Synthesis of 3,4-Dihydrothioxanthene-1,9-dione Analogs as Potential Antimalarial Agents [1]

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7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**), and a variety of analogs and derivatives were prepared as sulfur isosteric analogs of the acridinedione antimalarial agent, floxacrine. The compounds were devoid of antimalarial activity against *P. berghei* in mice.

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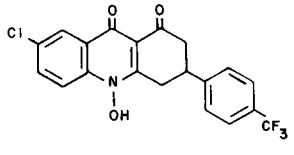
Novel structures which possess antimalarial activity are rare. Thus the report [2] that floxacrine (**1**) a member of a series of unique 3,4-dihydroacridine-1,9-diones possessed exceptional activity against both sensitive and drug-resistant strains of *Plasmodium berghei* [3-5] was exciting. Moreover this agent exhibited causal prophylactic activity in the *P. berghei* mouse model both subcutaneously and orally [6]. No information is available concerning the mode of action of this series, and only very little with regard to the structure activity relationships within the series. Members of this class are quite insoluble suggesting potential bioavailability problems, and there has been some implication of toxicity of floxacrine itself.

It was therefore of considerable interest to explore related structures. Our efforts at developing a more soluble less toxic modification led to a series of imines exemplified by **2** which showed greater potency without the dose related toxicity in the mouse screen shown by floxacrine [7].



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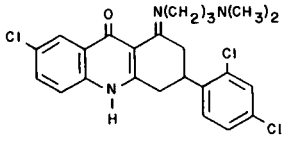
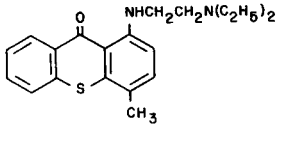


2

More far reaching structural modifications were of interest, and the knowledge that thioxanthones such as **3** have potent antiparasitic activity [8-9] led us to the synthesis of the sulfur isosteres of **1** and **2** *i.e.*, the 3,4-dihydrothioxanthene-1,9-diones exemplified by **4**. In this report we describe the synthesis of **4** and related compounds.



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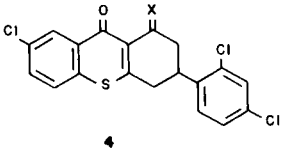


4

a X = O

b X = $N(CH_2)_3N(CH_3)_2$

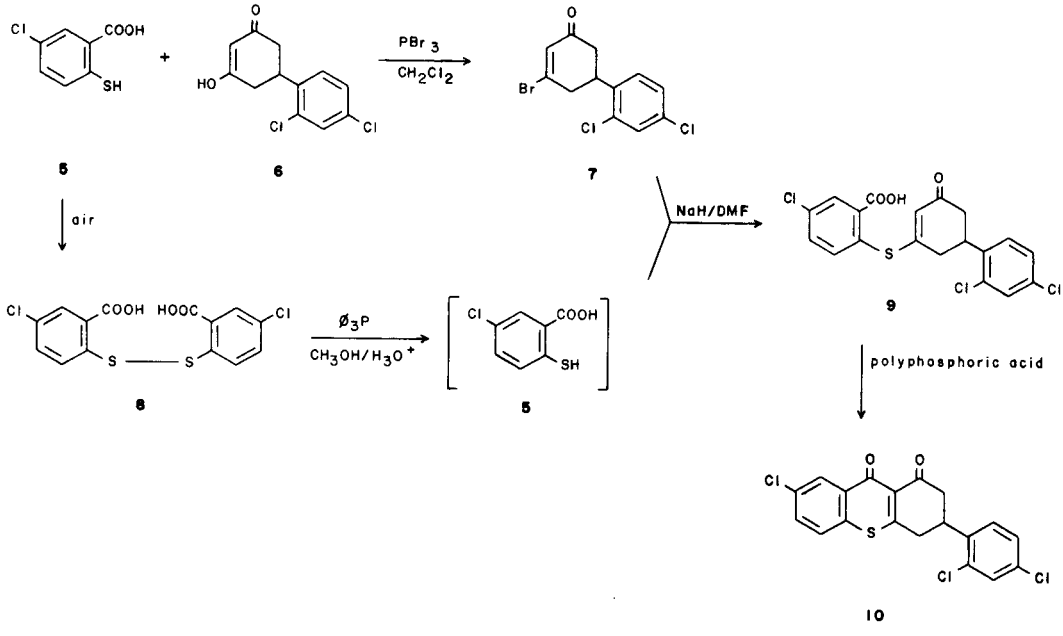
Chemistry.

Condensation of 5-chlorothiosalicylic acid (**5**) [10] with 5-(2,4-dichlorophenyl)-3-hydroxy-2-cyclohexen-1-one (**6**) [11] in polyphosphoric acid provided directly 7-chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**) in low yield (23%). A modified three step synthesis (Scheme I) afforded a modest improvement and resulted in a 33% yield of **10**. Thus cyclohexenone **6** was brominated with phosphorus tribromide to give **7**. On standing the thiophenol **5** was readily oxidized to the disulfide dimer (**8**). It could be reconverted to the thiophenol as needed with triphenyl phosphine [12]. Condensation of the sodium salt of **5** with the bromo compound **7** afforded the intermediate **9** in 82% yield. Cyclization in polyphosphoric acid then provided the desired dione **10**.

