1,019,783

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Xanthenes and Thioxanthenes

We, STERLING DRUG INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

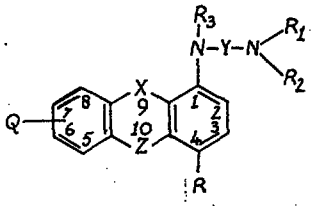
This invention relates to substituted thioxanthenes and xanthenes, and to their preparation.

This invention resides in the concept of a composition having a molecular configuration in which hydroxymethyl or formyl is attached to the 4-carbon atom of a thioxanthene, a thioxanthene-S-oxide or -dioxide, a xanthene, and 9-one or 9-ol derivatives thereof having attached to the 1-carbon atom thereof a (lower-secondary- or -tertiary-amino) - (polycarbon - lower - alkyl)amino substituent, and to an enzymatic oxidative process using the corresponding 4-methyl compounds as intermediates.

The corresponding 4-methyl compounds such as described and claimed in our Specification 704,416 are well known as schistosomicidal agents. Illustrative of these compounds are 1 - (2 - diethylaminoethylamino) - 4 - methylthioxanthen - 9 - one ("Miracil D") [Registered Trade Mark] and 1 - (2 - diethylaminoethylamino) - 4 - methylxanthen - 9 - one ("Miracil A") [Registered Trade Mark]. It has been found that the schistosomicidal activity of these illustrative compounds is retained and sometimes improved by varying the basic side chain substituent at the 1-position, by adding other ring substituents, by replacing the 9-one or 9-keto group (>C=O) by 9-ol (>CHOH) or by methylene ($>CH_2$), or by converting the 10-S of the thioxanthene to its oxide or dioxide derivative. On the other hand, all attempts to replace the 4-methyl group by other substituents have resulted in a complete loss of schistosomicidal effect.

We have now found that compounds of this type where 4-methyl is replaced by 4-hydroxymethyl or 4-formyl are highly active schistosomicidal agents, the 4-hydroxymethyl compounds being more active and less toxic than their 4-methyl precursors and the 4-formyl compounds having activity comparable to that of the precursors.

Embodiments of our invention are represented by the formula I



...I

where X is carbonyl (>C=O), hydroxymethylene (>CHOH) or methylene ($>CH_2$), Z is —O—, —S—, >SO or $>SO_2$, Q is hydrogen or from one to three substituents at positions 5, 6, 7 and 8 of the tricyclic ring selected from halo, lower-alkyl or lower-alkoxy, R is hydroxymethyl ($—CH_2OH$) or formyl (—CHO), Y is lower-alkylene having from two to four carbon atoms and having its two connecting linkages on different carbon atoms, R_3 is hydrogen or lower-alkyl, R_1 is hydrogen, lower-alkyl or lower-2-hydroxyalkyl and R_2 is lower-alkyl or lower-2-hydroxyalkyl, and where R_1 and R_2 taken with N, i.e., NR_1R_2, comprehends saturated N-heteromonocyclic radicals having five to six ring atoms, illustrated by piperidino, hexamethyleneimino, pyrrolidino, morpholino, piperazino and lower-alkylated derivatives thereof.

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Also comprehended by our invention are the 5,6,7,8-tetrahydro derivatives of Formula I.

The terms "lower-alkyl" and "lower-alkoxy", as used herein, e.g., as meanings for Q in formula I or for R_1, R_2 or R_3 (when lower-alkyl), mean alkyl and alkoxy radicals having from one to six carbon atoms, illustrated by methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, isobutyl, n-amyl, and n-hexyl, for lower-alkyl, and by methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy and n-hexoxy, for lower-alkoxy.

The term "halo", as used herein, e.g., as one of the meanings for Q in formula I, means chloro, bromo, iodo or fluoro, with chloro being preferred because of the ready availability and cost advantages of chloro intermediates.

The term "lower-2-hydroxyalkyl", as used herein, e.g., as meanings for R_1 and R_2 in formula I, are hydroxyalkyl radicals having from two to six carbon atoms and having the hydroxy group attached to the carbon atom that is one carbon atom removed from the side chain nitrogen atom, illustrated by 2 - hydroxyethyl, 2 - hydroxypropyl, 2- hydroxy - 2 - methylpropyl, 2 - hydroxybutyl, 2-hydroxy - 2,2 - dimethylpropyl, 2 - hydroxy-2 - ethylpropyl and 2 - hydroxyhexyl.

The term "lower-alkylene", as used herein, e.g., as represented by Y in formula I, are alkylene radicals having from two to four carbon atoms and having its connecting linkages on different carbon atoms, illustrated by

$$-CH_2CH_2-,$$

$$-CH(CH_3)CH_2-,$$

$$-CH_2\underset{|}{C}H(CH_3),$$

$$-CH(CH_3)\underset{|}{C}H(CH_3),$$

$$-CH(C_2H_5)CH_2-,$$

$$-CH_2CH_2CH_2-,$$

$$-CH_2CH_2\underset{|}{C}HCH_3$$

and

$$-CH_2CH_2CH_2CH_2-.$$

When NR_1R_2 of formula I comprehends (lower - alkylated) - N - heteromonocyclic radicals, lower-alkyl radicals can be attached to any available ring-atom and can vary preferably from one to three in number, e.g., 2 - methylpiperidino, 3 - ethylpiperidino, 4-methylpiperidino, 2,6-dimethylpiperidino, 2,4-dimethylpiperidino, 2,4,6-trimethylpiperidino, 3 - n - propylpiperidino, 2,2 - dimethylpiperidino, 2 - methylpyrrolidino, 2,5 - dimethylpyrrolidino, 2,3-dimethylmorpholino, 2-ethylmorpholino, 2-methylhexamethyleneimino, 2,7-dimethylhexamethyleneimino, 4 - methylpiperazino, 3-ethylpiperazino, and 2,4,6-trimethylpiperazino.

Our invention in its process aspect comprises subjecting a compound of formula I where Q, X, Z, Y, R_3 and NR_1R_2 have the meanings given for formula I but where R is methyl, to the fermentative enzymatic action of a microorganism capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl and/or 4-formyl, said microorganism being of an order selected from the group consisting of *Moniliales*, *Mucorales* and *Sphaeriales*. Not all species and genera of organisms within these orders are effective in the process, but whether a given specific organism is effective can readily be determined by following the general screening procedure described in the following paragraph.

A particularly preferred microorganism is *Aspergillus sclerotiorum*.

