-quinolinolato)copper(II) in 30 ml of chloroform was added, 2, 4, or 6 mmol of the respective N-halosuccinimide. The mixture was stirred on a magnetic stirrer hot plate for 3 hr keeping the volume nearly constant by addition of chloroform, as needed. The hot plate was set to maintain temperatures of 40–60°. At the end of the reaction period, the solvent was evaporated, and, for further study of the chelates, the residues were boiled several times in acetone, filtered, and dried. For the study of ligands, the residues were each dissolved in 5 ml of concentrated HCl, diluted to 25 ml with deionized H_2O, and treated with H_2S until completion of precipitation of Cu(II)S. The liquid was adjusted to about pH 5 with potassium acetate and extracted with chloroform. The quinolinols were obtained by evaporating a portion of the extract and examined by ir spectroscopy. Another portion of the chloroform extract was treated with N,O-bis(trimethylsilyl)acetamide to form trimethylsilyl derivatives, according to the method of Klebe, *et al.*,[13] and chromatographed.

7-Chloro-8-quinolinol-5-sulfonic Acid.—To a solution of 11.3 g (0.05 mol) of 8-hydroxyquinoline-5-sulfonic acid in 125 ml of H_2O was added 7.8 g (0.14 mol) of KOH and 250 ml of NaOCl (5.25% active chlorine). After stirring for 1.5 hr at room 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. The residual volume was doubled by addition of acetone, and the product was obtained by filtration and rinsing with acetone. The yield of compound was nearly quantitative and melted at 290–320° dec.[14]

7-Chloro-8-quinolinol.—A suspension of 10.5 g (0.04 mol) of 7-chloro-8-quinolinol-5-sulfonic acid in 250 ml of glacial acetic acid was heated under reflux with agitation for 48 hr until a clear solution was obtained. It was diluted to 1 l. with deionized H_2O, and NaOH pellets were added with stirring to pH 5. The product was removed by filtration, washed free of salts with deionized H_2O, and dried at 70°, overnight. The yield of compound was 6.3 g (87%), mp 150–155°. Purification was achieved by sublimation followed by crystallization from an equal mixture of methanol and dimethylformamide, mp 157–158°.[15]

Bis(7-chloro-8-quinolinolato)copper(II).—To a solution of 100 mg (0.5 mmol) of copper(II) acetate monohydrate in 80% aqueous methanol was added a solution of 180 mg (1.0 mmol) of 7-chloro-8-quinolinol in methanol, and the mixture was stirred for 1 hr. The chelate was obtained by filtration and boiled in acetone and again filtered off. This was repeated several times. The yield of compound was nearly quantitative, mp 302° dec.[16]

Anal. Calcd for $C_{18}H_{10}Cl_2N_2O_2Cu$: 51.38; H, 2.40; N, 6.66. Found: C, 51.50; H, 2.44; N, 6.56.

7-Bromo-8-quinolinol-5-sulfonic Acid.—A slurry of 24.3 g (0.1 mol) of 8-quinolinol-5-sulfonic acid monohydrate and 5.6 g (0.1 mol) of KOH was prepared in 25 ml of H_2O. Potassium hypobromite, prepared from 20 g (0.125 mol) of Br_2 and 14 g (0.25 mol) of KOH in 60 ml of H_2O, was added dropwise to the slurry at room temperature with agitation. The mixture was stirred for 1 hr after completion of addition of the hypobromite or until a negative starch–iodide test was obtained and was then adjusted to pH 1 with 48% HBr. Upon cooling to 5° in an ice bath, the product was obtained by filtration, washed successively with 1 vol each of H_2O, ethanol, and acetone, and dried at 70° for 2 hr. The yield of product was 29 g (95%), mp 253–257° dec. The material (22 g) was dissolved in 75 ml of H_2SO_4, diluted with 140 ml of H_2O, and cooled to 5°. The product was removed by filtration, and a second yield of compound was obtained on further dilution of the filtrate. The combined materials were recrystallized from H_2O to yield 18 g of pure compound, mp 280° dec.[17]

7-Bromo-8-quinolinol.—7-Bromo-8-quinolinol-5-sulfonic acid (30.4 g, 0.1 mol) was heated for 4 hr under reflux with stirring in a mixture composed of 30 g of H_2SO_4 and 270 g of acetic acid. The clear solution was diluted to 4000 ml with deionized H_2O and adjusted to pH 5 with KOH. The product was obtained by filtration, washing with H_2O, and drying at 70°, overnight. The yield of compound was 21 g (90%), mp 139–140°.[18]

Bis(7-bromo-8-quinolinolato)copper(II).—was prepared as was the 7-chloro-8-quinolinol copper chelate in nearly quantitative yield, mp 265° dec.