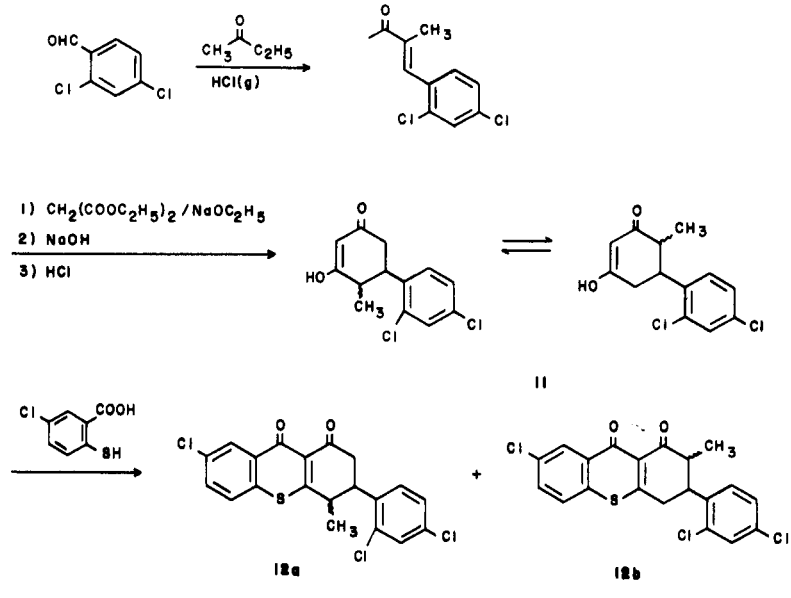
In order to prepare a 2-substituted analog we utilized the aldol condensation of 2,4-dichlorobenzaldehyde with 2-butanone to give 4-(2,4-dichlorophenyl)-3-methyl-3-buten-2-one [13]. Condensation with diethyl malonate followed by hydrolysis and decarboxylation afforded 5-(2,4-dichlorophenyl)-4-methyl-1,3-cyclohexanedione (**11**). Condensation of **11** with 5-chlorothiosalicylic acid (**5**) provided the desired dihydrothioxanthenedione as shown in Scheme II. The product consists of two possible pairs of diastereomers **12a** and **12b**, as indicated by the presence in the proton magnetic resonance spectrum of two separate methyl proton peaks. The pairs of diastereomers were not separated and were submitted for biological testing as a mixture.

Several derivatives of **10** were prepared for the purpose of increasing the solubility of the dihydrothioxanthenedione compounds. Condensation with *N,N*-dimethyl-1,3-propanediamine afforded the corresponding 1-enamine derivative (**13**). The enamine structure is preferred to the imine structure (**4b**) on the basis of spectral data. Full detail is provided in the experimental section. The enamine readily aromatized to the thioxanthenone (**14**) upon exposure to air. Treatment of **10** with hydroxylamine gave the 1-hydroxyimine derivative (**15**). Condensation of **10** with *N*-aminomorpholine provided the aromatized-1-hydr-

Scheme I



Scheme II



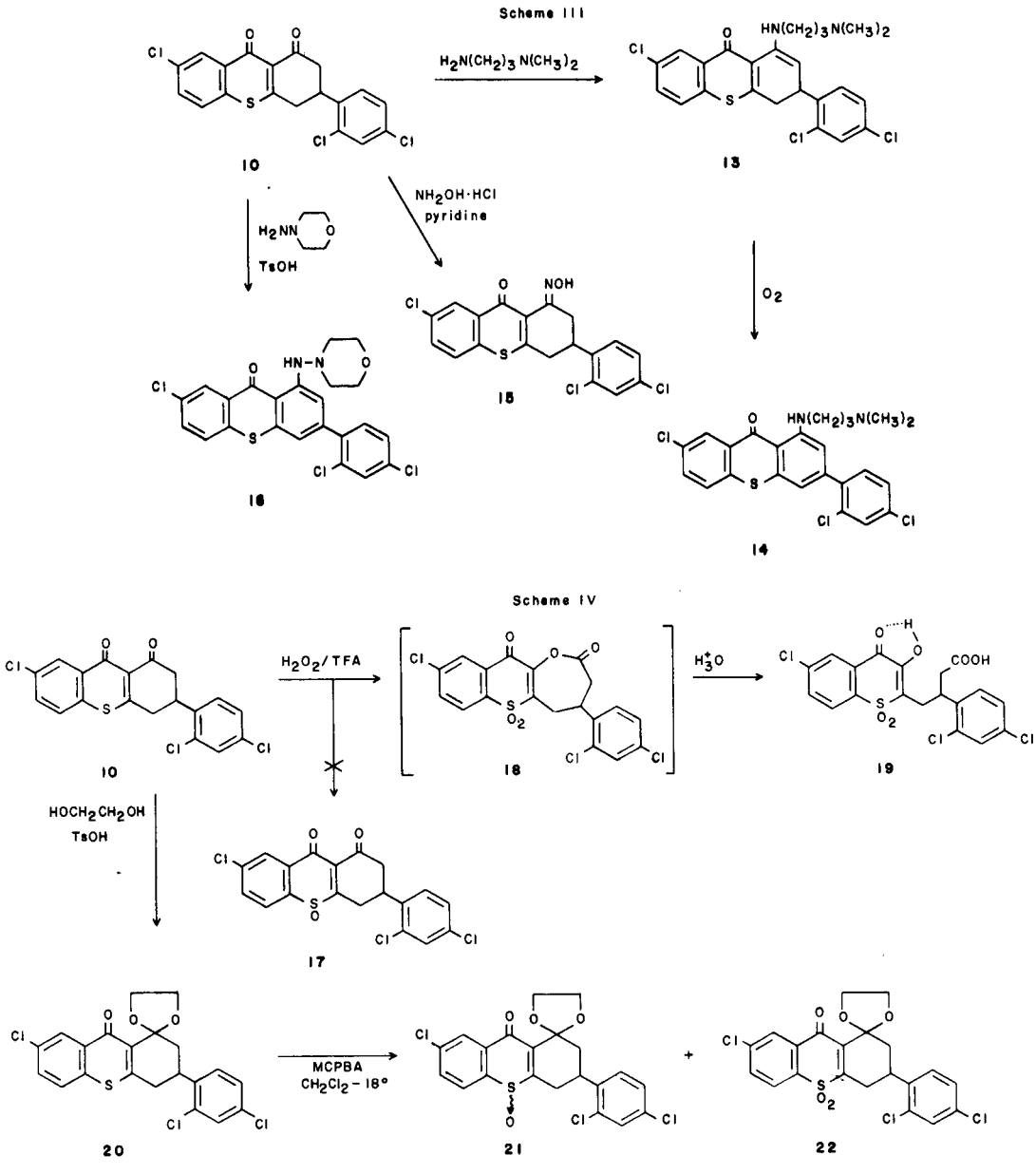
azinothioxanthenone derivative (**16**) as the sole product. These reactions are summarized in Scheme III.

