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ACKNOWLEDGMENTS AND ADDRESSES

Received June 22, 1973, from the *Research Institute of Pharmaceutical Sciences and the Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677*

Accepted for publication September 14, 1973.

Presented in part to the American Society of Pharmacognosy and to the Pharmacognosy and Natural Products Section, APhA Academy of Pharmaceutical Sciences, Jekyll Island, Ga., meeting, July 1973.

Supported by Contract HSM-42-70-109 from the National Institute of Mental Health and by the Research Institute of Pharmaceutical Sciences.

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Sulfide, Disulfide, and Sulfone Derivatives of 2-Phenylcinchoninic Acid as Antimalarial Congeners

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Abstract □ The diethyl ester of bis[6-(2-phenylcinchoninic acid)] sulfone, the corresponding sulfide and disulfide derivatives, and the disulfide acid were prepared. The results of chemotherapeutic testing for antimalarial activity are reported.

Keyphrases □ Bis[6-(2-phenylcinchoninic acid)] sulfone diethyl ester and sulfide and disulfide analogs—synthesized and screened as potential antimalarial agents □ Antimalarial agents, potential —synthesis and screening of bis[6-(2-phenylcinchoninic acid)] sulfone diethyl ester and sulfide and disulfide analogs □ Sulfones, aryl—synthesis and screening of bis[6-(2-phenylcinchoninic acid)] sulfone diethyl ester as a potential antimalarial agent

Elslager *et al.* (1) reported the relationship between chemical structure and antimalarial activity in a series of compounds related to 4,4′-sulfonyldianiline (I), also known as DDS and dapsone. Other investigators reported the synthesis and testing of a variety of sulfones with varying degrees of activity as antimalarial agents (2, 3).

As part of an effort directed toward the synthesis of potential antimalarial agents, it was decided to prepare bis[6-(2-phenylcinchoninic acid)] sulfone diethyl ester (II) as an analog of dapsone. Several structurally related compounds, bis[6-(2-phenylcinchoninic acid)] sulfide diethyl ester (III), bis[6-(2-phenylcinchoninic acid)] disulfide (IV), and bis[6-(2-phenylcinchoninic acid)] disulfide diethyl ester (V), were also prepared for possible structure–activity comparisons.

The synthetic approach to III and IV started with the condensation of the appropriately substituted amines, 4,4′-thiodianiline and *p*-aminophenyl disulfide, respectively, with benzaldehyde and pyruvic acid *via* the Doebner reaction (4). The intermediate acids were converted to the esters, III and V, by a standard procedure (5) for the preparation of aromatic esters. The sulfone was prepared by dichromate oxidation (6) of the corresponding sulfide.

Chemotherapeutic screening of these substances as potential antimalarial agents disclosed no significant antimalarial activity and no detectable host toxicity under the test conditions.

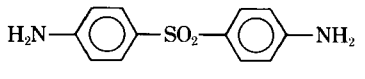
EXPERIMENTAL[1]

4,4′-Thiodianiline[2] and *p*-aminophenyl disulfide, prepared according to the method of Price and Stacy (7), were used.

Bis[6-(2-phenylcinchoninic Acid)] Sulfide Diethyl Ester (III) —To a stirred solution of benzaldehyde (21.2 g, 0.200 mole) in warm ethanol (80 ml), 4,4′-thiodianiline (21.6 g, 0.100 mole) was added rapidly and the resulting mixture was heated at reflux for 10 min. A solution of redistilled pyruvic acid (17.6 g, 0.200 mole) in ethanol (18 ml) was added dropwise over 30 min. The resulting mixture was refluxed and stirred continuously for an additional 6 hr, cooled to room temperature, and stirred overnight. After

[1] Melting points were determined on a Fisher-Johns or Thomas-Hoover melting-point apparatus and are uncorrected. IR spectra were recorded with a Beckman IR-8 spectrophotometer. NMR spectra were recorded with a Varian Associates A-60 spectrometer. Microanalyses were performed by Micro-Analysis, Inc., Wilmington, Del.

[2] Eastman Organic Chemicals, Rochester, N.Y.



