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Synthesis of Certain Thiaxanthones as Potential Schistosomicidal Agents

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Abstract□Twenty nine substituted thiaxanthone derivatives were synthesized for schistosomicidal evaluation. The compounds, 1-morpholino-4-methyl-6-nitrothiaxanthone and 1-(2-diethyl-aminoethyl-amino)-4-methyl-6-nitrothiaxanthone dipicrate were found to possess promising schistosomicidal activity against *Schistosoma mansoni* in mice.

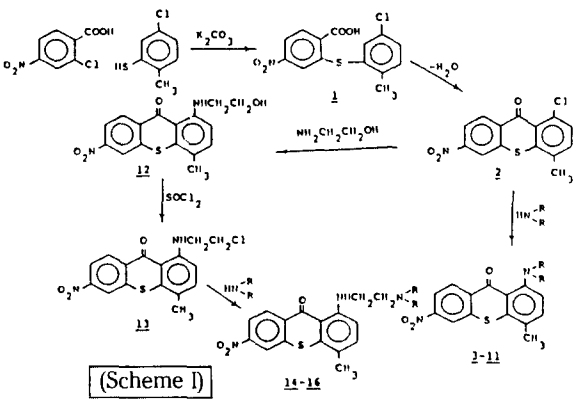
Keywords□Certain thiaxanthones—synthesized, schistocidal activity evaluated, 1-morpholino-4-methyl-6-nitrothiaxanthone and 1-(2-diethyl-aminoethyl-amino)-4-methyl-6-nitrothianthone dipicrate—synthesized, schistosomicidal activity against *Schistosoma mansoni* in mice evaluated.

The first major series of metal-free compounds with schistoso-micidal activity were the thiaxanthones. Lucanthone[1,2] and its metabolite hycanthone[3] were successfully used as schistosomicidal agents. Other thiaxanthone derivatives[4,5] were also reported to exhibit a promising schistosomicidal activity. In the last decade, several thiaxanthone derivatives were reported to possess a carcinostatic activity.[6,7] The present work describes the synthesis and characterization of some 1, 4, 6-trisubstituted thiaxanthones as oral schistoso-micidal agents.

RESULTS AND DISCUSSION

Synthesis of the Compounds

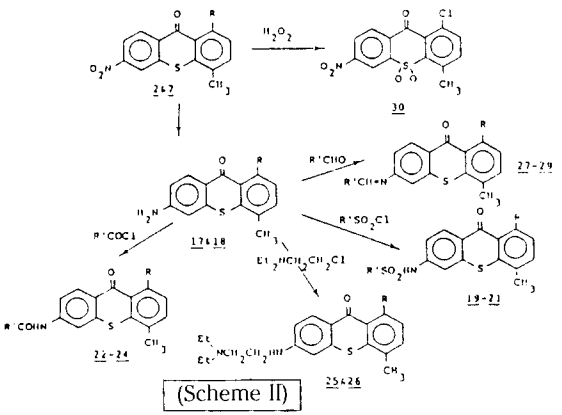
Condensation of 2-chloro-4-nitrobenzoic acid and 2-methyl-5-chlorothiophenol afforded 2-(2-methyl-5-chlorophenylmercapto)-4-nitrobenzoic acid **1.** The reaction was carried out by prolnged heation in dimethylformamide in presence of potassium carbonate, potassium iodide and copper as catalysts. Compound **1** was cyclized by heating in sulphuric acid to afford 1-chloro-4-methyl-6-nitrothia-xanthone **2**. Treatment of compound **2** with some secondary amines in dimethylformamide afforded the corresponding 1-substituted amino-4-methyl-6-nitrothiaxanthones **3-11** in poor yields. The free bases of compounds **8** & **10** were not isolated from the reaction mixture ascrystalline products, they were separated as their hydrochloride salts. Interaction of compound **2** with ethanolamine afforded compound **12** which was also separated as the hydrochloride salt. Treatment of compound **12** with thionyl chloride afforded compound **13,** which upon subsequent treatment with dimethylamine, diethylamine or dibenzylamine in dry benzene gave the corresponding 1-(2-dialkylamino-ethylamino)-4-methyl-6-nitrothiaxanthones **14-16.** Compound **15** was isolated in a crystalline form as the dipicrate salt (Scheme I).



(Scheme I)

The aminothiaxanthones **17** & **18** were prepared by reduction of their nitro analogues **2** & **7,** the reduction was carried out by the action of iron and hydrochloric acid in ethanol. Interaction of compounds **17** or **18** with benzene-or p-toluenesulphonyl chloride or some acid chlorides afforded the corresponding sulphonamides **19-21** or amides **22-24.** The reaction was carried out in pyridine at room temperature for 7 days. Fusion of com-

pound **17** or **18** with 2-diethylaminoethyl chloride afforded the corresponding 6-(2-diethylaminoethylamino) derivatives **25** & **26** in a poor yield. Fusion of compound **17** or **18** with m-nitrobenzaldehyde or 5-nitro-2-thenaldehyde afforded the corresponding Schiff's bases **27-29.** Treatment of compound **2** with hydrogen peroxide in acetic acid afforded compound **30** (Scheme II).



