Potential Antimalarial and Antischistosomal Agents. 6-Chloro-1-[α-(dialkylamino)-4-hydroxy- and alkoxy-*m*-toluidino]-4-methylthioxanthen-9-ones, Amodiaquine and Amopyroquine Relatives of Lucanthone (1)

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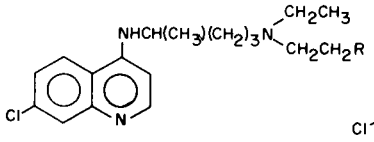
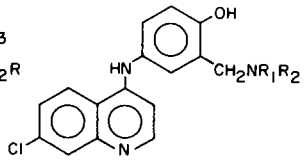
The 4-aminoquinoline drugs chloroquine (Ia), hydroxychloroquine (Ib), amodiaquine (IIa), amopyroquine (IIb), and cycloquine (III) comprise the most widely used class of antimalarial substances and are the drugs of choice against susceptible strains of malarial parasites. These



I

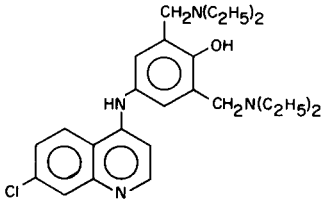
a, R = H
b, R = OH



II

a, $NR_1R_2 = N(C_2H_5)_2$

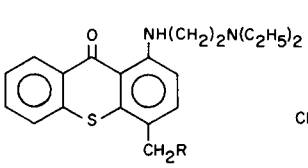
b, NR_1R_2 = N⟨ ⟩



III

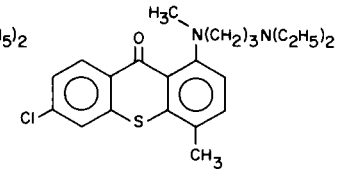
4-aminoquinolines are potent, fast-acting blood schizontocides, and display gametocytocidal action against *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*, but not against *Plasmodium falciparum* (3). However, they are ineffective against trematode infections caused by *Schistosoma* species.

A Variety of 1-[[(mono- and dialkylamino)alkyl]amino]-4-methylthioxanthen-9-ones exhibit antischistosome activity in experimental animals and in man (4). Notable among them are lucanthone (IVa) and hycanthone (IVb) which have been demonstrated to be effective against the



