the elimination of MeOH and the formation of (±)-**12**·HCl in the NMR spectrum. Anal. ($C_{21}H_{24}ClN$) C, H, N.

A sample of this salt was treated with aqueous $NaHCO_3$ and extracted with Et_2O. The Et_2O solution was dried over anhydrous $MgSO_4$ and 1.0 mL of CH_3I was added. The reaction mixture was allowed to stand for 1 h at 21 °C and evaporated to dryness on a rotary evaporator (the NMR spectrum was consistent with the methyl iodide salt derived from structure **12**). This salt was refluxed in ethanolic KOH for 30 min. The reaction mixture was then added to H_2O and extracted with pentane. The pentane layer was dried and evaporated to an oily residue. The NMR and IR spectra of this residue are identical with that of an authentic sample of 1-phenylnaphthalene.[28]

(28) C. J. Pouchert and J. R. Cambell, "Aldrich Library of NMR Spectra", Vol 4, Aldrich Chemical Co., Milwaukee, WI, 1974, p 28C.

***cis*-3-[*N*-(Cyclopropylmethyl)-*N*-methylamino]-1-phenyltetralin Hydrochloride (13b·HCl).** Hydrogenation of a sample of **12**·HCl (0.1 g) with 5% Pd/C in EtOH and workup by evaporation, conversion to the free amine with 5% $NaHCO_3$, and Et_2O extraction gave an oil which would not crystallize. The NMR spectrum indicated an approximate 9:1 mixture of **13b**/**13a**. This oil was dissolved in Et_2O, and HCl gas was passed into the flask. The resulting precipitate was recrystallized from ether–ethanol to give 0.06 g (60%) of **13b**·HCl: mp 152–154 °C; IR and NMR spectra differed from those of (±)-**13a** (see chemistry section for details); EIMS, *m/e* 291 (M^+).

Acknowledgment. This research was supported by NIDA Grant DA 01048. The authors thank Drs. R. E. Willette (NIDA, ADAMHA) and A. Jacobson (NIAMDD) for providing the biological data reported in this paper.

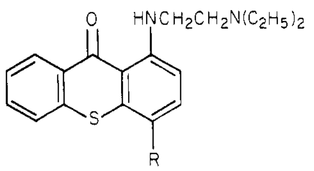
Ring-Hydroxylated Analogues of Lucanthone as Antitumor Agents

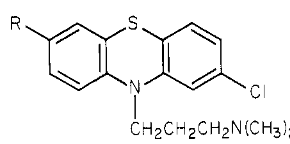
Sydney Archer,* Kenneth J. Miller, Rabindra Rej, Cecily Periana, and Lloyd Fricker

Chemistry Department, Cogswell Laboratory, Rensselaer Polytechnic Institute, Troy, New York 12181.
Received August 5, 1981

A series of ring-alkoxylated and ring-hydroxylated analogues of lucanthone was prepared and tested for antitumor activity. The most biologically interesting members of this group were the 7-hydroxylucanthone derivatives, **50** and **51**, which gave T/C values in the NCI P-388 antitumor screen of 188 and 265, respectively. The apparent association constants and ΔT_m values for a number of analogue–DNA complexes were determined to ascertain whether there was any quantitative correlation with biological activity. The most that can be said is that intercalation may be a necessary but far from sufficient condition for antitumor activity.

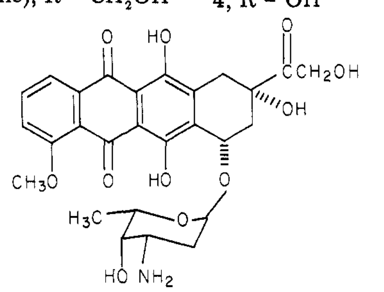
Several years ago Hirschberg reported that the antitumor activity of lucanthone (**1**) in L 1210 mice was abolished



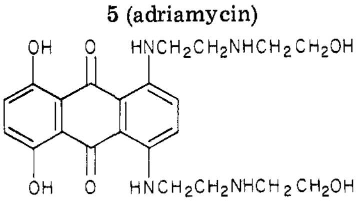


1 (lucanthone), R = CH_3
2 (hycanthone), R = CH_2OH

3 (chlorpromazine), R = H
4, R = OH



5 (adriamycin)