(Scheme II)

Schistocomicidal Screening

The hepatic shift method[8] which measures the change in worm distribution within the hepatic portal system and the change in the stages of development of viable eggs (Oogram)[9], were adopted for testing the schistosomicidal activity of the synthesized compounds against schistosoma mansoni infected mice. Groups of infected animals each of 6-8 animals were given separately the compounds in an oral dose of 50& 100 mg/kg twice daily for 5 days, 5 days after the last administration, the animals were subjected to procedures of examination of the worm distribution within the hepatic portal system[8] and the pattern of stages of development of viable eggs[9].

The preliminary results of schistosomicidal activity revealed that compounds **7** and **15** displays promising dose dependent activity against *Schistosoma mansoni* in mice as shown in tables I & II.

Table I. Effect of oral administration of compounds 7 & 15 twice daily for 5 days in a dose of 50 & 100 mg/kg on the distribution of worms within the hepatic portal system (Hepatic Shift) on *Schistosoma mansoni* infected mice

Mean % of worms in	Control* (6)	Compound 7 mg/kg		Compound 15 mg/kg	
		50 (6)	100 (6)	50 (7)	100 (8)
Liver	5.0	47.7	81.2	75.0	75.0
Portal Vein	30.0	46.6	18.8	20.0	25.0
Mesentric Vein	65.0	5.6	0	5.0	0

Table II. Effect of oral administration of compounds 7 & 15 twice daily for 5 days in a dose of 50 & 100 mg/kg on the stages of development of viable eggs (Oogram) on *Schistosoma mansoni* infected mice

Average % of egg number of of total	Control* (6)	Compound 7 mg/kg		Compound 15 mg/kg	
		50 (6)	100 (6)	50 (7)	100 (8)
First Stage	19.7	3.6	0	0.7	0
Second Stage	14.7	6.7	0	1.5	0
Third Stage	31.3	32.7	9.8	4.1	3.0
Fourth Stage	8.3	11.7	11.9	5.0	92.5
Mature Stage	26.0	44.4	78.3	88.7	92.5

*Untreated group of animals
The number of animals examined in each group is shown in parenthesis.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 1000 spectrometer in potassium bromide. The PMR spectra were recorded on a Varian EM-90 MHz instrument using TMS as the internal reference. The MS spectra were recoded on a Perkin-Elmer instrument operated at 70 eV. Satisfactory elemental analysis for C, H and S or N was obtained for all compounds.

2-(2-Methyl-5-chlorophenylmercapto)-4-nitrobenzoic acid 1

A mixture of 2-chloro-4-nitrobenzoic acid (10 g), 2-methyl-5-cholorothiophenol (7.9 g), anhydrous potassium carbonate (6.9 g), potassium iodide (1.5 g) and copper powder (1.5 g), in dimethylformamide (100 ml) was refluxed with stirring for 18 h. On cooling, the mixture was filtered, diluted with 1% sodium hydroxide soultion (500 ml), filtered and acidified with hydrochloric acid. The separated solid was then filtered and crystallized from aqueous-ethanol. mp 192°C, yield 30%. IR(cm^{-1}): 1700 (CO) and 1540 & 1350 (NO_2).

1-Chloro-4-methyl-6-nitrothiaxanthone 2

A mixture of compound **1** (50 g) and sulphuric and (60 ml) was heated on a steam bath for 2 h. On cooling, the reddish-brown solution was poured onto crushed ice (250 g) with stirring. The precipitated solid was filtered. washed with water, dried and crystallized from dimethyl-formamide. mp 238°C, yield 91%. IR(cm^{-1}): 1670 (CO) and 1530 & 1350 (NO_2). MS m/z (Rel. Int.): 305 M^+ (24.4), 277 (44), 259 (30.6), 231 (100), 216 (53.0), 151 (61.2), 111 (40.8).