General Screening Procedure

An illustrative general screening procedure used to evaluate the ability of microorganisms to transform 1 - (R_1R_2N - Y - NR_3) - 4 - methylthioxanthenes, -4-methylxanthenes and the above-noted derivatives is described as follows: Microorganisms to be screened are inoculated onto Sabouraud's agar slants or other agar base media suitable for growth. The inoculated slants are then placed in a 25°C. incubator and allowed to grow for one week. After one week's growth, the slant is removed and 15 ml. of sterile distilled water is added to it, and the spores and vegetative growth are loosened from the agar with a sterile needle. This suspension is then transferred to a flask containing 100 ml. of soy-dextrose medium of the composition:

Soybean meal	5 g.
Dextrose	20 g.
NaCl	5 g.
K_2HPO_4	5 g.
Yeast	5 g.
Tap water	1 l.
pH to	6.4

autoclave at 15 lbs. per sq. in. for 15 min.

and the flask is placed on a rotary shaker located in a 25°C. incubator and agitated at about 260 rpm for twenty-four hours. After this initial time period (first stage seed), 5 ml. of the submerged growth is added to duplicate flasks (250 ml.) containing the above-noted soy-dextrose medium. These flasks are placed in the shaker and allowed to grow from forty-eight to seventy-two hours at 25°C. after which 5 mg. of substrate (a 4-methylthioxanthene or 4-methylxanthene) dissolved in minimum amount of water, water-

ethanol, dimethylformamide, acetone or CH_3OH is added to one of the pair of flasks. The other flask receives only the solvent and serves as the control. These flaks are then agitated under the same conditions for an additional twenty-four hours before they are removed from the shaker. Growth characteristics and pH are noted, and to the whole beer of each flask is added two volumes of methylene dichloride. The flasks are then agitated at 200 rpm for two one minute intervals. The heavier methylene dichloride extract is then siphoned off and the solvent removed by warming in a water bath at about 60°C. Then each residue is dissolved in 1 ml. of methylene dichloride for application to thin-layer plate for chromatographic analysis (described below).

The nature of the material produced can be detected by thin-layer chromatography, and the 4-formyl- or 4-hydroxymethylthioxanthene or -xanthene and the corresponding intermediate 4-methylthioxanthene or -xanthene (if not completely converted) isolated by column chromatography on conventional adsorbants such as silica gel or alumina.

The screening samples were all chromatographed on silica gel thin-layer plates (~~T.C.L.~~) using a suitable system, a preferred one consisting of nine volumes of ethyl acetate and one volume of triethylamine. The 4-hydroxymethyl compound appears as a less mobile (more polar) spot than the intermediate 4-methyl compound in said preferred chromatographic system. The 4-formyl compound appears as a spot between the 4-methyl and 4-hydroxymethyl compounds. The silica gel containing the more polar spots is removed and each spot is eluted with absolute methanol and the eluates subjected to ultra-violet (UV) spectral analysis.

Large batch fermentations and procedures for isolating sufficient quantities of crystalline 4-hydroxymethyl and 4-formyl compounds for elementary analyses and schistosomicidal studies in specific examples hereinbelow will further illustrate aspects of our invention without, however, limiting it thereto.

The above-described general screening procedure and the batch fermentations given below in the specific examples are illustrative and can be varied in different ways: by using other microorganisms whose fermentative enzymatic action is capable of effecting the oxidation of said 4-methylthioxanthenes or 4-methylxanthenes to the corresponding 4-hydroxymethyl and/or 4-formyl compounds; by using other nitrogen sources in place of soy-bean meal, e.g., corn meal, oat meal, milk protein hydrolysates, other protein hydrolysates, corn steep liquor, and meat extract, by using other carbon sources in place of dextrose, e.g., sucrose, glucose, maltose, starch, and molasses, by varying the time of addition of the substrate after addition of the medium from 0 to 72 hours; by varying the initial pH from about 5.0 to about 7.5, preferably between 5.5 and 6.5; by varying the quantity of substrate; by varying the rate of stirring; and, by utilizing other modifications known in the fermentative art.

Our compounds of formula I are useful in the free base form or in the form of their acid-addition salts, and both forms are within the purview of the invention, and, in fact, are considered to be one and the same invention. The acid-addition salts are simply a more convenient form for use; and, in practice, use of the salt form inherently amounts to use of the base form. The acids which can be used to prepare the acid-addition salts are preferably those which produce, when combined with the free base, chemotherapeutically acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in chemotherapeutic doses of the salts, so that the beneficial properties inherent in the free base are not vitiated by side effects ascribable to the anions; in other words, the latter do not substantially affect the chemotherapeutic properties inherent in the cations. In practicing our invention, we found it convenient to employ the ~~hydrochloric~~ salt. However, other appropriate chemotherapeutically acceptable salts within the scope of the invention are those derived from mineral acids such as hydrobromic acid, hydriodic acid, nitric acid, phosphoric acid, sulfamic acid, and sulfuric acid; and organic acids such as acetic acid, citric acid, tartaric acid, lactic acid, methanesulfonic acid, ethanesulfonic acid, quinic acid, 3-hydroxy-2-naphthoic acid, pamoic acid (2,2^1-dihydroxy-1,1^1-dinaphthylmethane-3,3^1-dicarboxylic acid), naponic acid (1,5-naphthalenedisulfonic acid), giving the hydrobromide, hydriodide, nitrate, phosphate, sulfamate, sulfate, acetate, citrate, tartrate, lactate, methanesulfonate, ethanesulfonate and, quinate, 3-hydroxy-2-naphthoate, pamoate and naponate, respectively.

The acid-addition salts are prepared preferably by reacting the free base and acid in an organic solvent, e.g., ethanol, in which case the salt separates directly or can be obtained by concentration of the solution.

Although chemotherapeutically acceptable salts are preferred, all acid-addition salts are within the scope of our invention. All acid-addition salts are useful as sources of the free base form even if the particular salt per se is not desired as the final product, as for example when the salt is formed for purposes of purification or identification, or when it is used as an intermediate in preparing a chemotherapeutically acceptable salt by ion exchange procedures.

Also encompassed by our invention are simple esters of our 4-hydroxymethyl compounds, for example, lower-alkanoates (e.g., acetate, propionate, and butyrate), benzoates

(e.g., benzoate, and 3,5-dinitrobenzoate), carbanilate, as well as conventional aldehyde characterizing derivatives of our 4-formyl compounds, for example, semicarbazone, and thiosemicarbazone, said esters and aldehyde derivatives being useful to further characterize and identify our 4-hydroxymethyl and 4-formyl compounds.

The molecular structures of the compounds of our invention are established by their nuclear magnetic resonance, infrared and ultraviolet spectra, and corroborated by the correspondence of calculated and found values for the elementary analyses.

The following examples will further illustrate the invention without, however, limiting it thereto.