IV

a, R = H
b, R = OH

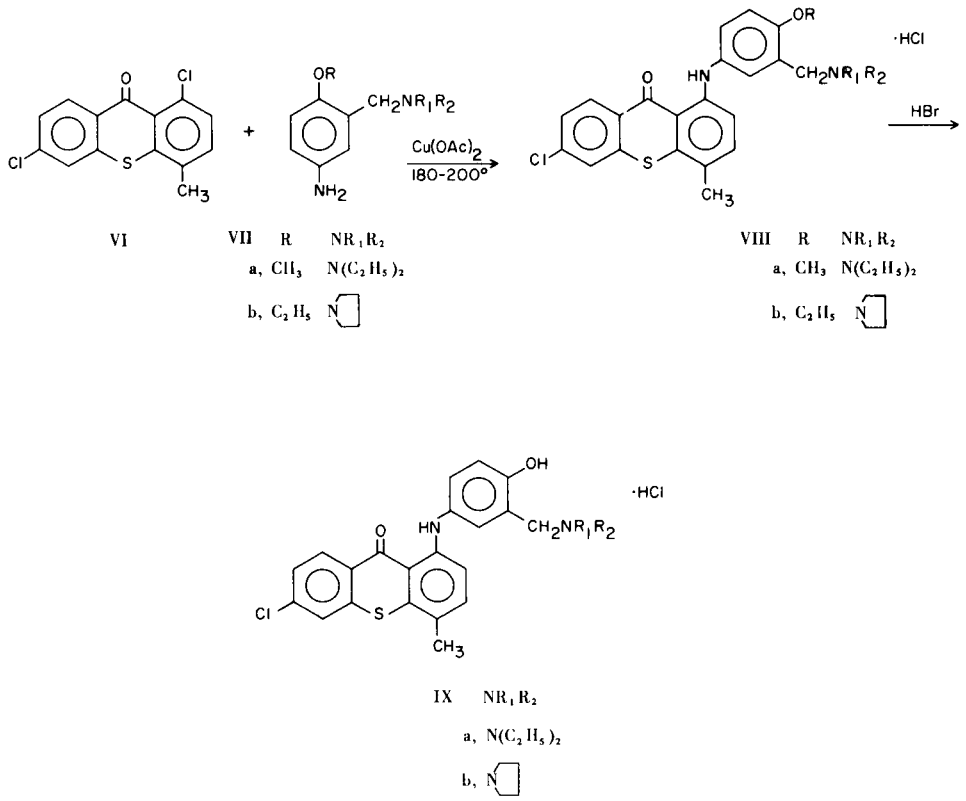


V

human pathogens *Schistosoma haematobium* and *Schistosoma mansoni* (4). In contradistinction, the 1-amino-4-methylthioxanthen-9-ones exemplified by lucanthone (IVa) and 6-chloro-1-[[[[3-(diethylamino)propyl]methyl]amino]-4-methylthioxanthen-9-one (V) (5) lack appreciable effects against the plasmodia of malaria. Since the substitution of an α-(dialkylamino)-4-hydroxy-*m*-toluidino function for the aliphatic diamine side-chain in the chloroquine (IVa) molecule affords compounds (e.g. amodiaquine, amopyroquine, and cycloquine) with potent biological properties, it was of interest to prepare representative 6-chloro-1-[α-(dialkylamino)-4-hydroxy- and alkoxy-*m*-toluidino]-4-methylthioxanthen-9-ones (VIIIa and b, IXa and b) for evaluation as potential antimalarial and antischistosomal agents.

The proposed synthesis route (Chart I) was to condense 1,6-dichloro-4-methylthioxanthen-9-one (VI) with an N^{α}, N^{α}-dialkyl-6-alkoxytoluene-α,3-diamine (VII) to give the 6-chloro-1-[α-(dialkylamino)-4-alkoxy-*m*-toluidino]-4-methylthioxanthen-9-ones (VIII), which upon treatment with hydrobromic acid should afford the corresponding 6-chloro-1-[α-(dialkylamino)-4-hydroxy-*m*-toluidino]-4-methylthioxanthen-9-ones (IX). Early efforts to prepare 6-chloro-1-[[3-[(diethylamino)methyl]-*p*-anisidino]-4-methylthioxanthen-9-one (VIIIa) were unsuccessful. Attempts to condense N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (VIIa) (6,7) with 1,6-dichloro-4-methylthioxanthen-9-one (VI) (8) in refluxing phenol

Chart I



VI

VII R NR_1R_2
a, CH_3 $N(C_2H_5)_2$
b, C_2H_5 N

VIII R NR_1R_2
a, CH_3 $N(C_2H_5)_2$
b, C_2H_5 N

IX NR_1R_2
a, $N(C_2H_5)_2$
b, N

(178°) with or without potassium iodide afforded little, if any, product as indicated by thin layer chromatography (alumina-benzene). When the reaction was carried out utilizing the base of VIIa in a refluxing xylene-anhydrous potassium carbonate mixture, only a trace of the desired product was formed. However, 6-chloro-1-[3-[(diethylamino)methyl]-*p*-anisidino]-4-methylthioxanthen-9-one hydrochloride (VIIIa) and 6-chloro-4-methyl-1-[3-(1-pyrrolidinylmethyl)-*p*-phenetidino]thioxanthen-9-one hydrochloride (VIIIb) were successfully prepared in 37% and 72% yields, respectively, by fusing N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine (VIIa) and 1-(5-amino-2-ethoxybenzyl)pyrrolidine (VIIb) with 1,6-dichloro-4-methylthioxanthen-9-one (VI) at 180-200° in the presence of cupric acetate and sodium acetate under nitrogen.