Anal. Calcd for $C_{18}H_{10}Br_2N_2O_2Cu$: C, 42.42; H, 1.98; N, 5.50. Found: 42.67; H, 1.96; N, 5.42.

7-Iodo-8-quinolinol. Method A.—7-Amino-8-quinolinol hemisulfate[5] (21.0 g, 0.1 mol) was dissolved in a mixture of 75 ml of H_2O and 75 g of ice. To the solution was added 44 ml of 47% HI (0.24 mol), and the magnetically stirred mixture was brought to 0° in an ice–acetone bath. Powdered $NaNO_2$ (14.5 g, 0.21 mol) was added in small portions during 0.5 hr and stirring was continued 1 hr longer, after which 59 ml (0.32 mol) of HI was added, and stirring was continued 0.5 hr longer. The cooling bath was removed, the mixture was allowed to come to room temperature, and 200 mg of copper powder was added. After heating the material to 75–80° for 15 min, it was brought to boiling and heated until N_2 evolution ceased. Insoluble materials were removed by filtration, and elemental iodine was reduced with $NaNSO_3$. The solution was adjusted to approximately pH 5 by adding potassium acetate, and the product was obtained by filtration and washing with deionized H_2O. Additional product was obtained from the insoluble residue by extraction with 10% NaOH, filtration, and acidification with acetic acid to pH 5. The combined yields were 8.7 g, mp 100–140°. The material was steam distilled and recrystallized twice from 70% aqueous ethanol to yield 3 g (11%) of product mp 108–109°.

Anal. Calcd for C_9H_6INO: C, 39.88; H, 2.23; I, 46.82; N, 5.17. Found: C, 39.73; H, 2.13; I, 47.29; N, 4.78.

Method B.—A uniform suspension of 16.6 g (0.047 mol) of bis(8-quinolinolato)copper(II) in 1000 ml of $CHCl_3$ was prepared by magnetic stirring. N-Iodosuccinimide (21.2 g, 0.094 mol) was added in portions during 5 min, and the mixture was allowed to stir for 2 hr. The product was removed by filtration, washed with acetone, and suspended in 1000 ml of 6 *N* HCl. After stirring the suspension overnight, the insoluble material was removed by filtration and washed three times with 100-ml portions of 6 *N* HCl. The material was suspended in H_2O and the suspension adjusted to pH 5 with potassium acetate. 7-Iodo-8-quinolinol was filtered off, washed with deionized H_2O, and dried at 70°, overnight. The yield of compound was 21.6 g (85%), mp 109–110°. The absence of 8-quinolinol and 5,7-diiodo-8-quinolinol was demonstrated by gas chromatography.[19]

Bis(7-iodo-8-quinolinolato)copper(II).—was prepared in the same manner as the chloro analog in nearly quantitative yield, mp 263° dec.

Anal. Calcd for $C_{18}H_{10}I_2N_2O_2Cu$: C, 34.73; H, 1.70; N, 4.72. Found: C, 34.77; H, 1.58; N, 4.55.

Registry No.—Bis(8-quinolinolato)copper(II), 10380-28-6; bis(7-chloro-8-quinolinolato)copper(II), 21713-28-0; bis(7-bromo-8-quinolinolato)copper(II), 21713-29-1; 7-iodo-8-quinolinol, 21713-32-6; bis(7-iodo-8-quinolinolato)copper(II), 21713-26-8.

(11) R. G. W. Hollingshead, "Oxine and Its Derivatives," Vol. 3, Butterworth and Co. Ltd., London, 1956.

(12) 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 to which was attached a Varian Aerograph Model 20 recorder. A stainless steel column, 5 ft × 0.125 in. o.d., was packed with 5% QF-1 (Analabs, Hamden, Conn.) coated on 80–100 mesh Chromosorb W, previously treated with hexamethylsilazane. The instrument was operated at a column starting temperature of 175° which was programmed at 12°/min to 250°. The injector and detector temperatures were maintained at 230 and 250°, respectively, while the flow rate of nitrogen was 28 ml/min. Thin layer chromatography was carried out on Eastman chromatogram sheets 6060, containing silica gel with fluorescent indicator. The solvent employed was a 3:1 mixture of chloroform and toluene (v/v).

(13) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

(14) Lit. mp >300°: A. L. Coll and G. P. Coll, *Afinidad*, **28**, 163 (1951).

(15) Lit. mp 156°: A. Albert and D. Magrath, *Biochem. J.*, **41**, 534 (1947).

(16) Compound was mentioned in ref 15 but not characterized.

(17) Lit.[14] mp 280° dec.

(18) Lit.[9] mp 138°.

(19) Gas chromatographic conditions are described in footnote 12.