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Synthetic Schistosomicides. II. 1-[(Dialkylaminoalkyl)-methylamino]-4-methyl-10-thiaxanthenones[1]

EDWARD F. ELSLAGER, J. F. CAVALLA,[2] W. D. CLOSSON,[3] AND DONALD F. WORTH

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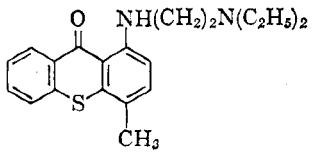
Several 1-[(dialkylaminoalkyl)methylamino]-4-methyl-10-thiaxanthenones have been prepared by condensing a 1-chloro-4-methyl-10-thiaxanthenone with an *N,N*-dialkyl-*N'*-methylalkylenediamine, or by allowing 1-[methyl(2-chloroethyl)-amino]-4-methyl-10-thiaxanthenone to react with the appropriate amine. A number of the title compounds are highly effective against *Schistosoma mansoni* in mice.

The discovery of the antischistosome activity of Miracil D (I)[4] stimulated the synthesis of many related compounds as potential antischistosome agents. These include various thiaxanthenones,[5-7]



I

xanthenones,[7-9] acridones,[7,9] and anthraquinones,[7,9] as well as certain azaxanthenones,[10,11] azathiaxanthenones,[11,12] thiachromanones,[13] thiochromones,[14] *N*-(9'-xanthenyl)carbamates,[15] *N*-(9-xanthenyl)-amides,[16] tetrahydroquinolines,[17,18] diphenylsulfides,[1] and *p*-toluidine derivatives.[18,19]

The dialkylaminoalkylamino derivatives reported prior to the initiation of the work described herein contained a secondary aromatic amine, a structure characteristic of the 4- and 8-aminoquinoline antimalarials. It has been suggested that the antimalarial activity of the 4-, 6-, and 8-aminoquinolines is dependent on the possibility of formation of tautomeric quinone forms involving the ring nitrogen and the nuclear amino group.[20] On the assumption that generalities which may apply to certain antimalarial series do not necessarily extend to schistosomiasis chemotherapy, we initiated the synthesis of various 1-[(dialkylaminoalkyl)methylamino]-4-methyl-10-thiaxanthenones. The thiaxanthenones described in the present communication are represented by formula III, where X is a hydrogen or chlorine atom, Y is an alkylene radical, and R_1 and R_2 designate alkyl or hydroxyalkyl radicals, or taken together with —N< a saturated heterocyclic ring.

The above compounds (Table II) were prepared by the condensation of a 1-chloro-4-methyl-10-thiaxanthenone (II)[5] with various *N,N*-dialkyl-*N'*-methylalkylenediamines (Table I) in boiling pyridine, or by allowing 1-[methyl(2-chloroethyl)-amino]-4-methyl-10-thiaxanthenone hydrochloride [V, where X is —H, and Y is —$(CH_2)_2$—], to react

(1) For previous paper in this series, see E. F. Elslager, M. Maienthal, and D. R. Smith, *J. Org. Chem.*, **21**, 1528 (1956).

(2) Work done at the Parke, Davis Research Laboratories, Staines Rd., Hounslow, Middlesex, England.

(3) Present address, Department of Chemistry, Harvard University, Cambridge, Mass.

(4) Office of the Publication Board, Department of Commerce, Washington, D. C., Report No. 981; W. Kikuth, R. Gönnert, and H. Mauss, *Naturwiss.*, **33**, 253 (1946); H. Mauss, *Chem. Ber.*, **81**, 19 (1948).

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(6) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 747, 757 (1951); T. M. Sharp, *J. Chem. Soc.*, 2961 (1951); D. Ll. Hammick and D. C. Munro, *J. Chem. Soc.*, 1077 (1952); T. Y. Shen, E. F. Rogers, and L. H. Sarett, Abstracts of Papers, 136th Meeting, American Chemical Society, Atlantic City, New Jersey, Sept. 1959, p. 37-O; *Soc. des Usines Chemiques Rhone-Poulenc*, British Pat. **690,465** and **690,466**, Apr. 22, 1953; British Pat. **698,003**, Oct. 7, 1953; S. Kushner, U. S. Pat. **2,656,357**, Oct. 20, 1953.