1-Substituted amino-4-methyl-6-nitrothiaxanthones 3-12

A mixture of compound **2** (0.005 mole) and the ap-

propriate amine (0.01 mole; 0.005 mole in case of piperazine) in dimethylformamide (25 ml) was refluxed for 15 h. The reaction mixture was then poured onto crushed ice (100 g) with stirring. The separated solid was filtered, washed with ammoniated water, dried and either crystiallized from the proper to afford the compounds **3, 4, 5, 6, 7, 8, 9,** & **11** or dissolved in ether (20 ml) and mixed with ethanol previously saturated with hydrogen chloride gas to precipitate compounds **8, 10, 12** as their hydrochloride salts (Table III). IR of compound **12**: 1610 (CO), 1450 & 1340 (NO_2), 1430 (NH) and 3500 (OH). PMR (δ ppm) for compound **7** in $CDCl_3$: 7.4-8.6 (m, 5H, Ar-H), 4.1 (m, 4H, C_3, CH_5 of morpholine), 3.2 (m, 4H C_2 & C_6 of morpholine), 2.5 (s, 3H CH_3). MS for compound **7** m/z (Rel. Int.): $365M^+$ (55.4), 259 (82.1), 271 (100), 195 (25.8)

1-(2-Chloroethylamino)-4-methyl-6-nitrothiaxanthone 13:

A mixture of compound **12** (1 g) and thionly chloride (10 ml) was heated under refulx on a steam bath for 3 h. The excess thionyl chloride was removed by distillation under reduced pressure. The residue left was dissolved in chloroform and extracted with cold dilute ammonia solution, dried over anhydrous sodium sulphate and the solvent was then evaporated on a waster bath. The remaining crude product was then crystallized from pet. ether-benzene. mp 168°C, yield 65%.

1-(2-Dialkylaminoethylamino)-4-methyl-6-nitrothiaxanthones 14-16:

A mixture of compound **13** (0.005 mole) and the appropriate secondary amine (0.01 mole) in dry benzene (25 ml) was refluxed for 4 h. The selvent and the excess amine were then removed by distillation under reduced pressure. The residue left was either crystallized from the proper solvent to afford the free bases **14** & **16** or dissolved in hot ethanol and mixed with slight excess of picric acid solution in ethanol and the precipitated dipicrate salt **15** was filtered and crystallized (Table III).

1-Chloro or Morpholino-4-methyl-6-aminothiaxanthones 17 & 18:

To a suspension of compound **2** or **7** (0.01 mole) and iron powder (3 g) in ethanol (25 ml), hydrochloric acid (3 ml) was added with stirring. The mixture was heated under reflux for 6 h. On cooling, the reaction mixture was neutralized with 10% sodium hydroxide solution where the amino derivatives **17** & **18** were precipited filtered and crystallized from aqueous-ethanol. Compound 17: mp 187°C, yield 40%, compound **18**: 1110 (ethereal) oxygen of morpholine). PMR for compound 17 in DMSO-d6: 6.7-7.4 (m, 5H, Ar-H), 3.2 (s, 2H NH_2), 2.3 (s, 3H CH_3).

1-Chloro or morpholino-4-methyl-6-arylsulphonmido, acylamino or aroylaminothiaxanthoes 19-21 & 22-24:

The arylsulphonyl chloride or the acid chloride (0.01 mole) was added to a solution of compound **17** or **18** (0.01 mole) in pyridine (40 ml). The mixture was left at room temperature for 7 days. The mixture was then poured onto crushed ice (50 g), the precipitated solid

Table Ⅲ. 1-Substituted Amino or 1-(2-Dialkylaminoethylamino)-4-methyl-6-nitrothiaxanthones 3-12 & 14-16.

Comp. No.	$-N\begin{matrix}R\\R\end{matrix}$	Cryst.* Solv.	mp ℃	Yield %	Molecular Formula
3	$-N(CH_3)_2$	AM	142	25	$C_{16}H_{14}N_2O_3S$
4	$-N(C_2H_5)_2$	AM	146	20	$C_{18}H_{18}N_2O_3S$
5	$-N(CH_2C_6H_5)_2$	AM	124	36	$C_{28}H_{22}N_2O_3S$
6	$-N(CH_2CH_2OH)_2$	AM	140	33	$C_{18}H_{18}N_2O_5S$
7	Morpholino	DMF	220	47	$C_{18}H_{16}N_2O_4S$
8	Piperidino	AE	176 (d)	40	$C_{19}H_{18}N_2O_3S.HCl$
9	4-Methylpiperazino	Methanol	165	38	$C_{19}H_{19}N_3O_3S$
10	Pyrrolidino	EE	173 (d)	38	$C_{18}H_{16}N_2O_3S.HCl$
11	$4-C_{14}H_8NO_3S$-piperazino	Methanol	137 (d)	20	$C_{32}H_{24}N_4O_6S_2$
12	$-NHCH_2CH_2OH$	Ethanol	130 (d)	35	$C_{16}H_{14}N_2O_4S.HCl$
14	$-N(CH_3)_2$	Ethanol	137	50	$C_{18}H_{19}N_3O_3S$
15	$-N(C_2H_5)_2$	AE	198	35	$C_{20}H_{23}N_3O_3S.2C_6H_3N_3O_7$
16	$-N(CH_2C_6H_5)_2$	EE	72	40	$C_{30}H_{27}N_3O_3S$

*AM = Aqueous-methanol, AE = Aqueous-ethanol and EE = Ethanol-ether.