An attempt to oxidize the dione **10** to the corresponding sulfoxide **17** by treatment with hydrogen peroxide in trifluoroacetic acid followed by aqueous work up resulted in a material which all evidence indicates to be **19**. Baeyer-Villiger oxidation to give **18** as an intermediate followed by ring opening during aqueous work up provides a rational explanation for this sequence (Scheme IV). Treatment of **10** with *m*-chloroperoxybenzoic acid in trifluoroacetic acid gave similar results.

Protection of the ketone in **10** by treatment with ethylene glycol to give the 1-ethylene ketal (**20**) followed by oxidation with *m*-chloroperoxybenzoic acid provided the sulfoxide (**21**) and sulfone (**22**) derivatives. Hydrolysis of the thylene ketals (**21** and **22**) was not attempted since the ketal derivatives exhibited improved solubility properties and we reasoned that they might serve as reasonable prodrug modifications of their corresponding ketone analogs.

Biology.

The dihydrothioxanthene-1,9-dione analogs and their derivatives were administered in a single dose to mice infected with a normal drug-sensitive strain of *P. berghei*



[14] and all were devoid of antimalarial activity at 640 mg/kg, the highest dose level tested.

In the acridinedione analogs related to floxacrine, suppressive antimalarial activity decreased drastically once the tricyclic ring was aromatized [15]. The dihydrothioxanthene-1,9-dione analog (**13**) oxidized readily to its aromatized derivative (**14**) upon exposure to air. Possibly under biological conditions such facile oxidation might account for its lack of antimalarial activity.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (^1H nmr) spectra were obtained using a Varian Associates EM-390 or Bruker B-NC-12 instrument. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane as internal standard. Mass spectra were determined on a Finnigan 1015 quadruple spectrometer. The ir spectra were determined on a Digilab FTS14 or Nicolet MX1 spectrophotometer as necessary to confirm the structure.

For elemental analyses, samples were weighed in a Cahn 23 Automatic Electrobalance. The C, H, and N analyses were performed on a Perkin-Elmer 240. Halogens were analyzed on a Brinkman Potentrograph E436. For measuring water content, the sample was dissolved in a 20% solution of pyridine in methanol and was then titrated with Karl-Fisher Reagent. Sulfur content was determined by titration with 0.02*N* of barium chloride. The results of elemental analyses for compound submitted for biological testing were within ± 0.4% of the calculated values.

All starting materials were commercially available unless otherwise

indicated.

5-Chlorothiosalicylic Acid (**5**).

This compound was prepared according to the procedure of Katz, *et al.*, [10]. A solution of 103 g (0.66 mole) of 5-chloroanthranilic acid, 26.4 g (0.66 mole) of sodium hydroxide and 41.0 g (0.60 mole) of sodium nitrite in 650 ml of water was added slowly to a mixture of 150 ml of hydrochloric acid and 200 g ice in 200 ml of water at a rate such that the temperature was maintained below 5°. After the addition was complete, the solution was stirred at 0° to 5° for 30 minutes and then neutralized with solid potassium acetate to *p*H 7. The cold solution was run in a thin stream into a solution of 290 g (1.80 mole) of potassium ethyl xanthate in 800 ml of water which had been preheated to 75-80°. The temperature was maintained at 75-80° until the evolution of nitrogen ceased. The brown oil which separated from the aqueous solution was separated and dissolved in 500 ml of 10% aqueous sodium hydroxide solution. The solution was then heated at 75-80° for two hours. To the reaction mixture was added 50 g of sodium hydrosulfite and the resulting solution was heated at 80-90° for ten minutes. The solution was filtered, the filtrate was acidified with hydrochloric acid to *p*H 5 and then extracted with methylene chloride (1000 ml × 2). The methylene chloride solution was washed successively with 1000 ml of water and 500 ml of a saturated sodium chloride solution, dried (magnesium sulfate) and concentrated *in vacuo* to give a cream solid. Recrystallization from methanol and drying *in vacuo* at 62° for 16 hours gave 80.5 g (71%) of the product as white crystals, mp 184-187° (lit [10] mp 192-194°).