(7) N. Steiger, U. S. Pat. **2,732,373** and **2,732,374**, Jan. 24, 1956.

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(18) H. Mauss, H. Kölling, and R. Gönnert, *Med. u. Chem. Abhandl. med-chem. Forschungsstätten I. G. Farbenind.*, **5**, 185 (1956).

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(20) F. Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

TABLE I. *N,N*-DIALKYL-*N'*-METHYLALKYLENEDIAMINES $CH_3NH—Y—N(R_1)R_2$

Y	NR_1R_2	B.P.	Mm.	Refractive Index	°C.	Yield Purified, %	Procedure	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
—$CHCH_3CH_2$—	$N(CH_3)_2$	132–135	*a*	1.4234	25	51	I	$C_6H_{16}N_2$	62.0	62.3	13.9	13.7	24.1	23.9
—$(CH_2)_2$—	$N[CH(CH_3)_2]_2$	172–178	*a*	1.4357	25	52	I	$C_9H_{22}N_2$	68.3	68.3	14.0	14.0	17.7	17.3
—$(CH_2)_2$—	$N[(CH_2)_2CH_3]_2$	104–105	11.0	1.4390	20	62	I	$C_{11}H_{26}N_2$[b]					15.0	15.2
—$(CH_2)_2$—	$N(CH_2)_5$	162–168	*a*	1.4622	25	68	I	$C_8H_{18}N_2$	67.5	67.3	12.8	13.0	19.7	19.4
—$(CH_2)_3$—	$N(C_2H_5)_2$	171–174	*a*	1.4395	20	50	I	$C_8H_{20}N_2$[c]					19.4	19.0
—$(CH_2)_2$—	$NC_2H_5(CH_2)_2OH$	69–71	0.8	1.4613	20	50	II	$C_7H_{18}N_2O$[d]	57.5	57.5	12.4	12.5	19.2	19.0
—$(CH_2)_2$—	$NC_2H_5CH_2C(OH)(CH_3)_2$	64–65	1.0	1.4525	20	43	II	$C_9H_{22}N_2O$[e]	62.0	62.3	12.7	12.7	16.1	16.0
—$(CH_2)_2$—	$N[(CH_2)_2OH]_2$	132–133	0.9	1.4831	20	25	II	$C_7H_{18}N_2O_2$[f]	51.8	52.1	11.2	11.4	17.3	17.0

[a] Distilled at atmospheric pressure. [b] Prepared previously in 66–70% yield by the hydrolysis of *N',N'*-dibutyl-*N*-methyl-*N*-(*p*-nitrosophenyl)ethylenediamine, R. Munch, G. T. Thannhauser, and D. L. Cottle, *J. Am. Chem. Soc.*, **68**, 1297 (1946). [c] Prepared previously in 65% yield by the hydrolysis of *N',N'*-diethyl-*N*-methyl-*N*-(*p*-nitrosophenyl)-1,3-propanediamine, R. Munch, G. T. Thannhauser, and D. L. Cottle, *J. Am. Chem. Soc.*, **68**, 1298 (1946). [d] Picrate, plates from ethanol, m.p. 148–150°. *Anal.* Calcd. for $C_7H_{18}N_2O$·$2C_6H_3N_3O_7$: C, 39.9; H, 4.5; N, 17.7. Found: C, 39.6; H, 4.8; N, 17.5. [e] Picrate, large rhomboids from aqueous ethanol, m.p. 104–106°. *Anal.* Calcd. for $C_9H_{22}N_2O$·$2C_6H_3N_3O_7$: C, 38.0; H, 4.0; N, 18.5. Found: C, 38.0; H, 4.2; N, 18.5. [f] Picrate, rugged needles from ethanol, m.p. 152–153°. *Anal.* Calcd. for $C_7H_{18}N_2O_2$·$2C_6H_3N_3O_7$: C, 36.8; H, 3.9; N, 18.1. Found: C, 37.2; H, 4.3; N, 18.4.

with an excess of the appropriate amine. Although the secondary amine attached to the thiaxanthenone nucleus in Miracil D is not usually basic enough to provide stable salts, presumably because of hydrogen bonding, the tertiary amine group in compounds of general structure III is more basic and allows the isolation of the compounds as stable dihydrochlorides.

