C_6H_6 and then petr ether to give 3.5 g (80%) of **7**, mp 254–256° dec. This reaction was repeated again on the same scale and the combined product, without further identification was treated with 85% $H_2NNH_2 \cdot H_2O$ (0.9 g, 0.015 mole) and a mixture of 810 ml of ethanol–890 ml of $CHCl_3$. After heating under reflux for 2 hr, the soln was acidified with 0.1 *N* HCl and heated under reflux for another 15 min. The soln was evapd and the residue boiled with 500 ml of EtOH and filtered to remove insoluble solid (discarded). The filtrate was heated under reflux overnight and concd to dryness, and the yellow residue was dissolved in EtOH and filtered over silica gel with EtOH as eluant. Evaporation gave 1.1 g of **8** which was recrystd from EtOH–C_6H_6, mp 274–276°, nmr (DMSO-d_6) δ 4.1 (s, 2H), 6.5, 7.0 (q, 2H, J_{AB} = 2.5 Hz). *Anal.* ($C_{15}H_{11}ClN_2O_2$) C, H, N.

7-Chloro-9-hydroxy-1,3-dihydro-5-phenyl-2*H*-benzodiazepin-2-one 4-Oxide (9). A soln of **8** (1 g, 0.0035 mole) in a mixture of 100 ml of CH_2Cl_2–50 ml of $CHCl_3$ was treated with *m*-chloroperbenzoic acid (0.8 g, 0.0046 mole) and stirred overnight at room temp. The ppt was filtered, washed with CH_2Cl_2–petr ether (1:1), and air-dried to yield 0.75 g (70% of **9**, mp 235–239° dec). Recrystn from C_6H_6–CH_3OH gave white needles, mp 236–238° dec. *Anal.* ($C_{15}H_{11}ClN_2O_3$) C, H, N.

5-Benzoyl-7-chloro-2*H*-1,4-benzoxazin-3(4*H*)-one (10). A suspension of **6** (2.5 g, 0.01 mole) in 25 ml of C_6H_6 was treated dropwise with bromoacetyl bromide (2.4 g, 0.012 mole) in 3 ml of C_6H_6 and then heated under reflux for 1.5 hr. After cooling to *ca.* 50°, the soln was decanted from a gummy residue and poured into a stirred mixture of 100 ml of CH_2Cl_2–100 ml of ice H_2O. After being made alk with $NaHCO_3$ (satd), the organic phase was separated, washed, dried, and concd. The gummy residue was dissolved in CH_2Cl_2–C_6H_6 (3:1) and filtered over Florisil to give after concn 2.6 g (70%) of the bromoacetamido deriv of **6** as off-white crystals, mp 145–147°. This solid was dissolved in 50 ml of CH_2Cl_2 and was added dropwise with stirring to 15 ml of liquid NH_3. After all the NH_3 had evapd, H_2O was added and the CH_2Cl_2 layer was separated, washed, dried, and concd to give 1.8 g of greenish yellow solid, mp 115–120°. After filtering over silica gel with the aid of EtOAc–hexane, **10** was obtained as yellow crystals, mp 128–130°. Recrystn from CH_2Cl_2–hexane gave yellow needles, mp 134–135°, ir ($CHCl_3$) ν_{max} 1700 cm^{-1} (C=O). *Anal.* ($C_{15}H_{10}ClNO_3$) C, H, N.

Acknowledgment. The authors are indebted to the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. T. Williams and Mr. S. Traiman; and to Dr. F. Scheidl and his staff for the microanalyses.

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Antifungal Activity of 7- and 5,7-Substituted 8-Quinolinols†

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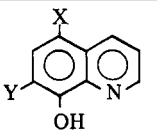
Although 8-quinolinol and some of its derivatives have been known to exhibit excellent antifungal properties, the mechanism of action of this class of compounds is not yet fully understood. A systematic approach has been undertaken to study 8-quinolinol and its derivatives with respect to structure–activity relationships and cell penetration of their copper(II) chelates.[1-4] As part of this study, it was of interest to examine the fungitoxicity of the 7-halo- and 5,7-dihalo-8-quinolinols in which the two substituents of the disubstituted derivatives were different. In addition to these compounds, four nitro-8-quinolinols were included to complete earlier reports,[3,4] as was also 5,7-difluoro-8-quinolinol.[2]

