Experimental Section[6]

2-(4-Chlorophenyl)-7-(2-[1-azacycloheptyl]-1-hydroxyethyl)-quinoline (Ie).[7] 7-Methylquinoline (Ia).—A mixture (62%) of 5- and 7-methylquinolines was obtained by the Richter and Smith modification[8] of the Skraup reaction, treatment with Ac_2O, and steam distillation. After three partial freezing operations, the solid remaining was recrystallized from C_6H_{14} to yield 34.7 g (24%) of white plates, mp 37–39°, lit.[9] mp 39°.

2-(4-Chlorophenyl)-7-methylquinoline (Ib).—Under N_2 *p*-chlorobromobenzene (0.1 mole) in 500 ml of Et_2O was brought to reflux and 0.1 mole of 22% BuLi solution in C_6H_{14} added and the exchange allowed to take place for 10 min.[10] Ia (0.1 mole) was added as a solid followed by the immediate addition of 450 ml of C_6H_6. The mixture was refluxed for 20 min, 100 ml of EtOH and 150 ml of $C_6H_5NO_2$ were added, the volatile solvents removed by distillation, and the red $C_6H_5NO_2$ solution was refluxed for 20 min followed by steam distillation of the now green solution to remove $C_6H_5NO_2$. The residue was removed by filtration, washed with hot H_2O, and extracted with CCl_4 and the residue from the extract recrystallized from C_6H_{12} (decolorizing C) to give 15 g (64%) of white crystals, mp 141–142°; lit.[11] mp 143–144°.

2-(4-Chlorophenyl)-7-quinolinecarboxaldehyde (Ic, Sommelet Method).—Ib (0.04 mole), 150 ml of CCl_4, 0.1 g of I_2, and 30 ml of H_2O were refluxed and irradiated with a 150-W lamp while 0.044 mole of Br_2 in 70 ml of CCl_4 was added dropwise in 4 hr. The yellow precipitate (81% of which 72% was the α-bromomethyl compound by nmr analysis) was removed by filtration and washed with CCl_4. The crude product (10.7 g) in 160 ml of $CHCl_3$ was mixed with $(CH_2)_6N_4$ (0.14 mole) in 160 ml of $CHCl_3$. After 3 days, the quaternary salt (14 g) was filtered off and washed with $CHCl_3$. A solution of 0.1 mole of $(CH_2)_6N_4$, 100 ml of AcOH, 2 ml of concd HCl, and 30 ml of H_2O was refluxed while the quaternary salt (0.03 mole) was added portionwise in 6 hr. While hot, the solution was diluted with H_2O to cloudiness and cooled. The crystals were filtered, washed with cold H_2O–EtOH and hot H_2O, and recrystallized from EtOH to yield 2.8 g (26% from Me compound), mp 163–164°. *Anal.* ($C_{16}H_{10}ClNO$) C, H.

2-(4-Chlorophenyl)-7-epoxyethylquinoline (Id).—Under N_2 with magnetic stirring, DMSO (10.8 ml) and NaH (0.0194 mole) were heated at 65° for 45 min and cooled. At −10°, 10.8 ml of THF was added to the black solution and the mixture held there for 30 min and treated with Me_3SI (0.0194 mole) in 20.7 ml of DMSO within 1 min. Ic (0.00972 mole) in 20.7 ml of THF–DMSO was added in 2 min and the green solution stirred at −10° for 15 min and at 25° for 30 min. The mixture was poured over cracked ice and the precipitate filtered, dried, and recrystallized from EtOH (decolorizing C) to give 1.81 g, 66%, of light yellow plates, mp 139.5–141°. *Anal.* ($C_{17}H_{12}ClNO$) C, H.

Ie.—Id (0.0054 mole) and 17 g of azacycloheptane were heated at 115° for 14 hr and steam-distilled to remove amine. The brown, solid residue was recrystallized from aq EtOH (decolorizing C) to give 1.4 g, 68%, of beige tufts, mp 108.5–109.5°. *Anal.* ($C_{23}H_{25}ClN_2O$) C, H, N.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-dialkylamino-1-hydroxyethyl)quinoline (IIh-1 and -2).[12] 2,6-Dichloro-3-aminotoluene (IIb).—This compound, mp 51–53°, lit.[13] mp 59–60°, was made in 48% overall yield from 2,6-dichlorotoluene, IIa.

6,8-Dichloro-7-methylquinoline (IIc).—The Skraup reaction[8] of IIb, 0.3 mole, gave a dark precipitate which was recrystallized first from H_2O–EtOH and then from C_6H_{14} to yield 32 g, 51%, of beige-colored crystals, mp 97.5–98.5°. *Anal.* ($C_{10}H_7Cl_2N$) Cl.