The intermediate 1-chloro-4-methyl-10-thiaxanthenones (II) have been described previously.[5] 1-[Methyl(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone [IV, where X is —H, and Y is —$(CH_2)_2$—] was prepared by heating *N*-methylethanolamine and a mixture of 1-chloro-4-methyl-10-thiaxanthenone and its isomeric 4-chloro-1-methyl-10-thiaxanthenone in boiling pyridine. 1-[Ethyl-(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone hydrochloride, was prepared in a similar manner from *N*-ethylethanolamine. 1-[Methyl(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone was converted to 1-[methyl(2-chloroethyl)amino]-4-methyl-10-thiaxanthenone hydrochloride [V, where X is —H and Y is —$(CH_2)_2$—] by the action of thionyl chloride in chloroform.

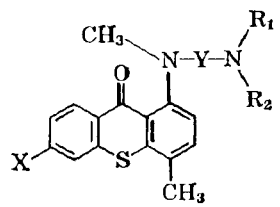
N,N,N'-Trimethylethylenediamine and *N,N*-diethyl-*N'*-methylethylenediamine are commercially available.[21] Other *N,N*-dialkyl-*N'*-methylalkylenediamines (Table I) were obtained by allowing a dialkylaminoalkyl chloride hydrochloride (VI) to react with an aqueous solution of methylamine in the presence of copper power and potassium carbonate. Side-chains containing hydroxy groups were prepared by the following route: chloroacetic acid methylamide (VIII)[22] was treated with a hydroxyalkylamine. The crude aminoamides of type IX could not be induced to crystallize and were reduced without further purification to the desired *N*-alkyl-*N*-hydroxyalkyl-*N'*-methylalkylenediamines

(21) The Ames Laboratories, Inc., South Norwalk, Conn.

(22) W. A. Jacobs, M. Heidelberger, and I. P. Rolf, *J. Am. Chem. Soc.*, **41**, 472 (1919).

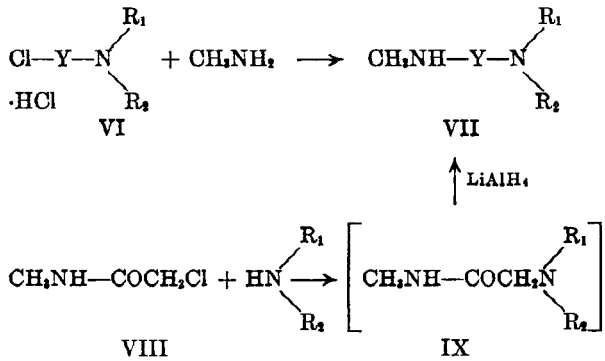
TABLE II

1-[(DIALKYLAMINOALKYL)METHYLAMINO]-4-METHYL-10-THIAXANTHENONES[a]