Freshly prepared 5-chlorothiosalicylic acid (**5**) upon exposure to air for two weeks exhibited properties not in agreement with its original structure. Thus it now had a mp >250° and showed absorption at 530 cm^{-1} (S-S stretching) and 660 cm^{-1} (possibly C-S stretching) in the infrared spectrum. Upon treatment with sodium hydrosulfite a small sample of this material was reconverted to **5**, as indicated by the mp 182-184° and infrared spectrum. We thus presume that **5** was readily oxidized to 2,2'-dithiobis[5-chlorobenzoic acid] (**8**).

Synthesis of 7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**) by Direct Condensation of 5-Chlorothiosalicylic Acid (**5**) and 5-(2,4-Dichlorophenyl)-1,3-cyclohexanedione (**6**).

A mixture of 2.46 g (13.00 mmole) of **5** and 2.57 g (10.00 mmole) of **6** in 50 ml of polyphosphoric acid was heated at 160-165° for four hours. The reaction mixture was cooled and poured into ice water. The grey solid was collected, washed successively with 1*N* sodium hydroxide solution, water and acetone. Recrystallization from *N,N*-dimethylformamide and drying at 71° *in vacuo* for 16 hours gave 1.03 g (23%) of the product as yellow needles, mp 252° dec.

Anal. Calcd. for $C_{19}H_{11}Cl_3O_2S$: C, 55.70; H, 2.71; Cl, 25.96; S, 7.83. Found: C, 55.61; H, 2.71; Cl, 25.94; S, 8.02.

3-Bromo-5-(2,4-dichlorophenyl)-2-cyclohexen-1-one (**7**).

A solution of 51.4 g (0.20 mole) of 5-(2,4-dichlorophenyl)-3-hydroxy-2-cyclohexen-1-one (**6**) [11] and 54.0 g (0.20 mole) of phosphorus tribromide in 300 ml of methylene chloride was heated at reflux for two hours and then cooled to room temperature. The reaction mixture was poured slowly into 500 ml of ice-water containing 40 g of sodium carbonate and extracted with methylene chloride (500 ml × 2). The organic layer was separated, washed successively with 500 ml of water and 500 ml of a saturated sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo* at 40° to give 51.5 g (80%) of the product as an off-white solid, mp 67-70°.

Anal. Calcd. for $C_{12}H_9BrCl_2O$: C, 45.03; H, 2.83; Br, 24.97; Cl, 22.16. Found: C, 44.80; H, 2.89; Br, 24.24; Cl, 22.31.

5-Chloro-2-[[5-(2,4-dichlorophenyl-3-oxo-1-cyclohexen-1-y]thio]benzoic Acid (**9**).

Compound **5** was regenerated *in situ* by treatment with triphenyl phosphine and water [12]. A solution of 18.6 g (0.05 mole) of 2,2'-dithiobis[5-chlorobenzoic acid] (**8**), 13.10 g (0.05 mole) of triphenyl phosphine, trace of hydrochloric acid as catalyst, and 0.90 g (0.05 mole) of water in 150 ml of methanol was stirred under nitrogen at room temperature for 15 minutes and then concentrated *in vacuo* at 60° to dryness. The solid residue which was assumed to contain 0.10 mole of 5-chlorothiosalicylic acid (**5**) was dissolved in 5.0 ml of *N,N*-dimethylformamide and added slowly to a suspension of 10.6 g (0.22 mole, 50% dispersion in mineral oil) of sodium hydride in 50 ml of *N,N*-dimethylformamide at ice bath temperature. After bubbling ceased, a solution of 32.0 g (0.10 mole) of 3-bromo-5-(2,4-dichlorophenyl)-2-cyclohexen-1-one (**7**) in 50 ml of *N,N*-dimethylformamide was added dropwise. After the addition, the resulting solution was stirred at ambient temperature for two hours and poured into 500 ml of ice-water. The aqueous solution was washed with ethyl ether (500 ml × 2) to remove triphenyl phosphine oxide and then neutralized with 6*N* hydrochloric acid to *p*H 7. The precipitate was collected, washed with 300 ml of water and recrystallized from acetonitrile to give 35.0 g (82%) of the product as an off-white solid, mp 146-149°; ^1H nmr (deuteriochloroform): δ 2.50-2.85 (m, 4H, $COCH_2$ and allylic *H*), δ 3.60-3.95 (m, 1H, benzylic *H*), δ 5.70 (s, 1H, COO*H*), δ 7.35-7.65 (m, 5H, aromatic *H*), δ 7.75 (d, 1H, J = 3 Hz, aromatic *H*); ir (potassium bromide): 3450-2400, 1720 (C=O), 1620, 1575, 1473, 1285, 1240, 1105 and 810 cm^{-1}.

7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**).