The crude products were purified by adsorption on Woelm acid aluminum oxide followed by elution with ethyl acetate and methanol-ethyl acetate. Compounds VIIIa and b were readily converted to 6-chloro-1-[α-(diethylamino)-4-hydroxy-*m*-toluidino]-4-methylthioxanthen-9-one (IXa) (75%) and 6-chloro-1-(4-hydroxy-α-1-pyrrolidinyl-*m*-toluidino)-4-methylthioxanthen-9-one (IXb) (79%) by boiling under reflux with 47% hydrobromic acid for 24 hours.

The hydrochloric acid salts of the 6-chloro-1-[α-(dialkylamino)-4-hydroxy- and alkoxy-*m*-toluidino]-4-methylthioxanthen-9-ones (VIIIa and b, IXa and b) described in the present communication were tested in mice against a Puerto Rican strain of *Schistosoma mansoni* (9,10) by Thompson and coworkers of these laboratories. Drugs were given in a powdered diet for 14 days and drug amounts are expressed as free base. None of the compounds effected a significant reduction of live schistosomes in mice at tolerated doses ranging from 92 to 187 mg./kg./day for 14 days.

The above compounds were also administered continuously in the diet for 6 days to mice infected with a normal drug-sensitive strain of *Plasmodium berghei* (11). Although the 6-chloro-1-[α-(dialkylamino)-4-alkoxy-*m*-toluidino]-4-methylthioxathen-9ones (VIIIa and b) lacked appreciable antimalarial effects at doses ranging from 131-147 mg./kg./day, the corresponding 6-chloro-1-[α-(dialkylamino)-4-hydroxy-*m*-toluidino]-4-methylthioxanthen-9-ones (IXa and b) exhibited good antimalarial activity. The SD_{90}'s (daily dose required for 90% suppression of the parasitemia) for IXa, IXb, and quinine were 44 mg./

kg., 100 mg./kg., and 74 mg./kg., respectively. Thus IXa was nearly twice as potentas quinine against *Plasmodium berghei* by drug-diet.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. NMR spectra were determined in deuteriochloroform with a Varian A-60 Spectrophotometer using tetramethylsilane as an internal standard. The infrared spectra were obtained with a Beckman IR-9 Spectrophotometer in potassium bromide discs.

1-(2-Ethoxy-5-nitrobenzyl)pyrrolidine Hydrochloride.

A mixture 250 g. (1.25 moles) of 2-(chloromethyl)-4-nitrophenetole (7), 180 g. (2.5 moles) of pyrrolidine, and 1 l. of benzene was heated under reflux for 4 hours and allowed to stand at room temperature overnight. The pyrrolidine hydrochloride which precipitated was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether, the mixture was filtered, and the ether filtrate was treated with an excess of a 2-propanol-hydrogen chloride mixture. The precipitate was collected by filtration, washed with ether, and dried, yielding 280 g. (78%), m.p. 216-219°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3 \cdot HCl$: C, 54.45; H, 6.68. Found: C, 54.91; H, 6.89.

1-(5-Amino-2-ethoxybenzyl)pyrrolidine Dihydrochloride (VIIb).

1-(2-Ethoxy-5-nitrobenzyl)pyrrolidine hydrochloride (269 g., 0.94 mole) was reduced in 1 l. of methanol over 20 g. of Raney nickel over a period of 40 hours at an initial hydrogen pressure of 50 p.s.i.g. The catalyst was removed and the reaction mixture was filtered into 2-propanol containing excess hydrogen chloride. The mixture was concentrated to 300 ml. and cooled. The product was collected by filtration and recrystallized from ethanol to give 234 g. (82%) of a white solid, m.p. 218-223°.

Anal. Calcd. for $C_{13}H_{20}N_2O \cdot 2HCl \cdot 0.25\ H_2O$: C, 52.44; H, 7.61. Found: C, 52.43; H, 8.07.

6-Chloro-4-methyl-1-[3-(1-pyrrolidinylmethyl)-*p*-phenetidino]-thioxanthen-9-one Hydrochloride (VIIIb).