2-(*p*-Chlorophenyl-6,8-dichloro-7-methylquinoline (IId).—IId was made from 0.125 mole of IIc by the same method used for preparation of Ib. IId was obtained in 86% yield as beige needles, mp 134.5–136.5° from C_6H_{14}; analytical sample, mp 135.8–137.4°. *Anal.* ($C_{16}H_{10}Cl_3N$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-bromomethylquinoline (IIe).—IId (0.1 mole) in 1.3 l. of CCl_4 was refluxed and irradiated with a 150-W flood-lamp while 0.113 mole of *N*-bromosuccinimide was added portionwise and the final mixture refluxed 15 hr. The CCl_4 was evaporated, and the residue was washed thoroughly (H_2O), dried, and recrystallized from CCl_4 to give 34 g, 80%, of beige, powdery crystals, mp 177–180.5°; analytical sample, mp 180.2–181.2°. *Anal.* ($C_{16}H_9BrCl_3N$) C, H.

2-*p*-Chlorophenyl-6,8-dichloro-7-quinolinecarboxaldehyde (IIf).—IIe (0.08 mole) was treated with 0.08 mole each of NaOEt and Me_2CHNO_2 in EtOH according to the method of Hass and Bender[14] and gave, after recrystallization from EtOAc 16.3 g (60%) of pale yellow crystals, mp 199–201.5°; analytical sample, mp 200–201°. *Anal.* ($C_{16}H_{18}Cl_3NO$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-epoxyethylquinoline (IIg).—IIg was made in the same manner as Id from 0.05 mole of IIf. The residue from Et_2O extraction was chromatographed on silica gel (Baker's) using C_6H_{14}–C_6H_6 as an eluting solvent. Early fractions indicated by tlc that a pure substance was being eluted (R_f 0.34, 50% C_6H_6–C_6H_{14}) which recrystallized from MeCN gave 6.5 g, 38%, of pale yellow crystals, mp 159–161°; analytical sample, mp 162.1–16.24°. *Anal.* ($C_{17}H_{10}Cl_3NO$) Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-dibutylamino-1-hydroxyethyl)quinoline (IIh-1).—IIg (0.00856 mole) in 20 ml of Bu_2NH was heated and stirred at 115° for 19 hr and the excess amine removed by steam distillation. The residue was chromatographed on silica gel using C_6H_6–EtOAc as the developing solvent. When the eluted solute was pure (R_f 0 with C_6H_6; R_f 0.2–0.3 with C_6H_6–EtOAc), it was recovered and recrystallized from C_6H_{14} giving 2.1 g, 51%, of yellow crystals, mp 80–82.8°. *Anal.* ($C_{25}H_{29}Cl_3N_2O$) C, H, Cl.

2-*p*-Chlorophenyl-6,8-dichloro-7-(2-[*N*-3-azabicyclo[3.2.2]-nonyl]-1-hydroxyethyl)quinoline (IIh-2).—IIg (0.0088 mole) and 3-azabicyclo[3.2.2]nonane[15] (0.0177 mole) in 20 ml of toluene were refluxed 24 hr and then steam distilled. The residue was chromatographed using silica gel and C_6H_6–EtOAc. A second chromatography was necessary using C_6H_6–20% EtOAc. The solute was recrystallized from C_6H_{14} giving 0.2 g of light yellow needles, mp 169–173°, R_f 0.46 (C_6H_6 and silica gel); not tested for activity because of small sample size. *Anal.* ($C_{25}H_{25}Cl_3N_2O$)C, H, Cl.

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(6) Analyses (by Galbraith Laboratories, Knoxville, Tenn.) are within 0.4% and recorded with the Editor. Melting points are uncorrected and were taken with A. H. Thomas Uni-Melt apparatus. Nmr spectra of new compounds are on file with the authors.

(7) From the Ph.D. Thesis of T. G. B., Vanderbilt University, Nashville, Tenn., 1970.

(8) F. Richter and G. F. Smith, *J. Amer. Chem. Soc.*, **66**, 396 (1944).

(9) I. M. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, New York, N. Y., 1936, p 808.

(10) H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem. Soc.*, **62**, 2327 (1940).

(11) H. Gilman, R. V. Christian, and S. M. Spatz, *ibid.*, **68**, 979 (1946).

(12) From part of the present Ph.D. work of L. C. W.

(13) J. B. Cohen and H. D. Dakin, *J. Chem. Soc.*, **79**, 1132 (1901); **81**, 1346 (1902).

