was obtained in 42% yield, mp $95.5-96^\circ$; 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-quinoxalinemethanols (11).—Data in Table I.

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

A. O. FITTON

Department of Chemistry and Applied Chemistry, University of Salford, Salford, England

AND FRANK RIDGWAY E. R. Squibb and Sons Ltd., Moreton, Wirral, England

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8-Hydroxyquinoline (oxine) and several of its derivatives are effective against Gram-positive and Gramnegative 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



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, attributable³ to the S proton *meta* coupled to the 6 proton (J = 2 Hz). That chlorosulfonation had proceeded in the S position was confirmed by the absence of the S proton in the spectrum of the sulfonyl chloride, and presence of the 6 proton as a singlet.

Attempts to synthesize the 5,7-dichloroquinoline-8thiol 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 $200-6.25 \ \mu g_{c}$ ml. The organisms were streaked onto the surface of the agar plate and minimum inhibiting concentration recorded after 24 and 48 hr. S-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 8quinolinol under the evaluation conditions applied.

Experimental Section⁴

5,7-Dichloroquinoline-8-sulfonic Acid.—A solution of 5,7dichloroquinoline (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 H₂O, and recrystd from H₂O to give the sulfonic acid (3.25 g) as prisms, mp 300°. Anal. (C₂H₅Cl₂NO₃S) C, H, N.

5,7-Dichloroquinoline-8-sulfonyl Chloride (a).—The temperature of an intimately ground mixture of 5,7-dichloroquinoline-8sulfonic acid (1 g) and PCl₅ (1.2 g) was gradually increased to 160°, then held there for 1 hr. POCl₃ was distd and the residue was added portionwise to crushed ice (20 g). The mixture was ground up and extracted (C₆H₆) and the extract was washed successively with aq NaHCO₃ and H₂O, then dried, and evaporated. Recrystallization of the residue from EtOAc gave product (0.5 g) as prisms: mp 140–141°; pmr (CDCl₃) τ 0.34 (quadruplet, J = 4.5 and 1.7 Hz) (H₂), 1.27 (quadruplet, J = 8.5 and 1.7 Hz) (H₄), 2.17 (H₆), 2.25 (quadruplet, J = 8.5 and 4.5 Hz) (H₃) ppm. Anal. (C₉H₄Cl₃NO₂S) C, H, N. (b).—A solution of 5,7-dichloroquinoline (10 g) in chloro-

(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 (H₂O), then triturated with 5% aq NaHCO₃, 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 $SnCl_2$ · $2H_2O$ (12 g) in concd HCl (25 ml) was added at 0° to a solution of 5,7-dichloroquinoline-8-sulfonyl chloride (4 g) in coned 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 H₂O and the ppt (3.6 g) was filtered, and re-

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					Streptu)coccus							;	
	~ - Staphylococ	snauv sno.	B. cei	reus	faeca	lis	E. c6	di	P. aerug	rinosu ~	-Saccharomyce	s cerevisiae	C. albi	cans
Derivative	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
8-Quinolinol	18.75	18.75	18.75	18.75	18.75	18.75	25.0	25.0	37.5	37.5	6.25	6.25	9.3	9.3
Tin 5,7-dichloroquinolin e-8- thiolate	50.0	50.0	37.5	37.5	50.0	50.0	37.5	37.5	37.5	37.5	50.0	50.0	50.0	50.0
Sodium 5,7-dichloroquinoline-														
8-thiolate	>128	>128					>128	> 128			>128	>128	>128	>128
1d	102.5	200					102.5	128			128	128	128	128
2	>200	>200					>200	>200			>200	>200	>200	>200

TABLE

crystd from DMSO to give the Sn salt as prisms, mp 340–342°. Anal. ($C_{18}H_8Cl_4N_8S_2Sn$) Sn.

Sodium 5,7-Dichloroquinoline-8-thiolate.—The above Sn salt (1 g) was stirred in a solution of NaOH (1.5 g) in H_2O (25 ml) overnight. The Na salt was filtered, washed with H_2O , and dried. Recrystallization of the dried residue (0.55 g) from EtOH gave the sodium salt as yellow needles, mp 280° dec.

5,7-Dichloro-8-quinolyl Disulfide.—To a solution of NaOH (1.5 g) and I₂ (0.25 g) in H₂O (100 ml) was added finely ground tin 5,7-dichloroquinoline-8-thiolate (1.4 g). The mixture was stirred overnight and then filtered and the residue was thoroughly washed with H₂O. Recrystallization of the dried residue from dioxane gave product (0.30 g) as yellow prisms, mp 219–220°. Anal. (C₁₈H₈Cl₄N₂S₂) C, H, N.

5,7-Dichloroquinoline-8-thiol.—To a stirred suspension of the above disulfide (0.25 g) in oxygen-free MeOH (25 m) were added successively, solutions of NaOH (0.65 g) in H₂O (5 m) and glucose (0.65 g) in H₂O (5 m). The mixture was stirred and heated under reflux for 3 hr, before evapn of the MeOH. The mixture was filtered and the residual Na salt was dissolved in H₂O (25 m). CO₂ was passed through the solution for 10 min, and the white ppt was filtered and dried *in vacuo*. Recrystallization from MeOH gave the thiol (0.1 g) as needles, mp 102-103°; pmr spectrum as expected. Anal. $(C_9H_5Cl_2NS)$ C, H, N.

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Structural Modification Studies of 3-Piperonylsydnone. 2. Synthesis of Piperonyl-Substituted Hydantoin, Thiohydantoin, Thiazolidinedione, Rhodanine, Imidazolinone, and Related Compounds¹

WILLIAM H. BURTON, WILLIAM L. BUDDE, AND C. C. CHENG

Midwest Research Institute, Kansas City, Missouri 64110

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The antimalarial activity of a mesoionic compound, 3-piperonylsydnone (I), against *Plasmodium berghei* was reported.² Preliminary structure-activity relationship studies^{2,3} revealed the importance of the piperonyl moiety for the antimalarial activity for compounds of this type. The mode of action of I is still unknown. One possible explanation for the many interesting biological activities exhibited



by the sydnones^{4,5} is that these compounds may interfere with the biochemical role of amino acids. It is certainly not improbable for 3-piperonylsydnone to act as an amino acid antagonist since the compound itself was prepared from an N-substituted amino acid (N-piperonylglycine).² Consequently, syntheses of certain piperonyl derivatives containing a hydantoin (IIa),

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