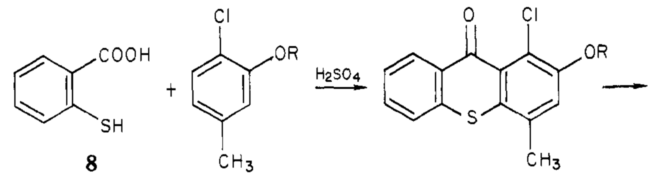
6

by pretreatment of the animals with the mixed-function oxidase inhibitor SKF-525A.[1] This result indicated that biotransformation of **1** was required for in vivo antitumor activity. Several analogues of lucanthone were tested as antitumor agents, but none showed interesting activity. Some years ago it was reported that the active metabolite of lucanthone in schistosomiasis was the hydroxylated derivative, hycanthone (**2**).[2] This compound is an antitumor agent also, but, like lucanthone, the antitumor activity of **2** in L1210 mice was also abolished by pretreatment of the animals with SKF-525A.[1] The identity of the mysterious antitumor biotransformation product of lucanthone remains unknown to this day.

Chlorpromazine (**3**) bears a structural resemblance to lucanthone in the sense that both drugs have tricyclic aromatic systems, the middle ring of which contains divalent sulfur and a dialkylaminoalkyl group attached directly to one of the ring atoms. The metabolism of **3** has been well studied. Just as in the case of **1**, the corresponding sulfoxide is a metabolite and another major metabolite is the 7-hydroxy derivative (**4**).[3] It has been shown that lucanthone (**1**) and hycanthone (**2**) intercalate into DNA.[4] Many naturally occurring intercalating antitumor agents, such as dactinomycin and adriamycin (**5**),[5] as well as synthetic anthraquinones, such as **6**,[6] have oxygen substituents on their planar (or nearly planar) polycyclic ring systems. Ring hydroxylation increased the

(1) E. Hirschberg, "Antibiotics", Vol. III, J. W. Corcoran and F. E. Hahn, Eds., Springer-Verlag, Berlin and Heidelberg, 1974, p 274.
(2) D. Rosi, G. Perruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, *J. Med. Chem.*, **10**, 867 (1967).
(3) D. A. Buyske and D. Dvornik, *Annu. Rep. Med. Chem.*, 1, 247 (1965).
(4) E. E. Gale, E. Cundliffe, P. E. Reynold, M. H. Richmond, and M. J. Waring, "The Molecular Basis of Antibiotic Action", Wiley, New York, 1972, pp 188 et seq.
(5) F. Arcamone, "Doxorubicin", Academic Press, New York, London, Toronto, Sydney, and San Francisco, 1981, pp 103–112.
(6) R. K.-Y. Zee-Chen, E. G. Podrebarac, C. S. Menon, and C. C. Cheng, *J. Med. Chem.*, **22**, 501 (1979).

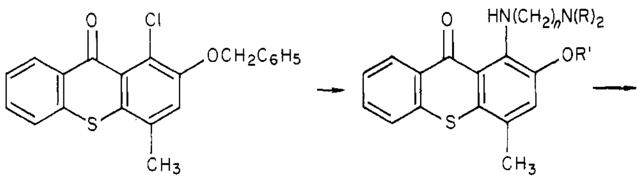
Scheme I



8

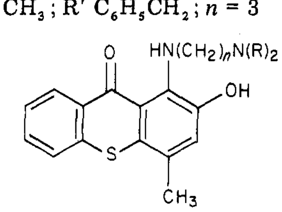
9, R = CH_3
10, R = H

11, R = CH_3
12, R = OH



13

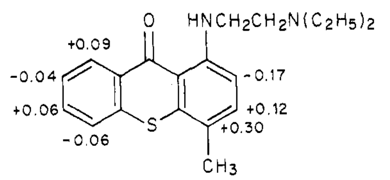
14, R = C_2H_5; R′ = CH_3; n = 2
15, R = CH_3; R′ = CH_3; n = 2
16, R = C_2H_5; R ′ = CH_3; n = 3
17, R = CH_3; R′ = CH_3; n = 3
18, R = CH_3; R′ = $C_6H_5CH_2$; n = 2
19, R = CH_3; R′ $C_6H_5CH_2$; n = 3