(14) H. B. Hass and M. L. Bender, "Organic Synthesis," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 932.

(15) V. L. Brown, Jr., and T. E. Stanin, *Ind. Eng. Chem., Prod. Res. Develop.*, **4**, 40 (1965). We are indebted to Dr. R. D. Clark and the Tenn. Eastman Co. for a generous sample of this compound.

Quinoxaline Studies. XVII.[1a] Potential Antimalarials. Some (*RS*)-α-(Dialkylaminomethyl)-6-chloro-2-quinoxalinemethanols[1b]

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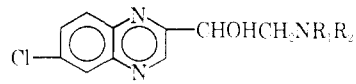
Previously reported[2] quinoxalinemethanols, similar to antimalarial quinolinemethanols, were without antimalarial activity. Because a chloro substituent in-

(1) (a) Paper XVI of this series, G. H. Fisher, P. J. Whitman, and H. P. Schultz, *J. Org. Chem.*, **35**, 2240 (1970); (b) Contribution No. 761 from the Army Research Program on Malaria, supported by the U. S. Army Medical Research and Development Command *via* Contract DADA 17-67-C-7064.

(2) H. R. Moreno and H. P. Schultz, *J. Med. Chem.*, **13**, 119 (1970).

Table I

(*RS*)-α-(Dialkylaminomethyl)-6-chloro-2-quinoxalinemethanols[a]



No.	Compound R_1 = R_2 =	Formula	Reaction time, (hr)	Reaction solvent, reflux	Recryst solvent	% yield	Mp dec, °C	Antimalarial activity, days life span increase, mouse, 640 mg kg[d]
1	Et	$C_{14}H_{18}ClN_3O$	4	Et_2NH	C_6H_{12}	45.9	78–79	0.5
2	*n*-Bu	$C_{18}H_{26}ClN_3O$	16	Dioxane	C_6H_{12}	47.2	71–72	0.1
3	*n*-Pe	$C_{20}H_{30}ClN_3O$	15	Dioxane	C_6H_{12}	39.0	24	0.4

[a] Average λ_{max} 207–208 mμ (ε 24,400), 239–240 (26,400), 326 (6100). [b] Pmr spectra of bases were as expected. [c] All analyses were for C, H, and N; values were within ±0.4% of the theoretical values. [d] Average life span of control mice infected with *P. berghei*, 6.2 days.

creases the activity of many quinolinemethanols,[3] it was hoped that chloroquinoxalinemethanols would also possess antimalarial capacity. The purpose of this paper is to report the syntheses of representative (*RS*)-α-(dialkylaminomethyl)-6-chloro-2-quinoxalinemethanols, incorporating diethylamino, di-*n*-butylamino, and di-*n*-pentylamino groups, for testing as antimalarials.

Chemistry.—Prior success[2] in transforming 2-quinoxalinecarboxylic acid into 2-quinoxalinemethanols justified developing first a procedure for making large quantities of 6-chloro-2-quinoxalinecarboxylic acid (**4**) for use in attaining the objective of this project.

The availability of 4-chloro-*o*-phenylenediamine (**1**) dictated its utilization for the preparation of 2-tetrahydroxylbutyl-6-chloroquinoxaline (**2**). Unfortunately, the facile condensation of *o*-phenylenediamine with sucrose earlier reported[4] to give 2-tetrahydroxybutylquinoxaline was not paralleled in this instance; **2** (and its 7-chloro isomer, **3**) was first prepared by cyclizing the *N,N'*-diglucosyl derivative of **1**. More usefully, direct condensation of **1** with glucose (and also fructose) in the necessary presence of H_2NNH_2, HOAc, and H_2O gave a 1:1 mixture of **2** and **3**. Condensation of **1** with *N*-D-glucosyl-*p*-toluidine, according to a general procedure of Weygand and Bergmann,[5] also gave mixed **2**(**3**). All attempts, physical or chemical, to separate **2** from **3** failed.

Therefore, oxidation of the mixed isomers was effected with Na_2O_2 in a heterogeneous C_6H_6–H_2O system. Fortunately the 1:1 mixture of 6-chloro-2-quinoxalinecarboxylic acid (**4**) and its 7-chloro isomer (**5**) was separable; **4** was insoluble, **5** moderately soluble (*ca.* 1 g/50 ml) in 9 *N* HCl.

Henseke and Jacobi[6] described the unequivocal, but lengthy, preparation of 2-methyl-6-chloroquinoxaline. Modification of a portion of their work enabled relatively easy preparation of pure 2-methyl-6-chloroquinoxaline which, oxidized *via* its styryl derivative, gave unequivocal **4**; the structure of **5** was therefore proved by difference.