EXAMPLE 1

Conversion of 1 - (2 - diethylaminoethylamino)-4-methylthioxanthen-9-one into the corresponding 4-hydroxymethyl and 4-formyl compounds was carried out as follows: 1-(2-diethylaminoethylamino) - 4 - methylthioxanthen-9-one as its hydrochloride was first subjected to the fermentative action of *Aspergillus sclerotiorum* (SWRI A_{24}, available at Sterling-Winthrop Research Institute, Rensselear, New York) using the above described general screening procedure. There were thus produced two or more polar products with concomitant loss of starting material as evidenced by thin layer chromatography. After preliminary studies in flasks which indicated that fermentations at substrate levels of 0.2 to 0.4 g/l were feasible, 10 liter fermentations were carried out in 14 liter stirred fermentation vessels containing 10 liters of sterile soy-dextrose medium composed of the following ingredients (weight per volume):

Soybean meal	2.0%
Dextrose	2.0%
Brewers yeast	0.5%
NaCl	0.5%
K_2HPO_4	0.5%
Tap water (pH adjusted to 6.4 with 10N HCl prior to autoclaving)	

Four fermentors were inoculated with a 10%, seventy-two hour old culture of *Aspergillus sclerotiorum* (SWRI A_{24}) incubated at 26°C. in 100 ml. of said sterile soy-dextrose medium contained in 500 ml. flasks. These flasks were aerated on a shaker rotating at 260 rpm. The inoculated fermentors were agitated at 450 rpm and aerated at a level of 4 liters of air per minute and at a temperature of 31°C. for forty-eight hours. At the end of this time, 3 g. of 1-(2-diethylaminoethylamino)-4-methylthioxanthen-9-one hydrochloride dissolved in 200 ml. of warm sterile water was added to each fermentor. An antifoam agent, e.g., UCON-LB 625 [Registered Trade Mark] (Union Carbide Chemicals), was added automatically as required. Aliquots from the tanks were taken and assayed periodically by transferring a portion of the dried extract to a thin layer silica gel plate using ethyl acetate with 1% ammonium hydroxide as developing solvent; 10% triethylamine was used in place of the ammonium hydroxide in other runs. When chromatography revealed that all or most of the starting material had disappeared, the fermentations were terminated. The total fermentation beer was acidified with hydrochloric acid and extracted twice with 20 liter portions of dichloromethane. Concentration of the extracts under reduced pressure and subsequent chromatography on a silica gel column (4 x 28 cm.) using increasing amounts of ethyl acetate in n-hexane followed by increasing amounts of methanol in ethyl acetate afforded, as orange-yellow microcrystals, 0.8 g. of 1-(2-diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one hydrochloride, m.p. 173.0—176.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{20}H_{24}N_2O_2S.HCl$: C, 61.13; H, 6.41; N, 7.13. Found: C, 60.97; H, 6.43; N, 7.16.

The nuclear magnetic resonance (NMR) spectrum of the above 4-hydroxymethyl product (in free base form) showed it to be lacking the methyl signal ($\delta^{CDCL_3}_{ppm} = 2.75$, with external reference of tetramethylsilane as $\delta^{CDL_3}_{ppm} = 0$) present in the 4-methyl precursor (in free base form) while a new signal ($\delta^{CDCL_3}_{ppm} = 5.10$) signified the presence of the two methylene protons of the 4-hydroxymethyl group. Its infrared (IR) spectrum (KBr) when compared with that of the 4-methyl intermediate showed an enhancement of intensity of the band in the OH/NH region near 3μ, confirming the introduction of an OH group. Its ultraviolet (UV) spectrum (in 95% ethanol) showed absorption bands like those of the corresponding 4-methyl compound, showing the presence of the same aromatic nucleus in the two compounds.

In another run following the above procedure both the 4-formyl and 4-hydroxymethyl compounds were isolated. As above, four 10 liter tanks were used. Five g. of 1-(2-diethylaminoethylamino) - 4 - methylthioxanthen-9-one hydrochloride was added to each tank and twenty-four hours later, the fermentation liquors of the tanks were combined and extracted with two 80 liter portions of methylene dichloride, but omitting the acidification of the total fermentation beer. The combined extracts were concentrated under reduced pressure; 500 ml. of methanol was added and the mixture filtered; and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was mixed with 125 g. of silica gel and air-

dried. About 300 ml. of n-hexane was thoroughly mixed with this material, the n-hexane removed by decantation and the material air-dried. The material was placed on an 1100 g. silica gel column (7 x 38 cm.) and developed with an eluant consisting of 40% ethyl acetate, 57.5% n-hexane and 2.5% triethylamine; 500 ml. fractions were collected. Fractions 11—23 contained some starting 4-methyl compound and the 4-formyl compound (indicated by ~~T.C.L.~~ T.L.C.), and were combined for purification on another column of 300 g. of silica gel (3.5 x 44 cm.). This column was developed with an eluant of 60% ethyl acetate, 37.5% n-hexane and 2.5% triethylamine, 500 ml. fractions being collected. Fractions 3—7, which contained the 4-formyl compound, were combined and taken to dryness, and the remaining solid was recrystallized from n-hexane-ethyl acetate to yield 1.18 g. of 1-(2-diethylaminoethylamino)thioxanthen-9-one-4-carboxaldehyde, m.p. 119.4—120.6°C. (corr.).

Anal. Calcd. for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05.

Found: C, 67.46; H, 6.40; N, ~~7.47~~ 7.74; S, 8.62.

The nuclear magnetic resonance (NMR) spectrum of the above 4-formyl product showed it to be lacking the methyl signal ($\delta \overset{CDCl_3}{ppm} = 2.75$, with external reference of tetramethylsilane as $\delta \overset{CDCl_3}{ppm} = 0$) present in the 4-methyl precursor while a new signal ($\delta \overset{CDCl_3}{ppm} = 11.1$) signified the presence of the proton attached to the 4-carbonyl group. Its infrared (IR)) spectrum (KBr) when compared with that of the 4-methyl intermediate showed a new band near 6μ which is characteristic of the C = O frequency.

Fractions 36—79 of the original column were combined and placed on a 1000 g. silica gel column (7 x 36 cm.) for chromatographic purification. The eluant used consisted of 40% ethyl acetate, 57.5% n-hexane and 2.5% triethylamine; one liter fractions were collected. After a T.L.C. on each fraction had been obtained, fractions 5—21 were combined and evaporated to near dryness. n-Hexane was added and the solid was collected to yield 6.97 g. of 1-(2-diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one, m.p. 92.2—95.4°C. (corr.).

Anal. Calcd, for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86; S, 8.99.

Found: C, 67.20; H, 6.49; N, 7.98; S, 8.49.

In the following Table A are listed other organisms which, when screened by the above-described fermentative screening procedure, have been found to effect the oxidation of 1 - (2 - diethylaminoethylamino) - 4 - methylthioxanthen-9-one to produce the corresponding 4-hydroxymethyl and 4-formyl compounds.

TABLE A

Order:	*Moniliales*		
	Aspergillus flavipes	ATCC	11013
	Aspergillus niger	„	11394
	Aspergillus sclerotiorum	CMI	56673
Order:	*Mucorales*		
	Mucor griseo-cyanus	ATCC	1207A
	Mucor parasiticus	„	6476
	Syncephalis nodosa	„	7943
	Thamnidium elegans	„	8997
Order:	*Sphaeriales*		
	Chaetomium globosum	SWRI	Ch_4
	Chaetomium nigricolor	ATCC	11211
	Didymella lycopersici	„	11847

ATCC = American Type Culture Collection number

CMI = Commonwealth Mycological Institute number

SWRI = Sterling-Winthrop Research Institute number

EXAMPLE 2

Following the procedure described in Example 1 with the modifications noted below, 4 - methyl - 1 - [2 - (2 - methylpiperidino) - ethylamino]thioxanthen - 9 - one (18 g. as its hydrochloride) was converted into its corresponding 4-hydroxymethyl and 4-formyl compounds. In order to obtain a sufficient amount of the 4-hydroxymethyl compound for biological evaluation, three 10 liter fermentations were carried out at substrate levels of 0.6 g./liter. A total of 3 g. of the 4-hydroxymethyl compound obtained from the concentrated extracts was chromatogrammed on a silica gel column (4.5 x 48 cm.) using 70% ethyl acetate, 29.5% hexane and 0.5% ammonium hydroxide as eluant, 400 ml. fractions being collected. Fractions 36—50 were combined and taken to dryness. The resulting solid was washed in distilled water and extracted with methylene dichloride; and the extract was filtered and evaporated to dryness, yielding 0.63 g. of 4 - hydroxymethyl - 1 - [2 - (2 - methylpiperidino) - ethylamino]thioxanthen - 9 - one, m.p. 121.8—125.0°C. (corr.).