20, R = C_2H_5; n = 2
21, R = CH_3; n = 2
22, R = C_2H_5; n = 3
23, R = CH_3; n = 3

apparent association constants (K_{app}) of some anthraquinone–DNA complexes.[7]

On the basis of these and other considerations, we postulate that the unknown active metabolite of lucanthone is a ring-hydroxylated analogue. It is known that mixed-function oxidase systems attack sites of high electron density on aromatic rings.[8] With the aid of a MINDO/3 program, an electron density map of lucanthone was constructed as shown in 7. The calculation confirmed our

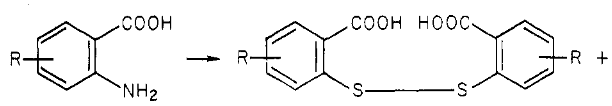


7

belief that C-2 was the site of highest electron density and also indicated that C-5 and C-7 are plausible sites for electrophilic attack. For this reason it was deemed prudent to synthesize and test for antitumor activity a group of 2-, 5-, and 7-monohydroxylated lucanthone derivatives and, if any were of biological interest, to expand the program to include other ring-hydroxylated analogues as well. In addition, the apparent association constants (K_{app}) and ΔT_m values of a few lucanthone derivatives complexed with purified calf thymus DNA were to be determined in order to see whether any correlation existed between these biophysical and antitumor properties.

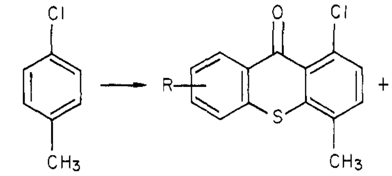
Chemistry. The preparation of the 2-hydroxylucanthone analogues is shown in Scheme I.

Scheme II

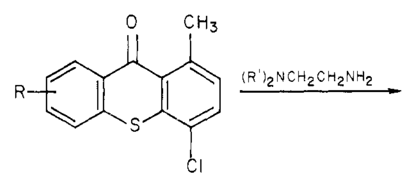


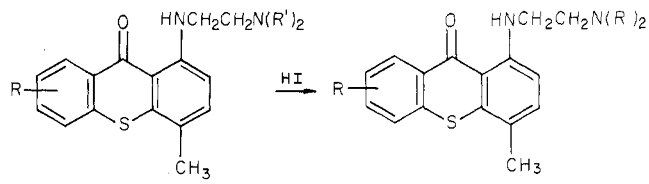
33, R = 3-OCH_3
34, R = 5-OCH_3
35, R = 6-OCH_3

36, R = 3-OCH_3
37, R = 5-OCH_3
38, R = 6-OCH_3



39, R = 5-OCH_3
40, R = 7-OCH_3
41, R = 8-OCH_3





42, R = 5-OCH_3; R′ = C_2H_5
43, R = 5-OCH_3; R′ = CH_3
44, R = 7-OCH_3; R′ = C_2H_5
45, R = 7-OCH_3; R′ CH_3
46, R = 8-OCH_3; R′ = CH_3
47, R = 8-OCH_3; R′ = CH_3

48, R = 5-OH; R′ = C_2H_5
49, R = 5-OH; R′ = CH_3
50, R = 7-OH; R′ = C_2H_5
51, R = 7-OH; R′ = CH_3
52, R = 8-OH; R′ = C_2H_5
53, R = 8-OH; R′ CH_3

Thiosalicyclic acid and 4-chloro-3-methoxytoluene reacted in sulfuric acid to give the thioxanthenone (**11**), which condensed with N,N-diethylethylenediamine to give **14**.[9] Demethylation of the 2-methoxythioxanthenone (**14**) with 48% HI gave **20**. The demethylation route to (**20–23**) proceeded smoothly in some cases but was unreliable in others, particularly where R = CH_3. The 2-(benzyloxy)thioxanthenone (**13**) was prepared from **12**, which in turn was obtained by condensing **8** with the phenol **10**. Debenzylation proved to be more reliable than demethylation in the conversion of **18** and **19** to **21** and **23**, respectively. The antitumor activities of these compounds are recorded in Table II.