The decision to use **4** as the precursor for the target chloroquinoxalinemethanols was the consequence of the observation that although both **4** and **5** were inactive as antimalarials, careful scrutiny of the test data showed **5** extended the mean life of test mice only 0.1 day, whereas **4** extended the mean life of test mice 0.9 day at dosages of 160 mg/kg.

From this point the desired synthetic objective was attained *via* the sequence 6-chloro-2-quinoxaloyl chloride (**6**), 6-chloro-2-diazoacetylquinoxaline (not isolated) (**7**), 6-chloro-2-chloroacetylquinoxaline (**8**), (*RS*)-α-(chloromethyl)-6-chloro-2-quinoxalinemethanol (not analyzed) (**9**), (*RS*)-6-chloro-2-quinoxalinepoxyethane (**10**), and (*RS*)-α-(dialkylaminomethyl)-6-chloro-2-quinoxalinemethanols (**11**).

The procedures used to prepare the above compounds were the same as those utilized for making the corresponding nonsubstituted quinoxalines,[2] except that compounds **11** were solids, easily purified, analyzed, and tested as free bases, rather than (as were the parent compounds) the pamoate salts. For the same reasons discussed in the prior paper,[2] utilization of the pmr spectra of **10** and **11** contributed to a successful chemical conclusion of this problem.

Table I summarizes data *re* the target compounds.

Biological Results.—All compounds were tested by the previously described procedure[7] for antimalarial activity against *Plasmodium berghei* in mice. All intermediates and target compounds were inactive and nontoxic. Data are recorded in Table I.

Experimental Section[8]

***N,N'*-Di-D-glucosyl-3,4-diaminochlorobenzene Dihemihydrate.**—A mixture of 36 g of D-glucose, 14.2 g of 3,4-diaminochlorobenzene, 0.2 g of NH_4Cl, and 300 ml of MeOH was stirred and refluxed for 1 hr. After cooling at 0° for 4 hr, 31 g (60.5%) of tan powder, mp 150–151°, was obtained. The crude material was recrystallized from three times from 1:1 MeOH–H_2O (7 ml g) to give 9.7 g (18.9%): mp 156–157° dec, of product; λ_{max} 216 mμ (ε 33,200), 249 (10,200), 299 (3200); $[\alpha]^{23.5}D$ −128.6° (*c* 2, DMF). *Anal.* ($C_{18}H_{27}ClN_2O_{16}\cdot 2.5\ H_2O$) C, H.

2-D-Arabinotetrahydroxybutyl-6(7)-chloroquinoxalines (2, 3). Method A.—A solution of 4.66 g of *N,N'*-di-D-glucosyl-3,4-diaminochlorobenzene, 0.32 g of N_2H_4, and 50 ml of 10% HOAc

(3) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, U.S. Government Printing Office, Washington, D. C., 1953.

(4) S. Gerchakov, P. J. Whitman, and H. P. Schultz, *J. Med. Chem.*, **9**, 266 (1966).

(5) F. Weygand and A. Bergmann, *Chem. Ber.*, **80**, 255 (1947).

(6) G. Henseke and R. Jacobi, *Justus Liebigs Ann. Chem.*, **684**, 146 (1965).

(7) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). The authors thank the staff of the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for transmitting the test results provided by Dr. L. Rane, University of Miami.

(8) Uv absorption spectra were obtained from samples at concentrations of 5 mg/l. of 95% EtOH (except acyl halides) using 1-cm silica cells. Pmr spectra, all referred to TMS, were determined at 60 MHz, 34°. Except in those instances where spectral data are presented, uv and nmr spectra were as expected.[2] All optical activities were observed on a Rudolph Model 63 polarimeter. Melting points, determined on a Thomas–Hoover apparatus, are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

was boiled for 30 min, cooled at 10° for 6 hr, and filtered to give 0.6 g (23.2%) of **2** (**3**), mp 178–179°. The crude product was recrystallized from 95% EtOH (50 ml/g) to give 0.3 g (11.6%): mp 181–181.5°; λ_{max} 210 mμ (ε 14,800), 239 (20,300), 323 (4600); $[\alpha]^{25}D$ −129.2° (*c* 2, DMF). *Anal.* ($C_{12}H_{13}ClN_2O_4$) C, H, Cl, N.

Method B.—A solution of 14.3 g of **1**, 18 g of glucose, 21.7 ml of HOAc, 4.8 ml of N_2H_4, and 100 ml of H_2O was refluxed 1 hr, then cooled 4 hr at 10° to give 7.5 g (26.5%), mp 171–177°, of crude **2**(**3**).