Anal. Calcd, for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.33.

Found: C, 69.25; H, 6.92; N, 7.21.

As in Example 1, the structure of this compound was confirmed by its NMR, IR and UV spectral analyses, its NMR signal of $\delta^{CDCl_3}_{ppm} = 5.18$ signifying the presence of the two methylene protons of the 4-hydroxymethyl group. It also lacked the methyl signal ($\delta^{CDCl_3}_{ppm} = 2.67$) of the 4-methyl intermediate.

Fractions 10—28 of the above fermentative oxidation were combined and taken to dryness; the solid was washed with distilled water and extracted with methylene dichloride; and the extract was filtered and evaporated to dryness, yielding about 0.16 g. 1 - [2 - (2 - methylpiperidino) - ethylamino]-thioxanthen - 9 - one - 4 - carboxaldehyde, m.p. 131—134°C. As in Example 1, its NMR and IR spectra confirmed the assigned structure, its NMR signal of $\delta^{CDCl_3}_{ppm} = 10.25$

signifying the presence of the single proton of the 4-CHO substituent.

EXAMPLE 3

Following the procedure described in Example 2, 4-methyl-1-(2-piperidinoethylamino)thioxanthen-9-one (as its hydrochloride, 6.0 g.) was converted into 4-hydroxymethyl-1-(2-piperidinoethylamino)thioxanthen-9-one (1.16 g.), m.p. 143.5—146.0°C. (corr.) and 1-(2-piperidinoethylamino)-thioxanthen-9-one-4-carboxaldehyde (98 mg.), m.p. 140°C. (recrystallized from ethyl acetate). The IR and NMR spectra of these compounds confirmed their structures, both NMR spectra lacking the 4-methyl signal ($\delta^{CDCl_3}_{ppm}$ = 2.72) of the 4-methyl precursor and containing, respectively, new signals of $\delta^{CDCl_3}_{ppm}$ = 5.18 (for two methylene protons of CH_2OH group) and $\delta^{CDCl_3}_{ppm}$ = 10.28 (for the formyl proton). The 4-hydroxymethyl compound was submitted for analysis.

Anal. Calcd. for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.57; N, 7.60.

Found: C, 68.66; H, 6.68; N, 7.20.

EXAMPLE 4

Following the procedure described in Example 1, 6-chloro-1-(2-diethylaminoethylamino)-4-methylthioxanthen-9-one (4.0 g. as its hydrochloride) was converted into 6-chloro-1-(2-diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one and 6-chloro-1-(2-diethylaminoethylamino)thioxanthen-9-one-4-carboxaldehyde. There was isolated 0.40 g. of the 4-hydroxymethyl compound, m.p. 114.8—116.8°C. (corr.).

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2S$: C, 61.45; H, 5.93; N, 7.17.

Found: C, 61.29; H, 5.90; N, 6.79. Its NMR, IR and UV spectral analyses confirmed its structure, its NMR spectrum having a signal of $\delta^{CDCl_3}_{ppm}$ = 5.10 (for the two methylene protons of the CH_2OH group).

EXAMPLE 5

Following the procedure described in Example 1, 1-(2-diethylaminoethylamino)-4-methylxanthen-9-one was converted into its corresponding 4-hydroxymethyl and 4-formyl compounds. One 10 liter fermentator was used. Four g. of the 4-methyl compound as its hydrochloride was added to the fermentator and twenty-four hours later the fermentation was terminated. The beer was extracted with methylene dichloride, the extract concentrated to remove the solvent, the concentrate (about 200 ml.) added to 50 g. of silica gel and the mixture placed on a 300 g. silica gel column (3.5 x 44 cm.). The column was developed with ethyl ether containing 2% triethylamine and 1% methanol, 200 ml. fractions being collected. On examination by T.L.C., fractions 4—7 were found to contain the 4-formyl compound and fractions 8—20 were found to contain the 4-hydroxymethyl derivative. Fractions 8—20 were combined, concentrated *in vacuo* and the remaining solid recrystallized from ethyl acetate to yield 1.41 g. of 1-(2-diethylaminoethylamino)-4-hydroxymethylxanthen-9-one, m.p. 131.0—132.8°C. (corr.).

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.10; N, 8.23.

Found: C, 70.72; H, 7.21; N, 8.22. Its structure was confirmed by its NMR, IR and UV spectral analyses, with it having an NMR signal of $\delta^{CDCl_3}_{ppm}$ = 5.2 (for the two methylene protons of the CH_2OH group).

EXAMPLE 6

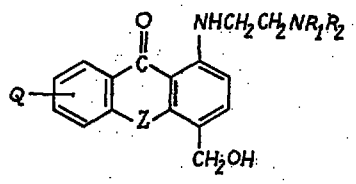
Following the procedure described in Example 1, 6-chloro-4-methyl-1-[2-(2-methylpiperidino)ethylamino]-thioxanthen-9-one (2.2 g. as its hydrochloride) was converted into the corresponding 4-hydroxymethyl and 4-formyl compounds. There was isolated 0.26 g. of 6-chloro-4-hydroxymethyl-1-[2-(2-methylpiperidino)ethylamino]thioxanthen-9-one, m.p. 141—145°C. Its NMR, IR and UV spectral data confirmed its structure, with it having an NMR signal of $\delta^{CDCl_3}_{ppm}$ = 5.11 (for the two methylene protons of the CH_2OH group).

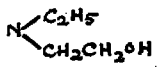
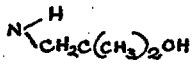
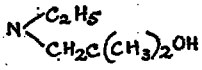
EXAMPLE 7

Following the procedure described in Example 1, 1-(2-diethylaminoethylamino)-4-methylthioxanthen-9-one-10,10-dioxide (1.5 g. as its hydrochloride) was converted into the corresponding 4-hydroxymethyl and 4-formyl compounds. There was isolated 0.37 g. of 1-(2-diethylaminoethylamino)-4-hydroxymethylthioxanthen-9-one-10,10-dioxide, m.p. 124—125.5°C. Its NMR, IR and UV spectral data confirmed its structure, with it having an NMR signal of $\delta^{CDCl_3}_{ppm}$ = 5.5 (for the two methylene protons of the CH_2OH group).