A mixture of 47.0 g (0.11 mole) of 5-chloro-2-[[5-(2,4-dichlorophenyl)-3-oxo-1-cyclohexen-1-yl]thio]benzoic acid (**9**) and 300 ml of polyphosphoric acid was heated and stirred vigorously under nitrogen at 90° for 72 hours and cooled. The mixture was poured into 1000 ml of ice water. The solid was collected and washed successively with 300 ml of 1*N* aqueous sodium hydroxide solution and 300 ml of water. Recrystallization from *N,N*-dimethylformamide and drying *in vacuo* at 67° for 16 hours afforded 23.0 g (51%) of the product as a yellow solid, mp 254° dec; ^1H nmr (trifluoroacetic acid): δ 3.40-3.55 (d, 2H, C_2-*H*, J = 8 Hz), δ 3.80-4.00 (d, 2H, C_4-*H*, J = 9 Hz), δ 4.1-4.50 (m, 1H, C_3-*H*), δ 7.30 ~ 7.60 (m, 3H), δ 8.17 (m, 2H), δ 8.90 (d, 1H, J = 2 Hz); ir (potassium bromide): 1695 (C=O), 1630 (C=O), 1590, 1530, 1480, 1405, 1345, 1100 and 810 cm^{-1}.

Anal. Calcd. for $C_{19}H_{11}Cl_3O_2S$: C, 55.70; H, 2.71; Cl, 25.96; S, 7.83. Found: C, 55.67; H, 2.71; Cl, 25.73; S, 8.12.

4-(2,4-Dichlorophenyl)-3-methyl-3-buten-2-one (**13**).

Hydrogen chloride gas was bubbled into a mixture of 35.0 g (0.20 mole) of 2,4-dichlorobenzaldehyde and 28.8 g (0.40 mole) of 2-butanone for two hours at 0°. The resulting mixture was kept cool in a refrigerator at 0° for 16 hours, poured into 300 ml of cold 2*N* sodium hydroxide solution and extracted with diethyl ether (500 ml × 3). The ether solution was dried over magnesium sulfate, filtered and the filtrate was concentrated *in vacuo* at 30° to give a dark brown solid, which was recrystallized from *n*-hexane to give 30.5 g (67%) of the product as a white solid, mp 72-73°; ^1H nmr (deuteriochloroform): δ 1.90 (s, 3H, C=C-CH_3), δ 2.42 (s, 3H, $COCH_3$), δ 7.25-7.55 (m, 4H, C=C*H* and aromatic *H*).

Anal. Calcd. for $C_{11}H_{10}Cl_2O$: C, 57.66; H, 4.40; Cl, 30.95. Found: C, 57.78; H, 4.32; Cl, 30.82.

5-(2,4-Dichlorophenyl)-4-methyl-1,3-cyclohexanedione (**11**).

To a cooled solution of 1.9 g (0.084 mole) of sodium spheres in 100 ml of ethanol was added 12.3 g (0.077 mole) of diethylmalonate. A solution of 16.0 g (0.070 mole) of 4-(2,4-dichlorophenyl)-3-methyl-3-buten-2-one in 100 ml of ethanol was added to this mixture and the resulting solution was heated at reflux for two hours, during which time a white solid precipitated. The reaction mixture was concentrated to dryness *in vacuo*, treated with 150 ml of 2*N* aqueous sodium hydroxide and filtered. The filtrate was heated at reflux for two hours, cooled, and acidified with cold 50% sulfuric acid to *p*H 2 at ice bath temperature. The resulting mixture was then heated at reflux for two hours and the gummy material solidified when the reaction mixture was cooled. The solid was collected and recrystallized from acetonitrile to give 7.50 g (40%, three steps) of a pale yellow solid, mp 182-184°; ^1H nmr (deuteriochloroform + DMSO-d_6): δ

0.85-1.1 (d, 3H, CH_3), δ 2.5 (m, 3H, $COCH_2$, and $COCHCH_3$), δ 3.5 (m, 1H, C_5-*H*), δ 5.45 (s, 1H, C_2-*H*), δ 7.15-7.3 (m, 3H, aromatic *H*), δ 7.9 (broad, 1H, O*H*). The ^{1}H nmr showed that the product exists in the 3-hydroxy-2-cyclohexen-1-one configuration.

Anal. Calcd. for $C_{13}H_{12}Cl_2O_2$: C, 57.58; H, 4.46; Cl, 26.15. Found: C, 57.68; H, 4.46; Cl, 26.18.

7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-2-methyl-1*H*-thioxanthene-1,9(2*H*)-dione, Hydrate (20:1) (**12a** and **12b**).

A mixture of 2.46 g (0.013 mole) of 5-chlorothiosalicylic acid (**5**) and 2.71 g (0.010 mole) of 5-(2,4-dichlorophenyl)-4-methyl-1,3-cyclohexanedione (**11**) in 50 ml of polyphosphoric acid was heated at 155-165° for five hours. The reaction mixture was cooled and poured into 400 ml of ice water. The tan solid was collected and washed successively with 50 ml of aqueous 1*N* sodium hydroxide, 50 ml of water and 10 ml of acetone. Recrystallization from *N,N*-dimethylformamide and drying at 91° *in vacuo* for 16 hours gave 1.0 g (23%) of the product as a gold solid, mp 142-144°; ^{1}H nmr (DMSO-d_6): δ 0.80 ~ 1.00 (d, 3H, CH_3, J = 3 Hz), δ 2.90-3.85 (m, 5H, C_1, C_2, and C_3-*H*), δ 7.67 (dd, 1H, J = 2, 9 Hz), δ 7.77-8.10 (m, 4H), δ 8.30 (d, 1H, J = 3 Hz); ir (potassium bromide): 1692 (C=O), 1630 (C=O), 1585, 1530, 1475, 1397, 1278, 1097 and 812 cm^{-1}.