Recrystallization gave 7 g (24.5%), mp 180.5–181° dec, of **2** (**3**); uv and [α], as above. All attempts to separate **2** and **3** failed.

Condensation of fructose with **1** gave 26.4% of **2** (**3**); of *N*-D-glucosyl-*p*-toluidine with **1** gave 22% of **2**(**3**); **2** (**3**) has also been reported[9,10] synthesized by reaction of **1** with fructose-1-phenylhydrazone.

6(7)-Chloro-2-quinoxalinecarboxylic Acids (4, 5).—To a stirred cold suspension of 40 g of Na_2O_2 (98.4%) in 135 ml of H_2O and 135 ml of C_6H_6 was added 28.4 g of **2** (**3**). The mixture was heated to 50°, at which temp spontaneous reaction occurred; its temperature was maintained at 60 ± 2° for 65 min by intermittent cooling or heating; finally the mixture was refluxed (72°) for 10 min. After cooling to 15°, the suspension of crude Na salts of **4** and **5** was transformed into the mixed products in 66% yield in the same way as was the parent compound,[2] then twice recrystallized from 1:1 EtOH–H_2O (30 ml/g): 37.2%; mp 196–198° dec; λ_{max} 242 mμ (ε 25,000), 320 (3600), 331 (4500). *Anal.* ($C_9H_5ClN_2O_2$) C, H, Cl, N.

6-Chloro-2-quinoxalinecarboxylic Acid (4), Equivocal Preparation.—Crude, mixed **4** and **5** (80 g) was extracted three times at 24° for 16-hr intervals with 1 l. portions of 9 *N* HCl, each time separating solid from supernatant liquid by centrifugation. The final HCl-insoluble residue was filtered, rinsing the cake with 9 *N* HCl and H_2O. The filter cake of crude **4** was dissolved with warming in 1.5 l. of 0.15 *N* NaOH, and after clarification with decolorizing C and filter aid, the filtrate was adjusted to pH 1 with HCl to precipitate 32.4 g (40.5%), mp 223–224° dec, of pure **4**. For analysis material was recrystallized (66% recovery) from 95% EtOH (30 ml/g); same melting point; λ_{max} 209 mμ (ε 24,000), 245 (32,100), 320 (4500), 331 (7800). *Anal.* ($C_9H_5ClN_2O_2$) C, H, Cl, N.

Methyl 6-Chloro-2-quinoxalinecarboxylate, Equivocal.—A solution of 3 g of **4** in 30 ml of MeOH and 0.5 ml of H_2SO_4 was refluxed 3 hr, cooled at 0° for 3 hr, filtered, and triturated with H_2O–$NaHCO_3$ to give 3.2 g (100%), mp 147.5–148.5°, of Me ester of **4**. This material was twice recrystallized from CCl_4 (10 ml/g) to give 2.1 g (65.6%) of product; mp 147.5–148.5°; λ_{max} 208 mμ (ε 24,600), 247 (34,600), 321 (6600), 331 (7600); pmr ($CDCl_3$) δ ppm 4.13 (s, 3 H, CH_3), 8.05 (m, 3 H, aromatic), 9.69 (s, 1 H, heterocyclic). *Anal.* ($C_{10}H_7ClN_2O_2$) C, H, Cl, N.

Saponification of recrystallized Me ester of **4** gave **4** of the same melting point and mixture melting point above.

7-Chloro-2-quinoxalinecarboxylic Acid (5), Equivocal.—The HCl extracts rich in **5** (*vide supra*) were brought to pH 1 with NH_4OH, and after 12 hr at 0° were filtered. The first two HCl extracts of mixed **4** and **5** each gave 25% recovery (40 g total) from the starting mixture of **4** and **5**. Further HCl extracts had very little material dissolved in them; any present was recyclized with starting material, crude **4**(**5**).

Crude **5** (40 g) was refluxed in 400 ml of MeOH and 6 ml of H_2SO_4 for 3 hr; the crude ester was filtered from the cold solution, triturated with 400 ml of saturated $NaHCO_3$, then with 400 ml of H_2O to give 32.8 g of tan crystals, mp 151–152°. One recrystallization of this material from hot CCl_4, with treatment with decolorizing C and filter aid, gave 28.4 g of white crystals, mp 153–154°. The melting point was not changed with further recrystallizations.