A solution of 34.0 g. (0.12 mole) of 1-(5-amino-2-ethoxybenzyl)pyrrolidine dihydrochloride (VIIb) in 200 ml. of water was made strongly alkaline with 20 ml. of 50% aqueous sodium hydroxide and the mixture was extracted thoroughly with chloroform. The combined chloroform extracts were dried over anhydrous potassium carbonate, the drying agent was removed by filtration, and volatile materials were removed *in vacuo* on a rotary evaporator. 1,6-Dichloro-4-methylthioxanthen-9-one (8)(29.5 g., 0.08 mole based on 80% reactive isomer), 12.5 g. (0.15 mole) of anhydrous sodium acetate, and 0.5 g. of cupric acetate were then added, and the mixture was placed in an oil bath and stirred at 190° (external temperature) under nitrogen for 3 hours. The mixture was cooled to 80° and the residue was shaken with a mixture of 200 ml. of warm water, 10 ml. of 50% aqueous sodium hydroxide, and 200 ml. of chloroform. The chloroform layer was separated, and the aqueous layer was extracted with three 500 ml. portions of chloroform. The combined chloroform extracts were washed successively with water and two portions of 1 *N* hydrochloric acid and dried over anhydrous potassium carbonate. The chloroforom was removed *in vacuo*, the residue was dissolved in benzene, and the benzene solution was slurried with 1.5 kg. of Woelm acid (anionotropic) aluminum oxide activity grade I for 1.5 hours. The aluminum oxide slurry was collected by filtration and the benzene filtrate was discarded. The aluminum oxide was placed in a 5 l. sintered glass funnel and washed successively with two 4 l. portions of 50% benzene-50% ethyl acetate, four 1 l. portions of ethyl acetate, one 6 l. portion of 5% methanol-95% ethyl acetate, and one 4 l. portion of 10% methanol-90% ethyl acetate. The two 50% benzene-50% ethyl acetate extracts were combined and concentrated to give 15.0 g. of residue which was primarily unreacted chlorothioxanthen-9-ones; this material was discarded. All other extracts were combined, concentrated *in vacuo*, and the residue crystallized from acetone to give 18.2 g. (72% based on the 0.049 mole of 1,6-dichloro-4-methylthioxanthen-9-one consumed) of orange crystals, m.p. 234-236° dec.

Anal. Calcd. for $C_{27}H_{27}ClN_2O_2S \cdot HCl$: C, 62.91; H, 5.47; N, 5.44. Found: C, 63.06. H, 5.58; N, 5.35.

A small sample of the pure hydrochloride salt was converted to the base, m.p. 150-152°; infrared cm^{-1}, 2960(m), 2790(m), 1610(s), 1250(s); NMR spectrum, 4.06 δ (OCH_2CH_3, quartet), 3.70 δ ($ArCH_2N$, singlet), 2.26 δ ($ArCH_3$, singlet), 1.42 δ (CH_2CH_3, triplet).

6-Chloro-1-(4-hydroxy-α-1-pyrrolidinyl-*m*-toluidino)-4-methylthioxanthen-9-one Hydrochloride (IXb).

A mixture of 8.0 g. (0.0155 mole) of 6-chloro-4-methyl-1-[3-(1-pyrrolidinylmethyl)-*p*-phenetidino]thioxanthen-9-one hydrochloride (VIIIb) and 250 ml. of 47% hydrobromic acid was heated under reflux for 24 hours. The reaction mixture was cooled and poured into 300 ml. of 50% aqueous sodium hydroxide and 1 kg. of ice. The product was extracted with three 300 ml. portions of chloroform and the combined chloroform extracts were dried over anhydrous potassium carbonate. The chloroform was removed *in vacuo* and the residue was crystallized from acetone to give 6.0 g. (79%) of deep yellow crystals, m.p. 180-182°; infrared cm^{-1}, 2970(m), 2830(w), 1610(s), 1250(s); NMR spectrum, 3.77 δ ($ArCH_2N$, singlet), 2.21 δ ($ArCH_3$, singlet), the pyrrolidine protons gave broad multiplets at 2.5-2.8 δ and 1.6-2.0 δ.

