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Synthesis of Substituted Arylazothioxanthones as Potential Schistosomicidal Agents

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Abstract□A series of 1-chloro-4-methyl-6-arylazo-9H-thioxanthen-9-ones were synthesized and schistosomicidal activity evaluated. It was found that, 1-chloro-4-methyl-6-(2-hydroxy-1-naphthylazo)-9H-thioxanthen-9-one possessed a promising activity against *Schistosoma mansoni* in mice.

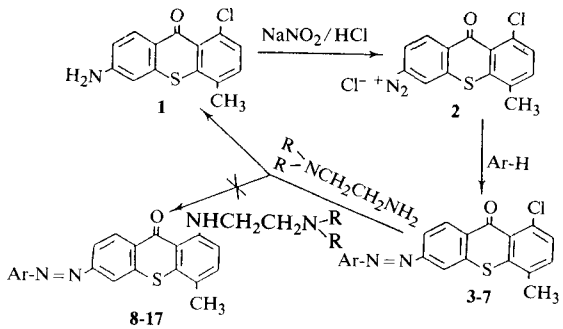
Keywords□Synthesis, Arylazothioxanthen-9-ones, Schistosomicidal activity.

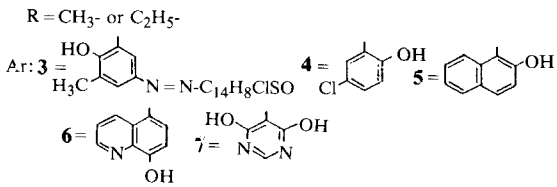
Thioxanthones were early used as potent schistosomicidal agents[1-3]. Promising schistosomicidal activity was also observed among a variety of naphthylazo compounds[4-6]. In continuation of our previous work[7], we wish to report the synthesis and characterization of certain thioxanthones carrying an arylazo moiety. The effect of the compound (**4**) following the intramuscular administration is also reported.

RESULTS AND DISCUSSION

Synthesis of the compounds

1-Chloro-4-methyl-6-amino-9H-thioxanthen-9-one (**1**), prepared by reduction of its nitro analogue[7], was diazotized with sodium nitrite in dilute hydrochloric acid solution to afford the diazonium salt (**2**), which was then coupled with o-cresol, p-chlorophenol, 2-naphthol, 8-hydroxyquinoline and barbituric acid to afford the corresponding diazo derivatives (**3-7**). The product obtained by the reaction of the diazonium salt (**2**) with o-cresol was bis derivative (**3**) rather than monodiazo derivative. Attempts to replace chlorine atom at position 1 with N,N-dimethyl or N,N-diethylethylenediamine failed to give the target compounds (**8-17**). Instead, an oxidation-reduction reaction took place resulting in the formation of the amino compound (**1**) as proved by acetylation and ^{1}H-NMR investigations. Precedently this type of reaction has been reported[8].





Schistosomicidal screening

The hepatic shift method[9] which measures the change in worm distribution within the hepatic portal system and the change in the stages of development of viable eggs (Oogram)[10], were adopted for measuring the schistosomicidal activity of the synthesized compounds against *Schistosoma mansoni* in mice. Groups of infected albino mice which consisted of 6-8 animals were injected with the compound in a dose of 50 & 100 mg/kg daily for 7 days. 5 Days after the final dose, animals were subjected to the examination of the worm distribution

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Table I. Recrystallization solvents, melting points, yield percentages and molecular formulae of compounds (3-7)

Comp. No.	Recryst. Solv.	mp °C	Yield %	Molecular Formulae
3	Chloroform	234	52	$C_{35}H_{22}Cl_2N_4O_3S_2$
4	Chloroform	265	40	$C_{20}H_{12}Cl_2N_2O_2S$
5	Ethanol-chloroform	291	65	$C_{24}H_{15}ClN_2O_2S$
6	Ethanol-chloroform	251	25	$C_{23}H_{14}ClN_3O_2S$
7	DMF	319	21	$C_{18}H_{11}ClN_4O_4S$

Table II. Effect of I.M. administration of Hycanthone & compound 4 daily for 7 days on the worm distribution within the hepatic portal system of *schistosoma mansoni* infected mice.

Organ	Control	% of Worms Hycanthone, mg/kg		Compound 4 mg/kg	
		50	100	50	100
Liver	5	100	0	75	75
Portal vein	30	0	0	25	20
Mesenteric vein	65	0	0	0	5

within the hepatic portal system[9] and the pattern of the stages of development of viable eggs[10]. Preliminary results showed that only compound (**4**) showed marked schistosomicidal activity. The effect of compound (**4**) on the worm distribution within the hepatic portal system is shown in Table II. From Table II, it can be seen that the distribution of worms in the hepatic portal system of the control animals follows the expected pattern, *i.e.* low percentage (5%) of the parasite present in the liver and high percentage (65%) remained in the mesentric vein and 30% in the portal vein. Hycanthone, a standard schistosomicidal drug, in a small dose (50 mg/kg) produced a complete hepatic shift of the worms to the liver (100%). At 100 mg/kg dose level, the drug presumbly killed all the worms since none was detected in the hepatic, portal or mesentric veins. Compound (**4**) produced a marked change in the worm distribution within the hepatic portal system, indicating its schistosomicidal activity.

The effect of compound (**4**) on the stages of development of viable eggs is shown in Table III. The control untreated animals showed a distribution of viable eggs in all stages of immature and

Table III. Effect of I.M. administration of Hycanthone & compound 4 daily for 7 days on the stages of development of viable eggs (Oogram) of *Schistosoma mansoni* infected mice.

Stages of embryogenesis	Control	% of Eggs Hycanthone, mg/kg		Compound 4, mg/kg	
		50	100	50	100
1	19.7	0	0	0	0.8
2	31.0	0	0	0	2.3
3	14.4	0	0	24.6	23.9
4	7.4	0	0	27.5	18.7
Mature	27.5	0	0	47.9	54.3

mature eggs. In case of hycanthone-treated mice, no viable eggs were found even in the mature stage at both dose levels. Also there were few dead eggs surrounded by inflammatory areas which may indicate the high efficacy of hycanthone in the doses given. Compound (**4**) in both dose levels decreased more the number of immature viable eggs in the stages 1 & 2 than that of the control group and increased the number of eggs in the mature stage.

EXPERIMENTAL

Instrumentation

Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H-NMR spectrum of compound (**3**) was recorded on a Varian EM 90 MHz spectrometer using TMS as an internal standard. Satisfactory elemental analysis of C, H and S was obtained for all compounds.

1-Chloro-4-methyl-6-arylazo-9H-thioxanthen-9-ones (3-7)

A cooled solution of sodium nitrite (0.7 g, 0.01 mole) in water (50 m*l*) was added to a cold solution of 1-chloro-4-methyl-6-amino-9H-thioxanthen-9-one (**1**) (2.7 g, 0.01 mole) in 10% hydrochloric acid solution (20 m*l*). After few minutes, the obtained diazonium salt solution (**2**), was added at 0 °C with stirring to a solution of the corresponding phenolic compound (0.01 mole) and sodium bicarbonate (1.9 g) in 50% aqueous-ethanol (200 m*l*). The reaction mixture was allowed to warm up to room temperature and left overnight. The precipitated solid was filtered, dried and crystallized. The ^{1}H-NMR spectrum of compound (**3**) in DMSO-d_6 displayed

signals at δ 2.3(s, 3H, CH_3), 2.5(s, 6H, CH_3) and 6.8-8.4(m, 12H, Ar-H). Recrystallization solvents, melting points, yield percentages and molecular formulae are listed in Table I.

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