The Me ester of **5** was saponified by refluxing 28.4 g in 320 ml of 1 *N* NaOH for 1 hr. Upon cooling, the Na salt of **5** precipitated from the basic solution. After adding 200 ml of warm H_2O, the solution was decolorized, filtered, and brought to pH 1 to give 26.4 g (33% recovery) from the original **4**(**5**) mixture, mp 223–224° dec.

For analysis **5** was recrystallized three times from MeOH (20 ml/g) (30% recovery), mp 225.5–226.5° dec. As with **4**, however, rate of heating and temperature at which a melting point sample was inserted into the melting point bath, gave values as low as 220–221° dec; mmp of **4** and **5**, 203.5–204° dec; λ_{max} 209 mμ (ε 24,500), 243 (30,900), 331 (4600). *Anal.* ($C_9H_5ClN_2O_2$) C, H, Cl, N.

Methyl 7-chloro-2-quinoxalinecarboxylate had mp 153–154°; λ_{max} 209 mμ (ε 24,400), 245 (37,700), 310 (3700), 334 (4500); pmr ($CDCl_3$) δ ppm 4.20 (s, 3 H, CH_3), 8.15 (m, 3 H, aromatic), 9.69 (s, 1 H, heterocyclic); mixture melting point with pure Me ester of **4**, mp 119–128°. *Anal.* ($C_{10}H_7ClN_2O_2$) C, H, Cl, N.

Saponification of a sample of Me ester of **5** gave **5** of the same melting point and mixture melting point as cited above.

This same procedure of esterification was used upon a sample of crude, mixed **4**(**5**) to give 69.5% tan mixed esters, mp 117–125°; solution in $CHCl_3$, decolorization, and evaporation of the solvent gave 66.5% colorless mixed esters, mp 119–130°.

It was concluded, therefore, that condensation of glucose with 3,4-diaminochlorobenzene gave *ca.* a 1:1 mixture of **2** and **3**, and that this mixture of isomers upon oxidation gave *ca.* a 1:1 mixture of **4** and **5**.

2-Methyl-6-chloroquinoxaline.—The preparation of this compound was adapted from Henseke and Jacobi.[6] A solution of 14.3 g of **1**, 16.8 ml of 12 *N* HCl, and 20 ml of MeCOCHO–H_2O (30%, tech) in 175 ml of H_2O was stirred at 80° for 20 min, 1 hr at 24°, and 12 hr at 0° to give 7.7 g (43.2%) of red crystals, mp 110–120°. This product[6] contained *ca.* 90% of 2-methyl-6-chloroquinoxaline and 10% of the 7-chloro isomer. For isolation of pure 6-chloro isomer from the reaction mixture, the crude product was steam distilled (100 ml of H_2O/g) to give 6.3 g (35.4%), mp 128–133°, which twice recrystallized from 1:2.5 EtOH–H_2O (35 ml/g), gave 4.6 g (25.8%) of white crystals, mp 133–134° (lit.[6] mp 131°; 7-Cl isomer, mp 91°). Repeated steam distillation and recrystallization did not change the melting point of the product: pmr ($CDCl_3$) δ ppm 2.74 (s, 3 H, CH_3), 7.75 (m, 3 H, aromatic), 8.75 (s, 1 H, heterocyclic). The splitting pattern of the aromatic H of this product was similar to that of the aromatic H of the Me ester of **4**, dissimilar to that of the Me ester of **5**.

trans-β-**(6-Chloro-2-quinoxalinyl)styrene.**—A mixture of 17.9 g of 2-methyl-6-chloroquinoxaline, 32 ml of PhCHO, 33.2 ml of Ac_2O, and 1.12 g of powdered NaOH was stirred at 125° for 4 hr. After cooling, 250 ml of H_2O was added, and the pH of the mixture was brought to pH 9 with solid K_2CO_3. The red oil was extracted into 300 ml of CCl_4, which was washed four times with 100-ml portions of 10% K_2CO_3, and three times with H_2O. After concentration, the crude product was steam distilled (H_2O, 650 ml) to remove starting materials, leaving a red, solid residue which was dissolved in 250 ml of $CHCl_3$. Washing with 10% K_2CO_3, H_2O, drying ($MgSO_4$), clarification (decolorizing C and filter aid), filtration, and concentration gave a red solid which was recrystallized from CCl_4 (100 ml) to give 7.71 g (28.9%) of powder, mp 143.5–145°. The crude product was three times recrystallized from 95% EtOH (50 ml/g) to give 6.08 g (22.8%) of orange crystals: mp 144.5–145°; λ_{max} 209 mμ (ε 25,700), 245 (10,800), 285 (19,500), 297 (19,500), 308 (inf); ir (Nujol) 1000 cm^{-1} (hence *trans*), no *cis* peaks; pmr ($CDCl_3$), δ ppm 7.78 (m, 10 H, aromatic, vinylic), 9.07 (s, 1 H, heterocyclic). *Anal.* ($C_{16}H_{11}ClN_2$) C, H, Cl, N.