Anal. Calcd. for $C_{20}H_{13}Cl_3O_2S \cdot 0.5H_2O$: C, 56.56; H, 3.09; Cl, 25.05; S, 7.55; H_2O, 0.21. Found: C, 56.16; H, 3.14; Cl, 24.71; S, 7.86; H_2O, 0.17.

7-Chloro-3-(2,4-dichlorophenyl)-1-[[3-dimethylamino)propyl]amino]-3,4-dihydro-9*H*-thioxanthen-9-one (**13**).

A mixture of 2.05 g (5.0 mmoles) of 7-chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**) in 50 ml of *N,N*-dimethyl-1,3-propanediamine was heated at reflux on a steam bath for two hours. The reaction mixture was filtered while hot and the filtrate was concentrated *in vacuo* at 70° to give a dark oily residue. The residue was partitioned between 100 ml of methylene chloride and 100 ml of water. The methylene chloride layer was separated, shaken with 100 ml of saturated sodium chloride solution and then dried over magnesium sulfate. The dried solution was filtered and concentrated *in vacuo* at 40° to give a yellow solid. Recrystallization from ethyl ether-petroleum ether (30°-60°) gave 1.05 g (43%) of the product as a deep orange solid, mp 132-134°; uv (methanol): λ max 244 nm (ε 25831), 294 (16743), 332 (5680), 346 (5433), 443 (4406); ms m/e: 492 (M^+), 406 (M^+- $(CH_2)_3N(CH_3)_2$), 347 (100, M^+-$C_6H_3Cl_2$), 86 ($(CH_2)_3N^+(CH_3)_2$); ^{1}H nmr (deuteriochloroform): δ 1.70 (m, 2H, CH_2), δ 2.10 (s, 6H, CH_3), δ 2.30 (t, 2H, NCH_2), δ 2.80 (m, 2H disappeared after D_2O wash, C_4-*H*), δ 3.30 (m, 2H, $NHCH_2$), δ 4.00 (m, 1H, C_3-*H*), δ 5.30 (d, 1H, disappeared after D_2O wash, C_2-*H*), δ 6.9-7.3 (m, 6H, aromatic *H*); ir (potassium bromide): 3260 (N-H), 1610, 1560, and 1255 cm^{-1}. The chemical shift at δ 5.30 ppm was assigned to the vinyl proton at the 2-position and the infrared absorption at 3260 cm^{-1} as hydrogen bonded N-H stretching. These confirmed the enamine rather than the imine structure of the product.

Anal. Calcd. for $C_{24}H_{23}Cl_3N_2OS$: C, 58.36; H, 4.69; N, 5.67. Found: C, 58.19; H, 4.86; N, 5.68.

7-Chloro-3-(2,4-dichlorophenyl)-1-[[3-(dimethylamino)propyl]amino]-9*H*-thioxanthen-9-one (**14**).

A solution of 4.91 g (0.01 mole) of **13** in 100 ml of methylene chloride was stirred at room temperature for 72 hours. The methylene chloride was removed *in vacuo* at 50° and the dark residue was chromatographed over 250 g of silica gel (70-230 mesh, 0.063-0.2 mm) with methylene chloride:methanol = 9:1 as the eluent to provide 2.50 g of an orange solid, R_f = 0.4. Recrystallization from ethyl ether and drying *in vacuo* at 30° for 16 hours gave 2.0 g (41%) of the title compound as brilliant orange crystals, mp 115-116°; uv (methanol): λ max 230 (ε 31282), 268 (39693), 346 (10083), 450 (8952); ^{1}H nmr (deuteriochloroform): δ 2.00 (m, 2H, CH_2), δ 2.30 (s, 6H, CH_3), δ 2.50 (t, 2H, NCH_2), δ 3.40 (m, 2H, $NHCH_2$), δ 6.60 (d, 1H, J = 2 Hz, aromatic *H*), δ 6.70 (d, 1H, J = 2 Hz, aromatic *H*), δ 7.30-7.60 (m, 5H, aromatic *H*), δ 8.5 (d, 1H, aromatic *H*); ir (potassium bromide): 3460, 3260 (N-H), 1610 (C=O), 1565, 1480, 1403, 1260 and 1206 cm^{-1}; ms m/e (rel. intensity): 490 (26, M^+), 432 (16), 419 (40), 402 (17), 292 (8), 97 (19), 85 (100). The proton resonances at δ 6.60 and δ 6.70 ppm were assigned to the aromatic protons at 2- and 4-positions, which showed meta coupling to one another.

Anal. Calcd. for $C_{24}H_{21}Cl_3N_2OS$: C, 58.60; H, 4.30; N, 5.70; Cl, 21.63; S, 6.52. Found: C, 58.36; H, 4.22; N, 5.60; Cl, 21.89; S, 6.77.

7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione, 1-Oxime Compound with *N,N*-Dimethylformamide (5:2) (**15**).

A mixture of 2.10 g (0.005 mole) of **10** and 0.70 g (0.01 mole) of hydroxylamine in 30 ml of pyridine was heated on a steam bath for three hours. The reaction mixture was cooled and poured into 100 ml of ice water and the solid was collected. It was triturated with 100 ml of boiling ethanol, filtered, and dried *in vacuo* at 70° for 20 hours to give 0.80 g (38%) of the product as a cream colored solid, mp 260-261°; ^{1}H nmr (trifluoroacetic acid), δ 3.20-4.10 (m, superimposed with CH_3 of *N,N*-dimethylformamide), δ 7.20-7.40 (m, 3H), δ 7.75 (m, 2H), δ 8.60 (d, 1H, J = 3 Hz).