X	Y	NR_1R_2	M.P.	Yield Purified, %	Procedure	Purification[b,c] Solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
Cl	$-(CH_2)_2-$	$N(CH_3)_2$	272–273	28	I	A	$C_{19}H_{21}ClN_2OS\cdot 2HCl\cdot 1^1/_2H_2O$[f]	49.5	49.8	5.7	5.6	6.1	6.2	23.1	22.4
H	$-CHCH_3CH_2-$	$N(CH_3)_2$	227–229	7	II	B	$C_{20}H_{24}N_2OS\cdot 2HCl\cdot {}^1/_4H_2O$[g]	57.5	57.3	6.4	6.5	6.7	6.7	17.0	16.3
H	$-(CH_2)_2-$	$N(C_2H_5)_2$	155–156 dec	53	II	B	$C_{21}H_{26}N_2OS\cdot 2HCl\cdot H_2O$	56.6	56.7	6.8	7.1	6.3	6.3		
Cl	$-(CH_2)_2-$	$N(C_2H_5)_2$	162–164	18	I	B	$C_{21}H_{25}ClN_2OS\cdot 2HCl\cdot {}^3/_4H_2O$[h]	53.1	53.1	6.0	6.2	5.9	5.9		
Cl	$-(CH_2)_2-$	$N[(CH_2)_2CH_3]_2$	114–116	27	I	A	$C_{23}H_{33}ClN_2OS\cdot 2HCl\cdot 3H_2O$[i]	52.5	52.6	7.2	7.1	4.9	5.0	18.6	18.5
H	$-(CH_2)_2-$	$N(CH_2)_5$	254–256 dec	46	IV	C	$C_{22}H_{26}N_2OS\cdot 2HCl$	60.1	60.3	6.4	6.4	6.4	6.4	16.1	16.0
Cl	$-(CH_2)_2-$	$N(CH_2)_5$	296–298 dec.	37	I	D	$C_{22}H_{25}ClN_2OS\cdot 2HCl\cdot H_2O$[j]	53.7	53.7	5.9	6.1	5.7	5.6		
Cl	$-(CH_2)_3-$	$N(C_2H_5)_2$	181–183	27	I	B	$C_{22}H_{27}ClN_2OS\cdot 2HCl\cdot 1^1/_2H_2O$[k]	52.5	52.8	6.4	6.8	5.6	5.9	21.2	21.1
Cl	$-(CH_2)_2-$	$NC_2H_5(CH_2)_2OH$	170–172	59	III	E	$C_{21}H_{25}ClN_2O_2S\cdot 2HCl$[d,e]	52.8	53.4	5.7	5.8	5.9	6.3		
Cl	$-(CH_2)_2-$	$NC_2H_5CH_2COH(CH_3)_2$	94–100	33	III	F	$C_{23}H_{29}ClN_2O_2S\cdot HCl$[d,e]	58.8	58.5	6.4	6.3	6.0	5.8		
Cl	$-(CH_2)_2-$	$N[(CH_2)_2OH]_2$	176–179	24	III	E	$C_{21}H_{25}ClN_2O_3S\cdot 2HCl$[e]	51.1	50.9	5.5	5.6	5.7	5.7	21.5	21.1

[a] The thiaxanthenones varied from pale yellow to pale orange in color. [b] A few drops of ethanolic hydrogen chloride or concentrated hydrochloric acid were added to all purification solvents. [c] A, acetone; B, ethanol-acetone; C, 2-propanol-acetone; D, ethanol–ethyl acetate; E, absolute ethanol–anhydrous ether; F, could not be crystallized from a variety of common solvents, obtained by treating an ethereal solution of the base with dry hydrogen chloride. [d] Extremely hygroscopic. [e] Dried at 60° in high vacuum for 4 hr. prior to analysis. Water determinations (Karl Fischer): [f] calcd. 5.9, found 5.5. [g] calcd. 1.1, found 1.1. [h] calcd. 2.8, found 2.6. [i] calcd. 9.4, found 9.3. [j] calcd. 3.7, found 3.5. [k] calcd. 5.4, found 5.4



(VII) with lithium aluminum hydride in dry tetrahydrofuran.

Most of the dialkylaminoalkyl chloride hydrochlorides (VI) employed in this work are commercially available.[23] 2-Di-*n*-butylaminoethyl chloride hydrochloride and 2-(1-piperidino)ethyl chloride hydrochloride, prepared by the action of thionyl chloride on the corresponding ethanolamines in chloroform,[24] were not purified, but were allowed to react in crude form with aqueous methylamine.

1-Ethylamino-2-methyl-2-propanol, previously prepared[5] by the action of ethylamine on isobutylene oxide, was prepared in 66% yield by lithium aluminum hydride reduction of *N*-ethyl-2-methyllactamide[25] in dry ether.