Of the compounds tested (Table II), the preparation of the following 8-quinolinols was previously reported: 7-fluoro,[5] 7-chloro,[6] 7-bromo,[6] 7-iodo,[6] 7-nitro,[7] 5-fluoro-7-iodo,[8] 7-bromo-5-chloro,[9] 5-chloro-7-iodo,[10] 5-bromo-7-chloro,[11] 5-bromo-7-iodo,[12] 5-bromo-7-nitro,[5] 7-chloro-5-iodo,[5] 7-bromo-5-iodo,[13] 5-iodo-7-nitro,[5] and 7-fluoro-5-nitro.[5]

Table I. 5,7-Disubstituted 8-Quinolinols



X	Y	Yield, %	Mp, °C[a]	Formula	Analyses
F	F	41	170–172[b]	$C_9H_5F_2NO$	C, H, F, N
F	Cl	61	172[c]	C_9H_5ClFNO	C, H, F, N
F	Br	91	172[d]	C_9H_5BrFNO	C, H, F, N
Cl	F	5.5	169–170[c]	C_9H_5ClFNO	C, H, F, N
Br	F	88	171–171.5[e]	C_9H_5BrFNO	C, H, Br, F, N
I	F	95	168–169[f]	C_9H_5FINO	C, H, F, I, N
Br	Cl	60	199–201[g]	$C_9H_5BrClNO$	C, H, N
I	Br	85	204 dec[h]	C_9H_5BrINO	C, H, N
Br	I	85	203 dec[i]	C_9H_5BrINO	C, H, N

[a] Analytical sample. [b] From cyclohexane–methylene chloride, *cf.* ref 16. [c] From EtOH. [d] From EtOH, *cf.* ref 17, where the compound was prepared but not characterized. [e] From cyclohexane–carbon tetrachloride. [f] From cyclohexane. [g] From MeOH, *cf.* ref 11, mp 189°. [h] From MeOH–DMF, *cf.* ref 13, mp 145–146°. [i] From MeOH–DMF, *cf.* ref 12.

All of the compounds were tested for purity by gas chromatographing their trimethylsilyl derivatives. It was found that a number of materials prepared by the methods of the literature were mixtures of products and not pure compounds. These had to be reinvestigated. 5-Iodo-7-chloro-8-quinolinol is typical of this group of compounds that was subsequently prepared correctly in an earlier work.[5] This was generally the case when it was desired to substitute a more electronegative halogen atom into the 7 position of a 5-halo-8-quinolinol which contained a less electronegative halogen substituent. The problem was overcome by starting with the halo-8-quinolinol which contained the more negative halogen atom in the desired position or by halogenating with the second halogen under controlled prototropic conditions.[14]

5,7-Difluoro-8-quinolinol was prepared by allowing 5-fluoro-8-quinolinol to react with trifluoromethyl hypofluorite. For the preparation of 7-chloro-5-fluoro-8-quinolinol, 5-fluoro-8-quinolinol was chlorinated by means of sulfuryl chloride in acetic acid, and 7-bromo-5-fluoro-8-quinolinol was also prepared from 5-fluoro-8-quinolinol by reaction with bromine in acetic acid. 5-Chloro-7-fluoro-8-quinolinol was prepared from 7-amino-5-chloro-8-quinolinol by a Baltz–Schiemann reaction, and 5-bromo- and 5-chloro-7-fluoro-8-quinolinols were obtained by halogenating 7-fluoro-8-quinolinol with the respective *N*-halosuccinimide in chloroform.

The data characterizing the new compounds are contained in Table I. All of the compounds were tested for antifungal activity according to published methods.[1] To Sabouraud

†This work was supported in part by the U. S. Public Health Service Grant No. AI-05808.

Table II. Minimal Antifungal Activity of 7- and 5,7-Substituted 8-Quinolinols[a]