Anal. Calcd. for $C_{19}H_{12}Cl_3NO_2S \cdot 0.4C_3H_7NO$: C, 53.44; H, 3.28; N, 4.32; Cl, 23.43; S, 7.06. Found: C, 53.36; H, 3.40; N, 4.40; Cl, 23.43; S, 7.33.

7-Chloro-3-(2,4-dichlorophenyl)-1-(4-morpholinylamino)-9*H*-thioxanthen-9-one (**16**).

A mixture of 2.05 g (5.0 mmole) of **10**, 0.61 g (6.0 mmole) of *N*-aminomorpholine and a trace of *p*-toluenesulfonic acid in 50 ml of ethanol was heated at reflux for 22 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* at 60° to give a dark solid. The solid was chromatographed over 70 g of silica gel (70-230 mesh, 0.063-0.2 mm) using methylene chloride as the eluent, to provide 0.70 g of dark red solid (R_f = 0.3). Recrystallization from *n*-hexane and drying *in vacuo* at 50° for 16 hours gave 0.55 g (22%) of the product as a deep red solid, mp 190-192°; uv (methanol): λ max 232 nm (ε 27688), 272 (36050), 343 (9541), 443 (7426); ^{1}H nmr (deuteriochloroform): δ 2.80-3.10 (broad, 4H, morpholine *H*), δ 3.80-4.00 (t, 4H, morpholine *H*), δ 6.80 (d, 1H, aromatic *H*, J = 2 Hz), δ 7.3-7.6 (m, aromatic *H* superimposed with chloroform resonance), δ 8.50 (d, 1H, J = 2 Hz), δ 10.7 (broad, 1H, NH).

Anal. Calcd. for $C_{23}H_{17}Cl_3N_2O_2S$: C, 56.16; H, 3.49; N, 5.70; Cl, 21.63; S, 6.52. Found: C, 56.17; H, 3.67; N, 5.80; Cl, 21.29; S, 6.69.

Attempted Oxidation of 7-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1*H*-thioxanthene-1,9(2*H*)-dione (**10**).

A solution of 30% aqueous hydrogen peroxide (0.24 ml, 2.0 mmole) was added to a cooled solution of 0.41 g (1.0 mmole) of **10** in 15 ml of trifluoroacetic acid. The reaction mixture was kept at 0° for three days and poured into 100 ml of ice water. The gummy solid was recrystallized from acetonitrile to give, instead of the desired sulfoxide derivative, 0.30 g (63%) of 6-chloro-β-(2,4-dichlorophenyl)-3-hydroxy-4-oxo-4*H*-1-benzothiopyran-2-butanoic acid 1,1-dioxide (**19**) as a pale yellow solid, mp 195-199°; ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 2.80 (d, 2H, CH_2COOH, J = 7 Hz), δ 3.00 (d, 2H, allylic *H*, J = 7 Hz), δ 4.30 (m, 1H, benzylic *H*), δ 7.00 ~ 7.40 (m, 3H, aromatic *H*), δ 7.70 ~ 8.10 (m, 3H, aromatic *H*), δ 9.0 ~ 10.5 (broad, 2H, O*H*, and COO*H*); ir (chloroform): 3515 (O-H from COOH), 3400 (hydrogen bonded O-H stretching), 1745 + 1710 (-C=O of -COOH monomer and dimer), 1471, 1408, 1305 and 1150 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}Cl_3O_6S$: C, 47.97; H, 2.75; Cl, 22.36; S, 6.74. Found: C, 48.21; H, 3.00; Cl, 22.06; S, 7.02.

7'-Chloro-3'-(2,4-dichlorophenyl)-3',4'-dihydrospiro[1,3-dioxolane-2,1'-[1*H*]thioxanthen]-9'(2'*H*)-one (**20**).

A mixture of 6.30 g (0.015 mole) of **10**, 6.34 g (0.10 mole) of ethylene glycol and a trace of *p*-toluenesulfonic acid in 500 ml of toluene was heated at reflux for 20 hours. A Dean Stark trap was used to remove the water generated. The reaction mixture was cooled and filtered and the filtrate was concentrated *in vacuo* to 100 ml. The solid precipitate was collected and recrystallized from methylene chloride-*n*-hexane to give 5.40 g (79%) of the title compound as a cream solid, mp 217-219°; ^{1}H nmr (deuteriochloroform): δ 2.25 (d, 2H, J = 9 Hz), δ 2.95 (d, 2H, J = 7 Hz), δ 3.70 ~ 4.05 (m, 1H), δ 4.05-4.40 (m, 2H), δ 4.40 ~ 4.70 (m, 2H), δ 7.30-7.65 (m, 5H, superimposed with chloroform), δ 8.50 (d, 1H, J = 3 Hz).

Anal. Calcd. for $C_{21}H_{15}Cl_3O_3S$: C, 55.58; H, 3.33; Cl, 23.44; S, 7.07. Found: C, 55.32; H, 3.30; Cl, 23.14; S, 7.26.

7'-Chloro-3'-(2,4-dichlorophenyl)-3',4'-dihydrospiro[1,3-dioxolane-2,1'-[1*H*]thioxanthen]-9'(2'*H*)-one, 10'-Oxide (**21**) and 7'-Chloro-3'-(2,4-dichlorophenyl)-3',4'-dihydrospiro[1,3-dioxolane-2,1'[1*H*]thioxanthen]-9'(2'*H*)-one, 10',10'-Dioxide (**22**).