The 1-[(dialkylaminoalkyl)methylamino]-4-methyl-10-thiaxanthenones listed in Table II were tested against *Schistosoma mansoni* in mice by P. E. Thompson and co-workers of these laboratories; when indicated, expanded studies were carried out against *S. mansoni* infections in hamsters and monkeys. Although details of these test results will be published elsewhere,[26] it is noteworthy that many of the thiaxanthenones prepared were potent schistosomicides. Several of these compounds were also effective against experimental tumors *in vitro* and *in vivo*.[27]

EXPERIMENTAL[28]

Methods for preparing N,N-dialkyl-N'-methylalkylenediamines (Table I). *Procedure I.* A solution of 2.0 moles of the appropriate dialkylaminoalkyl chloride hydrochloride in 500 ml. of water was slowly added to a stirred solution of 10.0 moles of 25% aqueous methylamine. The reaction mixture was held below 10°. Subsequently, 2.0 moles of anhydrous potassium carbonate and 2.0 g. of copper-bronze powder were added, and the mixture was boiled under reflux for 5 hr. The cooled reaction mixture was treated with 500 g. of solid sodium hydroxide, and the diamine extracted thoroughly with ether. The combined ether extracts were dried over anhydrous potassium carbonate, and the solvent removed on a steam bath. The residue was distilled through a twelve-inch Vigreux column to give the desired *N,N*-dialkyl-*N'*-methylalkylenediamines as colorless liquids.

Procedure II. To 26.9 g. (0.25 mole) of chloroacetic acid methylamide[22] was added 0.5 mole of the appropriate hydroxyalkylamine, and the mixture warmed gently. After a short inception period, the temperature rose rapidly, but was held below 90° with external cooling. The mixture was maintained at 90° for 2 hr., cooled, and dissolved in 200 ml. of 1-propanol. Upon the addition of 100 ml. of dry ether, the hydroxyalkylamine hydrochloride separated; the addition of dry ether (400 ml.) was continued until no further amine hydrochloride precipitated. The solution was decanted from the precipitated salt, shaken with magnesium sulfate to clarify, filtered, and concentrated *in vacuo* to an oil. The residual oil was repeatedly concentrated *in vacuo* from anhydrous benzene to remove traces of 1-propanol and water. The crude oil thus obtained could not be induced to crystallize, and was added dropwise with stirring to a suspension of 0.53 mole of lithium aluminum hydride in 300 ml. of dry tetrahydrofuran. The mixture was boiled under reflux with stirring for 15 hr., cooled in an ice-bath, treated cautiously with 35 ml. of water, and filtered. The solid was washed by boiling with ether and ethyl acetate, the mixture filtered, and the combined filtrates concentrated to an oil and the residue distilled *in vacuo*.

Methods for preparing 1-[(dialkylaminoalkyl)methylamino]-4-methyl-10-thiaxanthenones (Table II). *Procedure I.* A mixture of 0.07 mole of 1,7-dichloro-4-methyl-10-thiaxanthenone, 20 g. of the appropriate *N,N*-dialkyl-*N'*-methylalkylenediamine, and 20 ml. of pyridine was stirred and boiled under reflux for 18 hr. The mixture was cooled, 25 ml. of 50% aqueous potassium hydroxide solution was added, and the mixture steam distilled to remove volatile bases. Upon cooling, the residue was extracted thoroughly with chloroform, and the combined chloroform extracts dried over anhydrous potassium carbonate for 18 hr. The drying agent was collected by filtration, and the chloroform solution evaporated *in vacuo* to a red oil. The residue was extracted with ether, and the combined ether extracts (decolorizing charcoal) treated with anhydrous hydrogen chloride. The hygroscopic yellow solid that separated was collected by filtration and dried *in vacuo* at room temperature. Crystallization from the solvents indicated, to which a few drops of concentrated hydrochloric acid or ethanolic hydrogen chloride had been added, gave the pure hydrochlorides, which were allowed to equilibrate in the air prior to analysis.

Procedure II. A mixture of 0.07 mole of 1-chloro-4-methyl-10-thiaxanthenone, together with the isomeric 4-chloro-1-methyl-10-thiaxanthenone, 40 g. of pyridine, and 20 g. of the appropriate *N,N*-dialkyl-*N'*-methylalkylenediamine was heated under reflux for 18 hr., cooled, and treated with 25 ml. of 50% potassium hydroxide solution. After steam distillation to remove the volatile bases, the residue was cooled and the supernatant liquid carefully decanted. The residual cake was thoroughly extracted with hot 10% acetic acid, the acetic acid extracts combined, treated with decolorizing charcoal and made alkaline with sodium hydroxide solution. The precipitated base was extracted with chloroform, and the combined chloroform extracts dried over anhydrous potassium carbonate. The chloroform was evaporated *in vacuo*, the residue dissolved in dry ether, and the combined ether extracts treated with anhydrous hydrogen chloride. The yellow solids that separated were collected by filtration, washed with ether, and crystallized from the appropriate solvents, to which a few drops of concentrated hydrochloric acid or ethanolic hydrogen chloride had been added. The compounds were allowed to equilibrate in the air prior to analysis.