Table Ⅳ. 1-Chloro or Morpholino-4-methyl-6-substituted Thiaxanthones 19-29

Comp. No.	R	R′	Cryst.* Solv.	mp ℃	Yield %	Molecular Formula
19	Cl	C_6H_5-	DMF	260	78	$C_{20}H_{14}ClNO_3S_2$
20	Cl	$p-CH_3C_6H_4-$	Methanol	205	82	$C_{21}H_{16}ClNO_3S_2$
21	Morpholino	$p-CH_3C_6H_4-$	Methanol	220	72	$C_{25}H_{24}N_2O_4S_2$
22	Cl	C_6H_5-	Acetone	225	80	$C_{21}H_{14}ClNO_2S$
23	Cl	Et_2NCH_2-	AM	177	40	$C_{20}H_{21}ClN_2O_2S$
24	Morpholino	Et_2NCH_2-	AM	190	35	$C_{24}H_{29}N_3O_3S$
25	Cl		AM	160	18	$C_{20}H_{23}ClN_2OS.2C_6H_3N_3O_7$
26	Morpholino		AM	134	10	$C_{24}H_{31}N_3O_2S.2C_6H_3N_3O_7$
27	Cl	$m-NO_2C_6H_4-$	A	210	55	$C_{21}H_{13}ClN_2O_3S$
28	Morpholino	$m-NO_2C_6H_4-$	DMF	275	40	$C_{25}H_{21}N_3O_4S$
29	Morpholino	$2-C_4H_2NO_2S-$	A	180	55	$C_{23}H_{19}N_3O_4S_2$

*AM = Aqueous-methanol and A = Acetic acid.

was filtered, dried and crystallized from the proper solvent (Table IV).

1-Chloro or morpholino-4-methyl-6-(2-diethylaminoethylamino) thiaxanthones 25 & 26:

A mixture of compound **17** or **18** (0.01 mole) and 2-diethylaminoethyl chloride hydrochloride (0.02 mole) was heated under reflux on an oil bath at 150°C for 2 h. On cooling, the residue left was extracted with hot dilute acetic acid (50 ml), filtered, alkalinized with 2N sodium hydroxide solution and steam distilled. The residue left after steam distillation was extracted with ether, dried over anhydous sodium sulphate, evaporated to dryness, dissolved in hot ethanol and mixed with ethanolic picric acid solution. The precipitated dipicrate salt was filtered and crystallized (Table IV).

1-Chloro or morpholino-4-methyl-6-arylidene-aminothiaxanthones 27-29:

A mixture of compound **17** or **18** (0.01 mole) and p-nitrobenzaldehyde or 5-nitro-2-thenaldehyde (0.01 mole) was heated under reflux on an oil bath at 180°C for 2 h. On cooling, the residue left was washed with ethanol and crystllized from the proper solvent (Table IV).

1-Chloro-4-methyl-6-nitrothiaxanthone 10, 10-dioxide 30:

To a stirred mixture of compound **2** (1.5 g) in acetic acid (20 ml), 30° hydrogen peroxide solution (5 ml) was added. Stirring was continued for 4 h at room temperature and left overnight. The mixture was then heated on a water bath at 50°C for 6 h. On cooling, the separated product was filtered, dried and crystallized from dimethylformamide. mp 250°C, yield 35%.

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LITERATURE CITED

1. Kikuth, W. and Gönnert, R.: *Ann. Trop. Med. Parasitol.* **42,** 256 (1948).
2. Mauss, H.: *Chem. Ber.:* **81,** 19 (1948).
3. Rosi, D., Peruzzoti, G., Dennis, E.W., Berberian, D.A., Freele, H. and Archer, S.: *Nature (London)* **208,** 1008 (1965).
4. Archer, S., Rochester, L.B. and Jackman, M.: *J. Am. Chem. Soc.* **76,** 588(1954).
5. Kushner, S.: *U.S. Pat.* **2,** 656 (1953).
6. Nasr, Zayed, A. and Nabih, I.: *Die Pharmazie* **33,** 7 (1978).
7. Archer, S., Zayed, A., Rej, R. and Rugino, T.A.: *J. Med. Chem.* **26,** 1240 (1983).
8. Standen, O.D.: *Ann. Trop. Med. Parasitol.* **47,** 62 (1953).
9. Pelligrano, J., Olivira, C.A., Faria, J. and Cuhna, A.S.: *Am. J. Trop. Med. Hyg.* **11,** 2961 (1952).