Following the above-described screening procedure using *Aspergillus sclerotiorum* (SWRI A_{24}), the 4-hydroxymethylthioxanthen-9-ones and 4-hydroxymethylxanthen-9-ones of Table B, as well as the corresponding 4-formyl compounds, were prepared from the corresponding 4-methylthioxanthen-9-ones and 4-methylxanthen-9-ones, used as their hydrochlorides.

TABLE B



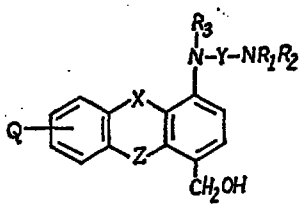
Example	Q	Z	NR_1R_2
8	6—Cl	S	
9	H	SO	$N(C_2H_5)_2$
10	7—Br	O	$N(C_2H_5)_2$
11	H	O	~~NC_5H_{10}~~ a)
12	H	S	
13	H	O	NC_6H_{12} b)
14	6—Cl	S	

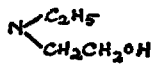
a) NC_5H_{10} = piperidino

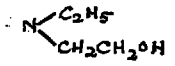
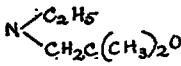
b) NC_6H_{12} = 2-methylpiperidino

Following the procedure described in Examples 1, 2 and 5 using the appropriate 1 - (R_1R_2N - Y - NR_2) - 4 - methylthioxanthene or -4-methylxanthene, the corresponding 4-hydroxymethyl compounds of Table C, as well as the corresponding 4-carboxaldehyde derivatives can be prepared.

TABLE C



Example	X	Z	R_3	Y	~~NR_2R_1~~ NR_1R_2	Q
15	CHOH	S	H	CH_2CH_2	$N(C_2H_5)_2$	H
16	CH_2	S	H	CH_2CH_2	$N(C_2H_5)_2$	H
17	C=O	SO	H	CH_2CH_2	$N(C_2H_5)_2$	H
18	CH_2	SO_2	H	CH_2CH_2	$N(C_2H_5)_2$	H
19	C=O	O	H	CH_2CH_2		H
20	CHOH	O	H	CH_2CH_2	$N(C_2H_5)_2$	H
21	CH_2	O	H	CH_2CH_2	$N(C_2H_5)_2$	H
22	C=O	O	H	$(CH_2)_3$	NC_5H_{10}a	6—Cl
23	C=O	O	H	$(CH_2)_4$	NC_4H_8b	7—CH_3
24	C=O	O	H	CH_2CH_2	$N(C_4H_9\text{-}n)_2$	8—OCH_3
25	C=O	O	H	$CH(CH_3)CH_2$	$N(CH_3)_2$	5—Cl
26	C=O	S	CH_3	CH_2CH_2	$N(C_2H_5)_2$	H
27	C=O	S	H	$CH_2CH(CH_3)$	$N(CH_3)_2$	H
28	C=O	S	H	CH_2CH_2	NC_4H_8b	H
29	C=O	S	C_2H_5	$(CH_2)_4$	$N(C_2H_5)_2$	5—CH_3
30	C=O	S	H	CH_2CH_2	$N(C_6H_{13}\text{-}n)_2$	7—Cl
31	C=O	S	H	CH_2CH_2	NC_4H_8Oc	7—Br
32	C=O	S	H	CH_2CH_2	NC_6H_{12}d	7—OC_2H_5
33	C=O	S	H	CH_2CH_2	NC_6H_{12}e	8—CH_3
34	C=O	S	H	CH_2CH_2	NC_7H_{14}f	6,7—$(OCH_3)_2$
35	C=O	S	H	CH_2CH_2	$N(C_2H_5)_2$	5,6,7—$(CH_3)_3$
36	C=O	S	H	CH_2CH_2	NHC_2H_5	H

Example	X	Z	R_3	Y	NR_2R_1	Q
37	C=O	S	H	CH_2CH_2	$NHCH_2CH_2OH$	H
38	C=O	S	H	CH_2CH_2		H
39	C=O	S	H	CH_2CH_2		H
40	C=O	S	H	CH_2CH_2	$N(CH_3)_2$	H
41	C=O	S	H	CH_2CH_2	$N(C_4H_9\text{-}n)_2$	H
42	C=O	O	H	CH_2CH_2	$N(CH_3)_2$	H
43	C=O	O	H	CH_2CH_2	$N(C_4H_9\text{-}n)_2$	H
44	C=O	O	CH_3	CH_2CH_2	$N(C_2H_5)_2$	H
45	C=O	S	H	CH_2CH_2	$N(CH_2CH_2OH)_2$	H
46	C=O	S	H	$(CH_2)_3$	$N(C_2H_5)_2$	H

a) NC_5H_{10} = piperidino

b) NC_4H_8 = pyrrolidino

c) NC_4H_8O = morpholino

d) NC_6H_{12} = hexamethyleneimino

e) NC_6H_{12} = 2,5-dimethylpyrrolidino

f) NC_7H_{14} = 2,6-dimethylpiperidino

EXAMPLE 47

Following the procedure described in Example 1, 4 - methyl - 1 - [2 - (2 - methylpiperidino)ethylamino]xanthen - 9 - one (5 g. as its hydrochloride) was converted into 4-hydroxymethyl - 1 - [2 - (2 - methylpiperidino)ethylamino]xanthen - 9 - one and 1-[2-(2 - methylpiperidino)ethylamino]xanthen - 9-one-4-carboxaldehyde. There was isolated 2.18 g. of the 4-hydroxymethyl compound, m.p. 134.0—136.2°C. (corr.).

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.65.

Found: C, 72.02; H, 7.32; N, 7.61.

NMR, IR and UV spectral analyses confirmed its structure.

The intermediate 4 - methyl - 1 - [2 - (2-methylpiperidino) - ethylamino]xanthen - 9 - one was prepared as follows: A mixture containing 6.2 g. of 1-chloro-4-methylxanthen-9-one, 12 g. of 2-(2-methylpiperidino)ethylamine and 12 ml. of pyridine was refluxed for eighteen hours and the solvent distilled off under reduced pressure. The residue was treated with dilute acetic acid and the mixture filtered. The filtrate was made alkaline with 35% aqueous sodium hydroxide solution and the oil that separated crystallized slowly. The mixture was extracted with chloroform and the extract dried over anhydrous magnesium sulfate. The chloroform was distilled off, the remaining oil dissolved in 50 ml. of absolute ethanol, the resulting solution treated with 3.7 ml. of 7.1N ethanolic hydrogen chloride and placed in a refrigerator. The resulting precipitate was collected, washed with absolute ethanol and dried for four hours at 80°C. *in vacuo* (20 mm.) to yield 6.2 g. of 4 - methyl - 1 - [2 - (2 - methylpiperidino) ethylamino]xanthen-9-one hydrochloride, m.p.

229.0—232.0°C. (corr.).

Anal. Calcd. for $C_{22}H_{26}N_2O_2.HCl$: Cl, 9.16; N, 7.24.

Found: Cl, 8.98; N, 7.40.