(23) 2-Dimethylamino-1-methylethyl chloride hydrochloride, 2-diethylaminoethyl chloride hydrochloride, 2-diisopropylaminoethyl chloride hydrochloride, and 3-diethylaminopropyl chloride hydrochloride, were purchased from the Michigan Chemical Corp., St. Louis, Mich.

(24) A modification of the procedure employed by H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 889 (1944), for the preparation of 3-diethylaminopropyl chloride hydrochloride, was used.

(25) R. F. Rekker and W. T. Nauta, *Rec. trav. Chim.*, **70**, 249 (1951).

(26) P. E. Thompson and co-workers, to be published.

(27) E. Hirschberg, A. Gellhorn, M. R. Murray, and E. F. Elslager, *J. Nat. Cancer Inst.*, **22**, 567 (1959).

(28) Melting points are uncorrected.

Procedure III. A mixture of 0.03 mole of 1,7-dichloro-4-methyl-10-thiaxanthenone, 0.04 mole of the appropriate *N*-alkyl-*N*-hydroxyalkyl-*N'*-methylalkylenediamine, and 10 to 25 ml. of pyridine was boiled under reflux for 16 hr. Upon cooling, the mixture was leached with 200 ml. of 2*N* hydrochloric acid, filtered, and the acid filtrates extracted with two 50-ml. portions of chloroform. The acid extracts were made alkaline with dilute potassium carbonate solution, and the basic solution extracted with three 75-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, and concentrated to a red oil. The residue was repeatedly evaporated from xylene *in vacuo* to free it from traces of pyridine, dissolved in 25 ml. of absolute ethanol, treated with ethanolic hydrogen chloride, and precipitated with absolute ether. For analysis, the thiaxanthenones were dried in high vacuum at 60° for 4 hr.

Procedure IV. A slurry of 6.0 g. (0.016 mole) of 1-[methyl-(2-chloroethyl)amino]-4-methyl-10-thiaxanthenone hydrochloride in water was made alkaline with sodium hydroxide and the base extracted with ether. The combined ether extracts were dried over anhydrous potassium carbonate and the ether removed *in vacuo*. The residue was dissolved in 25 ml. of piperidine and the solution was stirred and heated on the steam bath for 2 hr. The reaction mixture was cooled and poured into aqueous sodium hydroxide. The product was extracted with chloroform and the combined chloroform extracts were washed thoroughly with water and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, the chloroform was removed *in vacuo*, and the residue was dissolved in anhydrous ether and poured into ether containing excess ethanolic hydrogen chloride. The pale yellow solid was collected by filtration, dried *in vacuo* at 45°, and crystallized from a 2-propanol-acetone mixture.

1-[Methyl(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone. A mixture of 338 g. (1.3 moles) of 1-chloro-4-methyl-10-thiaxanthenone, mixed with 4-chloro-1-methyl-10-thiaxanthenone, 98 g. (1.3 moles) of *N*-methylethanolamine, and 500 ml. of pyridine was boiled under reflux with stirring for 18 hr. After cooling, a solution of 25 g. of potassium hydroxide in 50 ml. of water was added, and the mixture steam-distilled to remove volatile bases. The residue was cooled, filtered, and the solid dried for 18 hr. at 80° *in vacuo*. The crude solid was added to 1.2 l. of hot glacial acetic acid, and the solution diluted to 7 l. with hot water. The resulting suspension was brought to a boil and filtered. The pale yellow solid was washed with hot water and discarded. The acetic acid solution was made alkaline with saturated sodium hydroxide solution and the liberated base extracted with chloroform. The chloroform extracts were combined and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, and the chloroform evaporated *in vacuo* to yield a viscous oil that solidified upon cooling. The solid was suspended in 2 l. of boiling ether and filtered. Dry hydrogen chloride was bubbled into the ether solution to precipitate 45 g. of the yellow hydrochloride salt, m.p. 143–146°. The material which did not dissolve in the ether was crystallized from methanol to yield 70 g. of the base, m.p. 110–113°.

Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.1; H, 5.9; N, 4.7.

1-[Methyl(2-chloroethyl)amino]-4-methyl-10-thiaxanthenone hydrochloride. A solution of 42 g. (0.14 mole) of 1-[methyl(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone in 500 ml. of dry chloroform was added over a period of 0.5 hr. to a stirred solution of 35 g. (0.29 mole) of thionyl chloride in 500 ml. of chloroform heated under reflux. The mixture was boiled under reflux for 2 hr. and the chloroform removed *in vacuo* on the steam bath. The viscous residue solidified upon trituration with anhydrous ether. The brown solid was washed thoroughly with hot acetone and dried. Crystallization of the crude product from a dioxane-ether mixture (decolorizing charcoal) gave 16 g. (33%) of the hydrochloride salt, m.p. 151–153° dec.

Anal. Calcd. for $C_{17}H_{16}ClNOS \cdot HCl \cdot H_2O$: C, 54.9; H, 5.2; N, 3.8; Cl, 19.1; H_2O, 4.8. Found: C, 54.8; H, 5.4; N, 3.8; Cl, 19.1; H_2O, 5.1.

1-[Ethyl(2-hydroxyethyl)amino]-4-methyl-10-thiaxanthenone monohydrochloride. A mixture of 52 g. (0.2 mole) of 1-chloro-4-methyl-10-thiaxanthenone, mixed with 4-chloro-1-methyl-10-thiaxanthenone, 75 ml. of *N*-ethylethanolamine, 100 ml. of dry pyridine, and 0.5 g. of copper-bronze powder was stirred and boiled under reflux for 22 hr. Upon cooling, 20 g. of potassium hydroxide in 30 ml. of water was added, and the mixture steam-distilled for 3 hr. to remove volatile bases. The aqueous solution was decanted from the residual solid, and the solid was extracted thoroughly with chloroform. The combined chloroform extracts was exhaustively extracted with 10% acetic acid, and the combined acid extracts made alkaline with sodium hydroxide and the base extracted with chloroform. The chloroform extracts were washed with water and dried over anhydrous potassium carbonate. The chloroform was removed *in vacuo* to give an oil, which solidified upon cooling. The residue was dissolved in dry ether (decolorizing charcoal), and evaporated to give an oil, which was subsequently dissolved in methanol and treated with an excess of ethanolic hydrogen chloride and acetone. The yellow precipitate was collected by filtration and crystallized from an ethanol-acetone mixture to give 11 g. of yellow needles, m.p. 205° dec.

Anal. Calcd. for $C_{18}H_{19}NO_2S \cdot HCl$: C, 61.8; H, 5.8; N, 4.0. Found: C, 61.3; H, 5.8; N, 3.9.

1-Ethylamino-2-methyl-2-propanol.[5] To a stirred suspension of 20 g. (0.53 mole) of lithium aluminum hydride in 300 ml. of dry ether was added 46.9 g. (0.36 mole) of *N*-ethyl-2-methyllactamide[25] in 200 ml. of dry ether. The mixture was stirred and boiled under reflux for 12 hr. Upon cooling, the mixture was cautiously treated with 35 ml. of water, filtered, the filtrate concentrated to an oil, and distilled *in vacuo;* yield, 29.6 g. (66%), b.p. 54–56°/13 mm., n_D^{25} 1.4351.

Anal. Calcd. for $C_6H_{15}NO$: C, 61.5; H, 12.9; N, 12.0. Found: C, 62.1; H, 13.4; N, 11.8.

The hydrochloride crystallized from an ethanol-ether mixture as long needles, m.p. 155–158°.

Anal. Calcd. for $C_6H_{15}NO \cdot HCl$: C, 46.9; H, 10.5; N, 9.1. Found: C, 47.0; H, 10.6; N, 9.0.

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ANN ARBOR, MICH.
HOUNSLOW, MIDDLESEX, ENGLAND