		A. niger		*A. oryzae*		*Trichoderma viride*		*Trichophyton mentagrophytes*		*M. verrucaria*	
X	Y	S[b]	C	S	C	S	C	S	C	S	C
H	F	0.048	NA[c]	0.084	NA	0.018	0.048	0.012	0.018	0.018	0.018
H	Cl	0.017	NA	0.028	NA	0.011	NA	<0.0056	<0.0056	<0.0056	<0.0056
H	Br	0.013	0.22	0.013	0.22	<0.0045	<0.0045	<0.0045	0.0090	<0.0045	<0.0045
H	I	0.0074	0.31	0.033	NA	<0.0037	<0.0037	<0.0037	<0.0037	<0.0037	<0.0037
H	NO_2	0.33	NA	0.53	NA	0.053	0.16	0.016	0.016	0.074	0.11
F	F	0.044	NA	0.083	NA	0.017	0.061	0.022	0.088	0.011	0.011
F	Cl	0.015	0.33	0.020	0.48	<0.0051	<0.0051	<0.0051	0.010	<0.0051	0.010
F	Br	0.012	0.39	0.021	NA	<0.0041	<0.0041	<0.0041	0.0083	<0.0041	<0.0041
F	I	0.010	0.10	0.0024	NA	<0.0035	0.35	<0.0035	0.010	0.069	0.14
Cl	F	0.010	0.24	0.020	NA	<0.0051	0.12	<0.0051	<0.0051	<0.0051	<0.0051
Cl	Br	0.012	NA	0.015	NA	0.012	0.031	0.0077	0.012	<0.0039	0.0077
Cl	I	0.0098	NA	0.016	NA	0.013	NA	0.0098	0.0098	0.0065	0.0065
Br	F	0.012	0.39	0.024	0.41	0.012	NA	<0.0041	<0.0041	<0.0041	<0.0041
Br	Cl	0.0077	0.31	0.015	NA	<0.0039	0.027	<0.0039	0.0077	<0.0039	<0.0039
Br	I	0.0086	NA	0.057	NA	0.011	0.011	0.0057	0.0067	0.0057	0.0067
Br	NO_2	0.24	NA	0.22	NA	0.074	0.22	<0.0037	<0.0037	0.074	0.30
I	F	0.010	0.33	0.035	NA	0.010	NA	<0.0035	<0.0035	<0.0035	<0.0035
I	Cl	0.0098	0.13	NA		0.0098	0.036	<0.0033	0.0065	<0.0033	0.0065
I	Br	0.0086	NA	0.014	NA	0.0057	0.27	0.0057	0.017	0.0057	0.010
I	NO_2	0.20	NA	0.27	NA	0.13	0.16	0.013	0.013	0.25	0.28
NO_2	F	0.36	0.48	0.21	NA	0.048	0.048	<0.0048	<0.0048	0.062	0.96

[a]Min antifungal act., mmoles/l. [b]S = fungistatic, C = fungicidal. [c]NA = not active below 100 ppm, highest level tested.

dextrose broth (Difco) were added graded levels of test compound, dissolved in dimethyl sulfoxide, and inocula of each of *Aspergillus niger, Aspergillus oryzae, Trichoderma viride, Trichophyton mentagrophytes,* and *Myrothecium verrucaria.* After 6 days on a rotary shaker at 28°, records were made of all flasks that showed no apparent growth. These were diluted 1 to 100 in Sabouraud dextrose broth and incubated at 28° for 2 weeks to determine whether the inoculum was inhibited or killed. Thus, both fungistatic and fungicidal levels of test compound were established. The results are compiled in Table II.

It should be mentioned that the antifungal data on 7-fluoro-5-nitro-8-quinolinol are included as a correction of those in a previous report.[4] Similarly, the 7-nitro compounds included in this table are corrections for results also reported previously.[3] The errors resulted from rearrangements which were not recognized at the time the compounds were first believed to have been prepared. Later work[5,7] resulted in the preparation of the desired structures.

A comparison of the antifungal data on the 5- and 5,7-substituted 8-quinolinols reported earlier[2] with the results on the 7-substituted derivatives (Table II) reveals that in most cases the 7-halo-8-quinolinol is more fungitoxic than the corresponding 5-halo compound. 5,7-Difluoro- and 5,7-dichloro-8-quinolinols are about equally active with the 7-fluoro- and 7-chloro-8-quinolinols, respectively. The antifungal activity of 5,7-dibromo-8-quinolinol is very close to that of 5-bromo-8-quinolinol, and 5,7-diiodo-8-quinolinol is somewhat less active than 5-iodo-8-quinolinol. In the 7-halo series the order of fungitoxicity with respect to halogen is I = Br > Cl > F > H. The same pattern holds for the 7-substituted 5-fluoro-8-quinolinols, but no distinct pattern can be found among the remaining dihalo compounds. In general, isomeric disubstituted 8-quinolinols were nearly equally fungitoxic. The six most fungitoxic halo-8-quinolinols of the 25 compounds in the present and earlier[2] studies are the 7-bromo, 7-iodo, 7-chloro-5-fluoro, 7-bromo-5-fluoro, 5-chloro-7-fluoro, and 5-bromo-7-chloro derivatives.