6-Chloro-2-quinoxalinecarboxylic Acid (4), Unequivocal Preparation.—Over 90 min 4.4 g of $KMnO_4$ was added at 0° to a suspension of 2.67 g of *trans*-β-(6-chloro-2-quinoxalinyl)styrene in 95 ml of Me_2CO; the mixture was stirred 24 hr at 24°, filtered, and rinsed with AcMe. The filter cake was repeatedly washed with 400 ml of boiling H_2O, and after clarification the filtrate was brought to pH 2 with dilute H_2SO_4 to give 2.09 g (100%) of **4**, mp 220–220.5° dec, mmp with **4**, equivocally prepared, 221° dec.

Me ester (90%), mp 147.5–148° had mmp with Me ester of equivocal **4**, mp 147.5–148°, pmr spectrum, as above.

Compounds **6** through **11** were prepared by reported procedures,[2] and include per cent yield, mp, and (where different than expected) recrystn solvent, and spectral data. All analyses were for C, H, Cl, N, and were within ±0.4% of theory.

6-Chloro-2-quinoxaloyl chloride (**6**) was obtained in 75% yield, mp 103–103.5°.

7-Chloro-2-quinoxaloyl chloride was obtained in 66% yield: 122.5–123.5°; λ_{max} (hexane) 220 mμ (ε 9800), 248 (34,400), 253 (37,000), 299 (5300), 310 (5100), 338 (3400).

6-Chloro-2-chloroacetylquinoxaline (**8**) was obtained in 66% yield: mp 151.5–152° dec, Me_2CO–H_2O; λ_{max} 212 mμ (ε 11,600), 243 (16,200), 254 (15,300), 326 (8200), 339 (6200).

(*RS*)-α-**(Chloromethyl)-6-chloro-2-quinoxalinemethanol** (**9**)

(9) W. Bauer, Thesis, University of Greifswald, Greifswald, East Germany (1957).

(10) R. Knaak, Thesis, University of Greifswald, Greifswald, East Germany (1959).

was obtained in 42% yield, mp 95.5–96°; unstable; not analyzed; transformed into **10** at once.

(*RS*)-**6-Chloro-2-quinoxalineepoxyethane** (**10**) was obtained in 70% yield, ligroin (bp 66–75°), 93–94°.

(*RS*)-α-(**Di-*n*-alkylaminomethyl**)-**6-chloro-2-quinoxaline-methanols** (**11**).—Data in Table I.

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Synthesis and Antimicrobial Activity of 5,7-Dichloroquinoline-8-thiol and Its Derivatives

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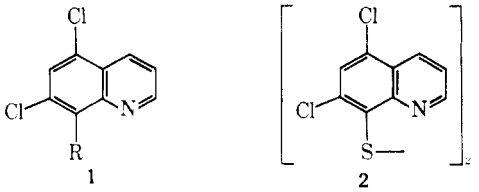
8-Hydroxyquinoline (oxine) and several of its derivatives are effective against Gram-positive and Gram-negative bacteria, and pathogenic fungi. In addition, halogenated 8-quinolinols are active against protozoa. Albert, *et al.*,[1] determined the minimal bacteriostatic concentrations of 8-quinolinol, 5-chloro-8-quinolinol, 7-chloro-8-quinolinol, and 5,7-dichloro-8-quinolinol, and showed that the chloro derivatives were superior to oxine against certain organisms.

Certain derivatives of the thio analog of 5,7-dichloro-8-quinolinol have now been prepared, and their bacteriostatic actions against various organisms determined. Although the tendency of 5,7-dichloroquinoline-8-thiol itself to undergo oxidation to the disulfide appears to be less than that of quinoline-8-thiol, under the test conditions considerable oxidation occurred, both with the dichlorothiol and also with its Na salt.