EXAMPLE 48

Following the procedure described in Example 1, 6 - chloro - 1 - (2 - diethylaminoethylamino) - 4 - methylxanthen - 9 - one (3 g. as its hydrochloride) was converted into the corresponding 4-hydroxymethyl and 4-formyl compounds. After three recrystallizations from ethyl acetate-n-hexane, there was obtained 0.350 g. of 6-chloro-1-(2-diethylaminoethylamino) - 4 - hydroxymethylxanthen-9-one, m.p. 130.0—132.8°C. (corr.).

Anal. Calcd. for $C_{20}H_{23}ClN_2O_3$: C, 64.08; H, 6.18; Cl, 9.46.

Found: C, 64.01; H, 6.40; Cl, 9.49.

EXAMPLE 49

Following the procedure described in Example 1, 1 - (2 - ethylaminoethylamino)-4-methylthioxanthen-9-one (10 g. as its hydrochloride) was converted into the corresponding 4-hydroxymethyl and 4-formyl compounds. After one recrystallization from ethyl acetate, there was obtained 0.91 g. of 1-(2-ethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one, m.p. 150.0 — 151.6°C. (corr.) with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; S, 9.72.

Found: C, 65.89; H, 6.05; S, 9.62.

EXAMPLE 50

1 - (2 - *diethylaminoethylamino*) - 4 - *hydroxymethylthioxanthen* - 9 - *ol* was prepared in two steps from 1 - (2 - diethylaminoethylamino)thioxanthen - 9 - one - 4 - carboxaldehyde as follows: 1 g. of 1 - (2 - diethylaminoethylamino)thioxanthen - 9 - one - 4 - carboxaldehyde was dissolved in 175 ml. of anhydrous warm methanol under an atmosphere of nitrogen. To the solution was added 0.2 g. of sodium borohydride whereupon evolution of hydrogen gas commenced immediately and the color of the solution turned from yellow to orange. After five minutes a sample was taken and on examination by T.L.C., it was determined that reduction had taken place to yield 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one. After an additional hour, no further reaction took place. To the reaction mixture was then added 0.4 g. of sodium borohydride; however, no further change occurred as determined by T.L.C. examination. The same was true after an additional 0.4 g. of sodium borohydride was added and the reaction mixture heated on a steam bath for five minutes. To the reaction mixture was then added about 2 g. of sodium ~~amalgam~~ and the mixture stirred for five hours. To the reaction mixture was added 200 ml. of ice water and the gummy precipitate that separated was collected and dissolved in methylene dichloride. The solution was washed with water, the methylene dichloride evaporated off, and the residue taken up in ethyl acetate. When no product was obtained from the ethyl acetate solution, the above aqueous mother liquor was placed in a refrigerator overnight whereupon a white solid separated. The solid was collected, washed with water and recrystallized from ethyl acetate to yield 0.289 g. of the product, 1 - (2 - diethylaminoethylamino)-4 - hydroxymethylthioxanthen - 9 - ol, m.p. 132.0—133.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{20}H_{26}N_2O_2S$: N, 7.81; S, 8.94.

Found: N, 7.89; S, 9.03.

EXAMPLE 51

Oxidation of 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one to yield its corresponding 10-oxide was carried out as follows: To a solution containing 6 g. of 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one in a minimum quantity of 5% aqueous acetic acid was added 30 ml. of 30% hydrogen peroxide. The reaction mixture was allowed to stand in a cold room over the weekend and then at room temperature for twelve hours; it was made basic with ammonium hydroxide and extracted three times with 200 ml. portions of methylene dichloride. The extracts were combined and taken to dryness. The residue was mixed 25 g. of silica gel and placed on a 250 g. silica gel column. The column was developed with ether plus 1% triethylamine and increasing amounts of methanol from 0.5% to 5%. The latter fractions (19—24) eluted with 5% methanol, 1% triethylamine and 94% ether were combined and the solvent removed to yield 0.56 g. of the product, 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one - 10 - oxide, m.p. 119.0—121.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{20}H_{24}N_2O_4S$: C, 64.49; H, 6.49; N, 7.52.

Found: C, 64.54; H, 6.19; N, 7.77.

Its structure was confirmed by NMR, IR and UV spectral analyses.

EXAMPLE 52

To a solution of 10 g. of 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one in 25 ml. of dimethylformamide was added 5.5 g. of pamoic acid in 25 ml. of ~~dimethylformamide~~. The solution was filtered and the filtrate placed in an ice bath for about two hours. The crystalline precipitate was collected and recrystallized from dimethylformamide to yield 3.0 g. of 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one pamoate, m.p. 212.5—214.0°C. (corr.) with decomposition.

Anal. Calcd. for $(C_{20}H_{24}N_2O_2S)_2.C_{23}H_{16}O_6$: S, 5.82; Base, 64.6.
Found: S, 5.79; Base, 64.7.

EXAMPLE 53

To a solution of 5 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one in 15 ml. of dimethylformamide was added a solution containing 2.65 g. of 3-hydroxy-2-naphthoic acid in 15 ml. of dimethylformamide. The hot solution was filtered and the filtrate placed in a freezer for two hours. The yellow crystalline precipitate was collected and recrystallized from dimethylformamide to yield 5.2 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one 3 - hydroxy - 2 - naphthoate, m.p. 220.5—222.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{20}H_{24}N_2O_2S.C_{11}H_8O_3$: S, 5.89; Base, 65.5.
Found: S, 6.06: Base, 66.2.

EXAMPLE 54

To a solution containing 1 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one in 0.9 ml. of pyridine was added 0.8 ml. of acetic anhydride and the mixture heated gently in a bath of warm water. In about five minutes light yellow crystals separated, filling the reaction mixture. Ether was added, and the crystalline product was collected and recrystallized from ether to yield 0.86 g. of 4-acetoxymethyl-1-(2 - diethylaminoethylamino)thioxanthen - 9 - one, m.p. 120.6—122.0°C. (corr.).

Anal. Calcd. for $C_{22}H_{26}N_2O_3S$: C, 66.30; H, 6.57; N, 7.03.
Found: C, 66.36; H, 6.83; N, 7.06.
Its structure was further confirmed by NMR, IR and UV spectral analyses.

EXAMPLE 55

One g. of 1 - (2 - diethylaminoethylamino)-4 - hydroxymethylthioxanthen - 9 - one and 1 g. of 3,5-dinitrobenzoyl chloride were dissolved in 3 ml. of pyridine and the mixture allowed to stand for ten minutes. The reaction mixture was then poured into about 50 ml. of water. The solid that separated was collected and washed successively with 5% sodium carbonate solution and water, and then recrystallized once from ethyl acetate and once from acetone to yield 0.34 g. of 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one 3,5-dinitrobenzoate, m.p. 144.0—145.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{27}H_{26}N_4O_7S$: N, 10.17; S, 5.82.
Found: N,10.02; S, 5.91.

EXAMPLE 56

A mixture of 1 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one and 2 ml. of phenyl isocyanate was warmed to effect solution. On cooling a crystalline solid separated. n-Hexane was added to remove the excess phenyl isocyanate. The solid was collected and recrystallized twice from acetone to yield 1.0 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one carbanilate, m.p. 165.0—165.6°C. (corr.) with decomposition.