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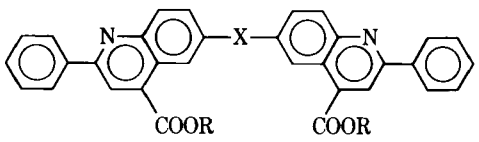

II: X = SO_2, R = C_2H_5

III: X = S, R = C_2H_5

IV: X = S—S, R = H

V: X = S—S, R = C_2H_5

evaporation of the ethanol, the residue was stirred thoroughly with a hot solution of sodium carbonate (10.6 g in 200 ml of water) and the hot slurry was filtered. The residue was treated twice more in a similar fashion with half of the previous quantity of hot sodium carbonate solution and subsequent filtrations. The combined filtrates were acidified with a slight excess of acetic acid, and the resulting precipitate was filtered and dried in air. The precipitated crude acid (30 g), ethanol (1200 ml), and concentrated sulfuric acid (32 ml) were refluxed for 10 hr. The ethanol was evaporated and the residue was diluted with water and filtered. The resulting crude ester was dissolved in ether, and the ethereal solution was washed twice with a saturated solution of sodium carbonate. The ethereal solution was evaporated, and the residue was dissolved in a minimum amount of ethyl acetate. This solution was placed on a silica gel[3] column and developed with cyclohexane–ethyl acetate (2:1) as eluant. Fractions judged similar by TLC were combined and evaporated to dryness. The residue containing the major component was recrystallized from ethanol to obtain 2.5 g (4.3%) of yellow crystals, mp 147–149.5°.

Anal.—Calc. for $C_{36}H_{28}N_2O_4S$: C, 73.95; H, 4.83; N, 4.79; S, 5.48. Found: C, 74.04; H, 4.81; N, 4.88; S, 5.78.

Bis[6-(2-phenylcinchoninic Acid)] Disulfide (IV)—This acid was prepared in a similar fashion from benzaldehyde (16.1 g, 0.152 mole), *p*-aminophenyl disulfide (19 g, 0.076 mole), and redistilled pyruvic acid (13.7 g, 0.156 mole). The crude acid, obtained by acidification of the carbonate extracts was recrystallized from dioxane to yield 3 g (7%) of a yellow solid, mp 287–289°.

Anal.—Calc. for $C_{32}H_{20}N_2O_4S_2$: C, 68.56; H, 3.60; N, 5.00; S, 11.44. Found: C, 68.57; H, 3.57; N, 4.88; S, 11.32.

Bis[6-(2-phenylcinchoninic Acid)] Disulfide Diethyl Ester (V)—A mixture of IV (1.8 g, 0.0032 mole), ethanol (75 ml), and concentrated sulfuric acid (2 ml) was heated under reflux for 10 hr and then concentrated to about 10 ml under reduced pressure. The ester was precipitated by the addition of concentrated ammonium hydroxide (10 ml) and water (10 ml), filtered, dried, and recrystallized from ethanol to yield 0.47 g (24%) of V as yellow crystals, mp 138–140°.

Anal.—Calc. for $C_{36}H_{28}N_2O_4S_2$: C, 70.11; H, 4.58; N, 4.54; S, 10.40. Found: C, 70.15; H, 4.58; N, 4.48; S, 10.15.

Bis[6-(2-phenylcinchoninic Acid)] Sulfone Diethyl Ester (II)—A cooled (15°) mixture of potassium dichromate (0.35 g), water (5 ml), and concentrated sulfuric acid (32 ml) was added slowly to a solution of III (0.58 g, 0.0010 mole), kept below 20° by external cooling, in acetic acid (5 ml, initially warmed to dissolve the ester). After the addition was completed, the reaction mixture was allowed to stand at room temperature for 90 min and then was poured into ice water (55 ml) with stirring, filtered, and washed with water until free of acid. The precipitate was recrystallized from ethanol to obtain 0.24 g (39%) of II, mp 205–207°.

Anal.—Calc. for $C_{36}H_{28}N_2O_6S$: C, 70.12; H, 4.58; N, 4.54; S, 5.20. Found: C, 70.07; H, 4.61; N, 4.72; S, 5.14.

Antimalarial Testing—Compounds II–V were screened for antimalarial activity and toxicity against *Plasmodium berghei* in mice and against *Plasmodium gallinaceum*, Strain B, in chicks according to standard procedures[4]. Results indicated that these compounds lacked noteworthy antimalarial activity and also toxicity to the hosts in doses up to 640 mg/kg in mice and in the range of 100–160 mg/kg in chicks.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 8, 1973, from the *College of Pharmacy, University of Rhode Island, Kingston, RI 02881*

Accepted for publication September 14, 1973.

Abstracted in part from a thesis submitted by P. L. Hsu to the University of Rhode Island in partial fulfillment of the Master of Science degree requirements.

[x] To whom inquiries should be directed.

[3] SilicAR, CC-7, 200-325 mesh, Mallinckrodt Chemical Works, St. Louis, Mo.

[4] Antimalarial testing, through the courtesy of Dr. Thomas R. Sweeney, Walter Reed Army Institute of Research, Washington, D.C., was performed at the University of Miami by previously published methods (8).