Anal. Calcd. for $C_{25}H_{23}ClN_2O_2S$: C, 66.58; H, 5.14; N, 6.21. Found: C, 66.45; H, 5.16; N, 5.93.

The above base (5.0 g., 0.011 mole) was dissolved in hot acetone and treated with 10 ml. of 22% hydrogen chloride in 2-propanol. Upon cooling, the red-brown hydrochloride salt was collected by filtration and dried *in vacuo* at 100° for 18 hours, yielding 4.4 g. (82%), m.p. 265° dec.

6-Chloro-1-[[3-[(diethylamino)methyl]-*p*-anisidino]-4-methylthioxanthen-9-one Hydrochloride (VIIIa).

N^{α},N^{α}-Diethyl-6-methoxytoluene-α,3-diamine dihydrochloride (6,7) (23.0 g., 0.082 mole) was converted to the free base and allowed to react with 20.0 g. (0.054 mole based on 80% reactive isomer) of 1,6-dichloro-4-methylthioxanthen-9-one (8) in the presence of 10.0 g. (0.12 mole) of anhydrous sodium acetate and 0.4 g. of cupric acetate. The reaction mixture was processed according to the procedure for VIIIb. The hydrochloride salt of the product (VIIIa) was obtained as orange crystals from acetone, m.p. 227-228°. Yield, 9.5 g. (37% based on the 0.051 mole of 1,6-dichloro-4-methylthioxanthen-9-one consumed).

Anal. Calcd. for $C_{26}H_{27}ClN_2O_2S \cdot HCl$: C, 62.02; H, 5.61; N, 5.57; Total Cl, 14.08; Cl^-, 7.04. Found: C, 62.12; H, 5.68; N, 5.45; Total Cl, 14.43; Cl^-, 7.16.

A sample of the pure hydrochloride salt was converted to the base, m.p. 127-128°; infrared cm^{-1}, 2960(m), 2800(w), 1610(s), 1250(s); NMR spectrum, 3.83 δ (OCH_3, singlet), 3.60 δ ($ArCH_2N$,

singlet), 2.57 δ (CH_2CH_3, quartet), 2.25 δ ($ArCH_3$, singlet), 1.04 δ (CH_2CH_3, triplet).

6-Chloro-1-[α-(diethylamino)-4-hydroxy-*m*-toluidino]-4-methylthioxanthen-9-one Hydrochloride (IXa).

6-Chloro-1-[[3-[(diethylamino)methyl]-*p*-anisidino]]-4-methylthioxanthen-9-one hydrochloride (VIIIa) (4.0 g., 0.008 mole) was refluxed with 200 ml. of 47% hydrobromic acid for 24 hours and the reaction mixture was processed according to the procedure for IXb. The base of product was obtained as bright yellow crystals from petroleum ether, m.p. 143-144°, yield, 2.7 g. (75%); infrared cm^{-1}, 2800(m), 1610(s), 1250(s); NMR spectrum, 3.73 δ ($ArCH_2N$, singlet), 2.63 δ (CH_2CH_3, quartet), 2.22 δ ($ArCH_3$, singlet), 1.11 δ (CH_2CH_3, triplet).

Anal. Calcd. for $C_{25}H_{25}ClN_2O_2S$: C, 66.28; H, 5.56; N, 6.19; Cl, 7.83. Found: C, 66.41; H, 5.51; N, 6.06; Cl, 7.84.

The pure base (3.0 g., 0.006 mole) was treated with hydrogen chloride according to the procedure for IXb to give 3.0 g. (93%) of the hydrochloride salt as red-brown crystals, m.p. 220-221°.

Acknowledgment.

The authors are indebted to Dr. Paul E. Thompson and co-workers for the antimalarial and antischistosomal testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and co-workers for determination of the spectral data.

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Received November 6, 1968 Ann Arbor, Michigan 48106