Anal. Calcd. for $C_{27}H_{29}N_3O_3S$: N, 8.84; S, 6.74.
Found: N, 8.72; S, 6.72.

EXAMPLE 57

A thiosemicarbazone of a formyl compound was prepared as follows: A mixture containing 1 - (2 - diethylaminoethylamino)-9 - oxo - 4 - thioxanthenecarboxaldehyde, 90 ml. of ethanol, 2.7 g. of thiosemicarbazide, 90 ml. of water and 6 ml. of acetic acid was heated at 70°C. in a water bath for three hours, cooled, neutralized with ammonium hydroxide and then made basic with 10% aqueous sodium hydroxide solution. The resulting precipitate was collected and recrystallized once from methanol and once from pyridine to yield 4.0 g. of 1-(2-diethylaminoethylamino) - 9 - oxo - 4 - thioxanthenecarboxaldehyde thiosemicarbazone, m.p. 209.2—211.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{21}H_{25}N_5OS_2$: N, 16.38; S, 15.00.
Found: N, 16.12; S, 14.99.

EXAMPLE 58

A semicarbazone of one of the 4-formyl compounds was prepared as follows: To a solution containing 5 g. of 1-(2-diethylaminoethylamino)9 - oxo - thioxanthen - 4 - carboxaldehyde in 100 ml. of ethanol was added a solution containing 2.5 g. of semicarbazide hydrochloride, 3.8 g. of sodium acetate and 50 ml. of water. The reaction mixture was heated on a steam bath for two hours, filtered and then allowed to cool. The filtrate was made basic with 10% aqueous sodium hydroxide solution. The resulting precipitate was collected and recrystallized from dimethylformamidemethanol to yield 4.7 g. of 1 - (2 - diethylaminoethylamino) - 9 - oxo - thioxanthene-4-carboxaldehyde semicarbazone, m.p. 274.0—275.0°C. (corr.) with decomposition.

Anal. Calcd. for $C_{21}H_{25}N_5O_2S$: N, 17.02; S, 7.79.
Found: N, 17.15; S, 7.93.

EXAMPLE 59

Following the procedure described in Example 1, 1 - (2 - diethylaminoethylamino)-4 - methyl - 5,6,7,8 - tetrahydrothioxanthen - 9-one (14 g. as its hydrochloride) was converted into the corresponding 4-hydroxymethyl and 4-formyl compounds. After one recrystallization from ethyl acetate, there was

obtained 2.3 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethyl - 5,6,7,8 - tetrahydrothioxanthen-9-one m.p. 125.6—127.2°C. (corr.).

Anal. Calcd. for $C_{20}H_{23}N_2O_2S$: N, 7.77; S, 8.90.

Found: N, 7.73; S, 9.23.

The 4 - hydroxymethylthioxanthenes and 4-hydroxymethylxanthenes of our invention when administered orally to hamsters infected with *Schistosoma mansoni* were found to clear completely the animals of the parasitic infection at dose levels lower than required for the corresponding 4-methyl compounds. Some of the compounds, e.g., 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one, 1 - [2 - (2 - methylpiperidino)ethylamino] - 4 - hydroxymethylthioxanthen - 9 - one, 1 - (2 - piperidinoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one and 6 - chloro - 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9-one, have ED_{50} values below 10 mg. per kg. per day ED_{50} meaning the effective dose necessary to clear 50% of the hamsters of the infection. These 4-hydroxymethyl compounds were also found to be less toxic than the corresponding 4-methyl compounds. The decrease in toxicity in going from the 4-methyl compounds to the 4-hydroxymethyl compounds is illustrated as follows: The intravenous (i.v.) LD_{50} (in mice) of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one was found to be 105 ± 9 mg./kg., compared with an i.v. LD_{50} of 48 ± 3 for the corresponding 4-methyl compound (HCl salt); LD_{50} meaning the dose lethal to 50% of the mice (10 mice tested at each of three dose levels); also, the i.v. ALD_{50} (in mice) of 1-(2-piperidinoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one was found to be >100 mg./kg., compared with an i.v. LD_{50} of 52 ± 5 mg./kg. for the corresponding 4-methyl compound (HCl salt), ALD_{50} meaning the approximate dose lethal to 50% of the mice (3 mice tested at each of three dose levels). As illustrative of the schistosomacidal activity of the 4-formyl compounds, 1 - (2 - diethylaminoethylamino)thioxanthen - 9 - one - 4 - aldehyde when tested in hamsters as noted above was found to have an ED_{50} approximately the same as that found for its 4-methyl precursor.

WHAT WE CLAIM IS:—

1. A process for producing a compound of Formula I (herein) where X is >C=O, >CHOH or $>CH_2$, Z is —O—, —S—, >SO or $>SO_2$, Q is hydrogen or one to three substituents at positions 5, 6, 7 and 8 of the tricyclic ring selected from halo, lower-alkyl or lower-alkoxy, R is $—CH_2OH$ (or an ester thereof) or —CHO (or semicarbazones of thiosemicarbazone thereof), Y is lower-alkyklene having from two to four carbon atoms and having its two connecting linkages on different carbon atoms, R_3 is hydrogen or lower-alkyl, R_1 is hydrogen, lower-alkyl or lower-2-hydroxyalkyl and R_2 lower-alkyl or lower-2-hydroxyalkyl where R_1 and R_2 taken with N also is piperidino, hexamethyleneimino, pyrrolidino, morpholino, piperazino or a lower-alkylated derivative thereof, or the 5, 6, 7, 8-tetrahydro derivative thereof, as well as an acid-addition salt thereof, which process comprises subjecting the corresponding 4-methyl compound to the fermentative enzymatic action of a microorganism capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl and to 4-formyl, said organism being of the order *Moniliales*, *Mucorales* or *Sphaeriaeles* and if desired, obtaining an acid-addition salt of a basic compound obtained.

2. A process according to claim 1, in which, in said Formula I, R is hydroxymethyl, X is >C=O and Z is —S—, and the microorganism used is capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl.

3. A process according to claim 1, in which, in said Formula I, R is hydroxymethyl, X is >C=O and Z is —O—, and the microorganism is capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl.

4. A process according to any one of the preceding claims, in which the microorganism used belongs to the genus *Aspergillus*.

5. A process according to claim 4, in which the microorganism used is *Aspergillus sclerotiorum*.

6. The process for producing compounds of Formula I herein, substantially as hereinbefore described and as set forth in the Examples.