Experimental Section‡

5,7-Difluoro-8-quinolinol. 5-Fluoro-8-quinolinol[8] (5.0 g, 0.031 mole) was dissolved in 300 ml of MeOH and cooled to −70°. To the solution was added trifluoromethyl hypofluorite (5.1 g, 0.048 mole) dissolved in 125 ml of trichlorofluoromethane at −70° with stirring. After 0.5 hr at this temperature, the cooling bath was removed, and the solvent was evaporated under a stream of air in a hood. The residue was suspended in H_2O and brought to pH 7 with $NaHCO_3$. The insoluble product was removed by filtration, washed with H_2O, and dried at 70° overnight. The product (2.5 g) melted at 165–170°.§

7-Chloro-5-fluoro-8-quinolinol. To a solution of 5-fluoro-8-quinolinol[8] (16.3 g, 0.1 mole) in 200 ml of acetic acid, sulfuryl chloride (13.1 g, 0.1 mole), dissolved in 25 ml of acetic acid, was added dropwise with stirring at 15–20° over 45 min. The reaction temperature was raised to 50°, and after 2 hr at this temperature, the mixture was brought to reflux for several minutes. After cooling, the solution was poured into 2 l. of deionized H_2O and was brought to pH 5 with NaOH. The product was obtained by filtering, washing with H_2O, and drying at 70° overnight. The crude compound weighed 12 g, mp 164–168°.

7-Bromo-5-fluoro-8-quinolinol. 5-Fluoro-8-quinolinol[8] (16.3 g, 0.1 mole), dissolved in 300 ml of acetic acid, was treated with Br_2 (16 g, 0.1 mole) in 80 ml of acetic acid dropwise with stirring at 20°. Stirring was continued for 15 min, after completion of addition of the Br_2. The mixture was poured into 2 l. of deionized H_2O, and the product was removed by filtering, followed by washing (H_2O) and drying at 70° overnight. The yield of compound was 22 g, mp 165–167°.#

5-Chloro-7-fluoro-8-quinolinol. 5-Chloro-7-amino-8-quinolinol monohydrochloride[3] (4.6 g, 0.02 mole) was suspended in 37 ml of THF and fluoroboric acid (48–50%, 18 ml) was added. Keeping the temperature at 0–10°, finely powdered $NaNO_2$ (15.2 g, 0.022 mole) was added in small portions with stirring. After the full amount of

‡Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Model 20 recorder. All of the compounds in this study (Table II) were established as being at least 99% pure by gas chromatographing the trimethylsilyl derivatives.[15] The column employed contained 1% Apiezon L on acid-washed chromosorb W (80–100 mesh) which was previously treated with dimethyldichlorosilane.

§The compound was mentioned in ref 16 but not characterized.

#The compound was mentioned in ref 17 but not characterized.

$NaNO_2$ was added, agitation was continued for an additional hr at 0–10°. The material was obtained by filtration on a sintered glass funnel, and washed with small portions of cold 1:1 EtOH–Et_2O (v/v) followed by cold Et_2O. The product was dried at 2 mm at 35° overnight, and a yield of 7.5 g (95%) of crude compound as the difluoroborate was obtained, mp 210–215 dec. The dried material was spread in a thin layer over the bottom of a Fernbach flask fixed with an air condenser and combusted with a flame. The product was heated with 30 ml of 10% H_2SO_4, cooled, diluted to 100 ml with H_2O, brought to pH 5 with dilute NaOH, and steam distilled. The crude product (0.5 g) was recovered by filtration and drying at 70° overnight, mp 147–155°. After sublimation (150° (2 mm)), 330 mg of compound was obtained, mp 167–170°.

5-Bromo-7-fluoro-8-quinolinol. 7-Fluoro-8-quinolinol[5] (2.5 g, 0.015 mole) in 100 ml of chloroform was stirred with *N*-bromosuccinimide (3.1 g, 0.0175 mole) for 1 hr. The chloroform was evaporated and the residue was slurried in 100 ml of H_2O and filtered. The product was dried at 70° overnight and weighed 3.5 g, mp 169–170°.

7-Fluoro-5-iodo-8-quinolinol was prepared from 2.0 g (0.012 mole) of 7-fluoro-8-quinolinol[5] and 3.0 g (0.12 mole, 90%) of *N*-iodosuccinimide in chloroform in the same manner as 5-bromo-7-fluoro-8-quinolinol. The yield of product was 1.8 g, mp 164–165°.

5-Bromo-7-chloro-8-quinolinol. To 11.2 g (0.05 mole) of 5-bromo-8-quinolinol,[14] dissolved in 300 ml of 10% NaOH, was added 100 ml of 5.25% sodium hypochlorite solution. The mixture was agitated for 2 hr and adjusted to pH 5 with acetic acid. The product was obtained after filtering, washing (H_2O), and drying at 70° overnight. The yield of product was 7.8 g, mp 188–195°. Purification was achieved by vacuum sublimation followed by crystallization from MeOH–DMF.