Chemistry.—5,7-Dichloroquinoline (**1a**) was prepared by the method of Elderfield and Kreuger,[2] and converted into its 8-sulfonyl chloride (**1c**) either by direct chlorosulfonation or indirectly by the action of PCl_5 on the 8-sulfonic acid (**1b**). Reduction of the sulfonyl



1

2

a, R = H
b, R = SO_3H
c, R = SO_2Cl
d, R = SH

chloride with $SnCl_2$ in concd HCl gave tin 5,7-dichloroquinoline-8-thiolate, which in the presence of NaOH and I_2 yielded 5,7-dichloro-8-quinolyl disulfide (**2**). Alkaline reduction of the disulfide gave 5,7-dichloroquinoline-8-thiol (**1d**). The pmr spectrum of 5,7-dichloroquinoline displayed a doublet at τ 1.97, attributable[3] to the 8 proton *meta* coupled to the 6 proton (J = 2 Hz). That chlorosulfonation had proceeded in the 8 position was confirmed by the absence of the 8 proton in the spectrum of the sulfonyl chloride, and presence of the 6 proton as a singlet.

Attempts to synthesize the 5,7-dichloroquinoline-8-thiol system by chlorination of quinoline-8-thiol, its benzoate or 8-quinolyldisulfide proved unsuccessful, and these reactions are under further investigation.

Biological Evaluation.—The antimicrobial activities of 5,7-dichloroquinoline-8-thiol and several related compounds were screened against both Gram-positive and Gram-negative bacteria, and yeasts. The following organisms were utilized: *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus faecalis* (Gram-positive), *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative), *Saccharomyces cerevisiae*, and *Candida albicans* (yeasts).

The compounds were dissolved in DMSO and added to nutrient agar (for bacteria) and sabouraud agar (for yeasts) to give a concentration range of 200–6.25 μg/ml. The organisms were streaked onto the surface of the agar plate and minimum inhibiting concentration recorded after 24 and 48 hr. 8-Quinolinol was screened as a control.

The results (see Table I) indicate a broad spectrum for tin 5,7-dichloroquinoline-8-thiolate, while showing its antimicrobial activity to be less than that of 8-quinolinol under the evaluation conditions applied.

Experimental Section[4]

5,7-Dichloroquinoline-8-sulfonic Acid.—A solution of 5,7-dichloroquinoline (3 g) in 25% oleum (15 ml) was heated at 140° for 40 hr, then added dropwise to crushed ice (50 g). The pptd acid was filtered, washed with H_2O, and recrystd from H_2O to give the sulfonic acid (3.25 g) as prisms, mp 300°. *Anal.* ($C_9H_5Cl_2NO_3S$) C, H, N.

5,7-Dichloroquinoline-8-sulfonyl Chloride (**a**).—The temperature of an intimately ground mixture of 5,7-dichloroquinoline-8-sulfonic acid (1 g) and PCl_5 (1.2 g) was gradually increased to 160°, then held there for 1 hr. $POCl_3$ was distd and the residue was added portionwise to crushed ice (20 g). The mixture was ground up and extracted (C_6H_6) and the extract was washed successively with aq $NaHCO_3$ and H_2O, then dried, and evaporated. Recrystallization of the residue from EtOAc gave product (0.5 g) as prisms: mp 140–141°; pmr ($CDCl_3$) τ 0.34 (quadruplet, J = 4.5 and 1.7 Hz) (H_2), 1.27 (quadruplet, J = 8.5 and 1.7 Hz) (H_4), 2.17 (H_6), 2.25 (quadruplet, J = 8.5 and 4.5 Hz) (H_3) ppm. *Anal.* ($C_9H_4Cl_2NO_2S$) C, H, N.

(**b**).—A solution of 5,7-dichloroquinoline (10 g) in chlorosulfonic acid (30 ml) was heated at 140° for 40 hr then cooled and added dropwise with stirring to crushed ice (250 g). The mixture was filtered and the residue was washed (H_2O), then triturated with 5% aq $NaHCO_3$, and refiltered. Recrystallization of the dried residue from EtOAc gave a product (6.2 g), identical with the above sample.

Tin 5,7-Dichloroquinoline-8-thiolate.—A solution of $SnCl_2 \cdot 2H_2O$ (12 g) in concd HCl (25 ml) was added at 0° to a solution of 5,7-dichloroquinoline-8-sulfonyl chloride (4 g) in concd HCl (25 ml). The yellow ppt was stirred at 0° for 1 hr then allowed to stand overnight at 0° before filtration. The residue was triturated with H_2O and the ppt (3.6 g) was filtered, and re-

(1) A. Albert, S. D. Rubbo, R. J. Goldacre, and B. G. Balfour, *Brit. J. Exp. Pathol.*, **28**, 69 (1947).

(2) R. C. Elderfield and G. L. Kreuger, *J. Org. Chem.*, **17**, 358 (1952).

(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Braunschweig, (1969) p 308.

(4) Melting points were determined on a Gallenkamp MF.370 apparatus and are uncorrected. Pmr spectra were determined on a Varian A60A spectrometer with TMS as internal reference. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.