7. A compound whenever prepared by a process according to any one of the preceding claims.

8. A compound of the formula I (herein) where X is >C=O, >CHOH or $>CH_2$, Z is —O—, —S—, >SO or $>SO_2$, Q is hydrogen or one to three substituents at positions 5, 6, 7 and 8 of the tricyclic ring selected from halo, lower-alkyl or lower-alkoxy, R is $—CH_2OH$ (or an ester thereof) or —CHO (or semicarbazones and thiosemicarbazones thereof), Y is lower-alkylene having from two to four carbon atoms and having its two connecting linkages on different carbon atoms, R_3 is hydrogen or lower-alkyl, R_1 is hydrogen, lower-alkyl or lower-2-hydroxyalkyl and R_2 is lower-alkyl or lower-2-hydroxyalkyl where R_1 and R_2 taken with N also is piperidino, hexamethyleneimino, pyrrolidino, morpholino, piperazino or a lower-alkylated derivative thereof, or a 5, 6, 7, 8-tetrahydro derivative thereof, or an acid-addition salt thereof.

9. 1 - (2 - Diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one.

obtained 2.3 g. of 1-(2-diethylaminoethylamino) - 4 - hydroxymethyl - 5,6,7,8 - tetrahydrothioxanthen-9-one m.p. 125.6—127.2°C. (corr.).

Anal. Calcd. for $C_{20}H_{28}N_2O_2S$: N, 7.77; S, 8.90.

Found: N, 7.73; S, 9.23.

The 4 - hydroxymethylthioxanthenes and 4-hydroxymethylxanthenes of our invention when administered orally to hamsters infected with *Schistosoma mansoni* were found to clear completely the animals of the parasitic infection at dose levels lower than required for the corresponding 4-methyl compounds. Some of the compounds, e.g., 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one, 1 - [2 - (2 - methylpiperidino)ethylamino] - 4 - hydroxymethylthioxanthen - 9 - one, 1 - (2 - piperidinoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one and 6 - chloro - 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9-one, have ED_{50} values below 10 mg. per kg. per day ED_{50} meaning the effective dose necessary to clear 50% of the hamsters of the infection. These 4-hydroxymethyl compounds were also found to be less toxic than the corresponding 4-methyl compounds. The decrease in toxicity in going from the 4-methyl compounds to the 4-hydroxymethyl compounds is illustrated as follows: The intravenous (i.v.) LD_{50} (in mice) of 1-(2-diethylaminoethylamino) - 4 - hydroxymethylthioxanthen-9-one was found to be 105 ± 9 mg./kg., compared with an i.v. LD_{50} of 48 ± 3 for the corresponding 4-methyl compound (HCl salt); LD_{50} meaning the dose lethal to 50% of the mice (10 mice tested at each of three dose levels); also, the i.v. ALD_{50} (in mice) of 1-(2-piperidinoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one was found to be >100 mg./~~kgk~~. kg., compared with an i.v. LD_{50} of 52 ± 5 mg./kg. for the corresponding 4-methyl compound (HCl salt), ALD_{50} meaning the approximate dose lethal to 50% of the mice (3 mice tested at each of three dose levels). As illustrative of the schistosomacidal activity of the 4-formyl compounds, 1 - (2 - diethylaminoethylamino)thioxanthen - 9 - one - 4 - aldehyde when tested in hamsters as noted above was found to have an ED_{50} approximately the same as that found for its 4-methyl precursor.

WHAT WE CLAIM IS:—

1. A process for producing a compound of Formula I (herein) where X is >C=O, >CHOH or $>CH_2$, Z is —O—, —S—, >SO or $>SO_2$, Q is hydrogen or one to three substituents at positions 5, 6, 7 and 8 of the tricyclic ring selected from halo, lower-alkyl or lower-alkoxy, R is $—CH_2OH$ (or an ester thereof) or —CHO (or semicarbazones of thiosemicarbazone thereof), Y is lower-alkyklene having from two to four carbon atoms and having its two connecting linkages on different carbon atoms, R_3 is hydrogen or lower-alkyl, R_1 is hydrogen, lower-alkyl or lower-2-hydroxyalkyl and R_2 lower-alkyl or lower-2-hydroxyalkyl where R_1 and R_2 taken with N also is piperidino, hexamethyleneimino, pyrrolidino, morpholino, piperazino or a lower-alkylated derivative thereof, or the 5, 6, 7, 8-tetrahydro derivative thereof, as well as an acid-addition salt thereof, which process comprises subjecting the corresponding 4-methyl compound to the fermentative enzymatic action of a microorganism capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl and to 4-formyl, said organism being of the order *Moniliales*, *Mucorales* or *Sphaeriaeles* and if desired, obtaining an acid-addition salt of a basic compound obtained.

2. A process according to claim 1, in which, in said Formula I, R is hydroxymethyl, X is >C=O and Z is —S—, and the microorganism used is capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl.

3. A process according to claim 1, in which, in said Formula I, R is hydroxymethyl, X is >C=O and Z is —O—, and the microorganism is capable of effecting oxidation of the 4-methyl group to 4-hydroxymethyl.

4. A process according to any one of the preceding claims, in which the microorganism used belongs to the genus *Aspergillus*.

5. A process according to claim 4, in which the microorganism used is *Aspergillus sclerotiorum*.

6. The process for producing compounds of Formula I herein, substantially as hereinbefore described and as set forth in the Examples.

7. A compound whenever prepared by a process according to any one of the preceding claims.

8. A compound of the formula I (herein) where X is >C=O, >CHOH or $>CH_2$, Z is —O—, —S—, >SO or $>SO_2$, Q is hydrogen or one to three substituents at positions 5, 6, 7 and 8 of the tricyclic ring selected from halo, lower-alkyl or lower-alkoxy, R is $—CH_2OH$ (or an ester thereof) or —CHO (or semicarbazones and thiosemicarbazones thereof), Y is lower-alkylene having from two to four carbon atoms and having its two connecting linkages on different carbon atoms, R_3 is hydrogen or lower-alkyl, R_1 is hydrogen, lower-alkyl or lower-2-hydroxyalkyl and R_2 is lower-alkyl or lower-2-hydroxyalkyl where R_1 and R_2 taken with N also is piperidino, hexamethyleneimino, pyrrolidino, morpholino, piperazino or a lower-alkylated derivative thereof, or a 5, 6, 7, 8-tetrahydro derivative thereof, or an acid-addition salt thereof.

9. 1 - (2 - Diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one.

10. 4 - Hydroxymethyl - 1 - [2 - (2 - methylpiperidino)ethylamino] thioxanthen - 9 - one.

11. 4 - Hydroxymethyl - 1 - (2 - piperidinoethylamino) - thioxanthen - 9 - one.

12. 6 - Chloro - 1 - (2 - diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one.

13. 1 - (2 - Diethylaminoethylamino)thioxanthen - 9 - one - 4 - carboxaldehyde.

14. 1 - (2 - Diethylaminoethylamino) - 4 - hydroxymethylxanthen - 9 - one.

15. 1 - (2 - Diethylaminoethylamino) - 4 - hydroxymethylthioxanthen - 9 - one - 10,10 - dioxide.

16. 1 - (2 - Diethylaminoethylamino) - 4 - hydroxymethyl - 5,6,7,8 - tetrahydrothioxanthen - 9 - one.

17. A compound according to *claim* 8 as herein described.

18. A pharmaceutical composition particularly for treatment of schistosomiasis comprising as an active ingredient the compound according to any one of claims 7 to 17 and a pharmaceutical carrier.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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