7-Bromo-5-iodo-8-quinolinol. 7-Bromo-8-quinolinol[6] (22.4 g, 0.1 mole) and fused potassium acetate (9.8 g, 0.1 mole) were dissolved in 250 ml of boiling 96% EtOH. I_2 (25.4 g, 0.1 mole), dissolved in 300 ml of 96% EtOH, was added dropwise with stirring to the boiling quinolinol solution over 0.5 hr. The mixture was kept under reflux for an additional 10 min, after completion of addition of the I_2. Aqueous $NaHSO_3$ was added to the mixture to reduce any unreacted I_2, and the mixture was refrigerated overnight. The product was removed by filtration, washed (96% EtOH), and dried under vacuum. The yield of compound was 29.8 g, mp 195–200° dec.

5-Bromo-7-iodo-8-quinolinol was prepared from 5-bromo-8-quinolinol[14] in the same manner as 7-bromo-5-iodo-8-quinolinol.

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Antimalarial Potency of 2-Benzoyl-4-quinolinemethanols†

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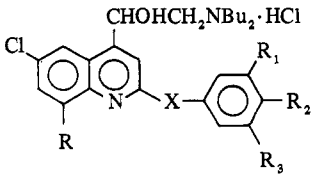
Received March 23, 1972

A major effort in the potent antimalarial series of 2-phenyl-4-quinolinemethanols[1,2] has been the design of effective members without phototoxicity.[3-5] Since the majority of agents causing phototoxic reactions are conjugated aromatic structures,[4-7] it seemed desirable in the above series to insulate the 2-phenyl substituent from the quinoline nucleus by a C atom. For this purpose we investigated, initially, the 4-quinolinemethanol derivatives (Ia, b, and j where R = Cl; R_{1-3} = H). Test results§ revealed that although



Ia, X = CH_2; R = Cl; R_{1-3} = H
Ib–i, X = CO; R and R_{1-3} = H, Cl, CF_3
Ij, X = CF_2; R = Cl; R_{1-3} = H

each lacked phototoxic effects, only Ib possessed a moderate level of antimalarial activity. Based on these findings, we proposed to enhance the antimalarial potency of Ib by incorporation of Cl and CF_3 substituents. The efficacy of such modification was reported in our earlier work.[8] The present communication, therefore, describes the synthesis and biological properties of 2-benzyl-, 2-benzoyl-, 2-(α,α-difluorobenzyl)-4-quinolinemethanols (Ia, b, j) and affirms the potent antimalarial action of Cl, CF_3 members (Ic–i) of the 2-benzoyl series.

Chemistry. The Pfitzinger condensation[9,10] of 5,7-dichloroisatin and $C_6H_5CH_2COCH_3$ afforded (18%) the desired 2-benzylcinchoninic acid[11] (IIIa, Table I). The latter was converted to the corresponding amino alcohol (Ia, Table II) *via* the usual reaction sequence.[10] Difficulty in preparing the acid chloride of IIIa with $SOCl_2$ was circumvented by means of PCl_5 in C_6H_6.

A convenient synthesis (Scheme I) of Cl, CF_3 containing 2-benzoylcinchoninic acids (IIIc–i, Table II) was developed which utilized appropriate phenylglyoxals (II, Table III) in the Doebner reaction[10,12] with commercial anilines. Requisite glyoxals (II) were obtained by DMSO oxidation[13] of the corresponding phenacyl bromides. Verification of the Doebner route to IIIc–i was provided by the unambiguous Pfitzinger synthesis of IIIc (Scheme II). The latter reaction also produced IIIb which had been previously obtained from IIIa and SeO_2 (47%), alkaline $KMnO_4$ (38%), or Br_2–

†This investigation was supported by the U.S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2950 and is Contribution No. 1051 from the Army Research Program on Malaria.

‡Affiliated with the Franklin Institute.

§Phototoxicity tests were carried out by Col. William E. Rothe, Division of Medicinal Chemistry, WRAIR, Walter Reed Army Medical Center, Washington, D.C. For details of the test procedure see ref 4. Antimalarial evaluation was conducted by Dr. L. Rane and coworkers, University of Miami, Miami, Fla. All test results were supplied by Drs. T. R. Sweeney and R. E. Strube, Walter Reed Army Institute of Research.