A solution of 4.50 g (0.01 mole) of **20** and 2.16 g (0.01 mole) of *m*-chloroperbenzoic acid in 300 ml of methylene chloride was maintained at −18° for four days and then poured into 200 ml of 1*N* sodium bicarbonate solution. The organic layer was separated, washed with 300 ml of water and then with 100 ml of a saturated sodium chloride solution. The methylene chloride solution was dried over magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo* at 40° to give 4.50 g of an oily residue, which contained three products and the starting material as indicated on tlc. The products were separated and purified by chromatography on 260 g of silica gel (70-230 mesh, 0.063-0.2 mm). When using methylene chloride:petroleum ether = 19:1 as the eluent, 0.95 g (20%) of the first fraction was isolated (R_f = 0.4), mp 203-204°. Afterward, methylene chloride:ethyl acetate = 19:1 was used as the eluent and 0.62 g of the second fraction was obtained as an oil (R_f = 0.3), which crystallized from toluene-*n*-hexane, mp 182-184°.

The first fraction was confirmed to be compound **22** from ^{1}H nmr, ir and microanalysis. The spectral data are as follows: ^{1}H nmr (deuteriochloroform): δ 2.00 ~ 2.15 (d, 2H, J = 9 Hz), δ 2.50-2.85 (m, 1H), δ 3.1-3.4 (dd, 1H, J = 4, 18 Hz), δ 3.5-3.9 (m, 1H), δ 3.95-4.5 (m, 4H), δ 7.15 (m, 2H), 7.35 (d, 1H, J = 3 Hz), δ 7.55-8.05 (m, 3H); ir (potassium bromide): 1676 (C=O), 1565, 1475, 1306 (O-S-O asymmetric stretching) and 1160 cm^{-1} (O-S-O symmetric stretching).

Anal. Calcd. for $C_{21}H_{15}Cl_3O_5S$: C, 51.92; H, 3.11; Cl, 21.90; S, 6.60. Found: C, 52.13; H, 3.24; Cl, 21.92; S, 6.80.

The ^{1}H nmr and ir spectra of the second fraction are as follows: ^{1}H nmr (deuteriochloroform): δ 2.10 (d, 2H, J = 9 Hz), δ 2.60 ~ 3.30 (m, 2H), δ 7.35 (d, 1H, J = 3 Hz), δ 7.60 (dd, 1H, J = 2.80), δ 7.80 (d, 1H, J = 9 Hz), δ 8.00 (d, 1H, J = 3 Hz); ir (potassium bromide): 1672 (C=O), 1560, 1476, 1329, 1310 and 1055 cm^{-1} (S-O stretching). The ^{1}H nmr indicated that the product is a mixture of the geometric isomers of the sulfoxide and gc shows the ratio to be 82:16.

Anal. Calcd. for $C_{21}H_{15}Cl_3O_4S$: C, 53.69; H, 3.22; Cl, 22.64; S, 6.82. Found: C, 53.82; H, 3.34; Cl, 22.41; S, 6.85.

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REFERENCES AND NOTES

[1] This paper is communication **52** of a series on antimalarial drugs. For paper **51** see J. Hung and L. M. Werbel, *Eur. J. Med. Chem.*, **18**, 61 (1983). This investigation was supported by US Army Medical Research and Development Command Contract DAMD-17-79-C9115. This is contribution number 1677 to the Army Research Program on Malaria.

[2] W. Duerckheimer, W. Raether and H. G. Seliger, German Patent DS 2,337,474 (1975); *Chem. Abstr.*, **83**, 9827w (1975).

[3] W. Raether and E. Fink, *Tropenmed.* **21**, 268 (1977).

[4] W. Raether and E. Fink, *ibid.*, **73**, 505 (1979).

[5] L. H. Schmidt, *Antimicrob. Agents Chemother.*, **16**, 475 (1979).

[6] D. E. Davidson, Jr., A. L. Ager, J. L. Brown, F. E. Chapple, R. E. Whitmire and R. N. Rossan, *Bull. W. H. O.*, **59**, 463-479 (1981).

[7] L. M. Werbel, US Patent 4,291,034 (1981); *Chem. Abstr.*, **96** 6611d (1982).

[8] D. M. Blair, *Bull. W. H. O.*, **18**, 989 (1958).

[9] R. Goennert and H. Koelling, "Drugs, Parasites and Hosts", L. G. Goodwin and R. H. Nimmo-Smith, eds, J. A. Churchill Ltd., London, 1962, p 29-42.

[10] L. Katz, L. S. Karger, W. Schroeder and M. S. Cohen, *J. Org. Chem.*, **18**, 1380 (1953).

[11] This compound was supplied by Ash Stevens Co. For preparation see reference [7].

[12] L. E. Overman, J. S. Moot and J. D. Overman, *Synthesis*, 59 (1974).

[13] Procedure of A. T. Nielsen and W. J. Houlihan in "Organic Reactions", Vol **16**, A. C. Cope, ed, Wiley, New York, 1968, p 81.

[14] The parenteral suppressive antimalarial screening was carried out by Dr. Arba L. Ager, Jr. at the University of Miami and test results were provided through the courtesy of Dr. T. R. Sweeney, Dr. E. A. Steck, and Mr. M. Musallam of the Walter Reed Army Institute of Research. For a description of the test method, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

[15] L. M. Werbel, unpublished data.