Similar difficulties were encountered in the 4-methoxy series. For example, 1-[[2-(diethylamino)ethyl]amino]-4-methoxythioxanthenone (**24**) was obtained as described by Blanz and French,[10] but could not be demethylated smoothly. Accordingly, 1-chloro-4-hydroxythioxanthenone (**25**) was prepared from **8** and p-chlorophenol. It was benzylated with benzyl chloride to afford 1-chloro-4-(benzyloxy)thioxanthenone (**26**), which upon treatment with the requisite diamines gave the 4-(benzyloxy)thioxanthenones **27–29** (Table I). Debenzylation with HI gave the corresponding 4-hydroxythioxanthenones **30–32** (Table II).

The preparation of the 5-, 7-, and 8-hydroxylucanthone analogues was carried out as shown in Scheme II.[9]

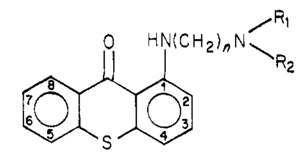
(7) J. C. Double and J. R. Brown, *J. Pharm. Pharmacol.*, **27**, 502 (1975).

(8) B. Testa and P. Jenner, "Drug Metabolism", Marcel Dekker, New York and Basel, 1976, p 45.

(9) S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4296 (1952).

(10) E. J. Blanz and F. A. French, *J. Med. Chem.*, **6**, 185 (1963).

Table I. Chemical and Biological Data on Alkoxylucanthone Analogues



no.	ring substituents	n	R	R[1]	emp formula	mp, °C	in vivo antitumor act. vs. P-388 lymphocytic leukemia[b] dose, mg/kg	T/C
14	2-OCH_3, 4-CH_3	2	C_2H_5	C_2H_5	$C_{21}H_{26}N_2O_2S{\cdot}C_4H_4O_4$	142–143	200	toxic[d]
							100	117
							50	115
15	2-OCH_3, 4-CH_3	2	CH_3	CH_3	$C_{19}H_{22}N_2O_2S$	90–91	200	129
							100	127
							50	96
16	2-OCH_3, 4-CH_3	3	C_2H_5	C_2H_5	$C_{22}H_{28}N_2O_2S{\cdot}C_4H_4O_4$[c]	148–149	200	toxic[d]
							100	toxic[d]
							50	102
17	2-OCH_3, 4-CH_3	3	CH_3	CH_3	$C_{20}H_{24}N_2O_2S{\cdot}2HI{\cdot}H_2O$	210–211	200	toxic[d]
							100	103
							50	100
18	2-$OCH_2C_6H_5$	2	CH_3	CH_3	$C_{25}H_{26}N_2O_2S$	127–128	NT[e]	NT[e]
24	4-OCH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S$	87–88[f]	200	100
							100	92
							50	92
27	4-$C_6H_5CH_2O$	2	C_2H_5	C_2H_5	$C_{26}H_{28}N_2O_2S$	103–104	NT	NT
28	4-$C_6H_5CH_2O$	2	CH_3	CH_3	$C_{24}H_{24}N_2O_2S$	174–175	NT	NT
29	4-$C_6H_5CH_2O$	3	CH_3	CH_3	$C_{25}H_{26}N_2O_2S$	130–132	NT	NT
42	5-OCH_3, 4-CH_3	2	C_2H_5	C_2H_5	$C_{21}H_{26}N_2O_2S$	147–149	200	116
							100	100
							50	113
43	5-OCH_3, 4-CH_3	2	CH_3	CH_3	$C_{19}H_{22}N_2O_2S$	176–177	NT	NT
44	7-OCH_3, 4-CH_3	2	C_2H_5	C_2H_5	$C_{21}H_{26}N_2O_2S$	81–82	100	147
							50	115
							25	115
45	7-OCH_3, 4-CH_3	2	CH_3	CH_3	$C_{19}H_{22}N_2O_2S$	139–141	200	toxic[d]
							100	135
							50	115
60	7-OCH_3, 4-CH_3	2	H	H	$C_{17}H_{18}N_2O_2S$	120–124	NT	NT
61	7-OCH_3, 4-CH_3	2	CH_3	H	$C_{18}H_{20}ON_2O_2S{\cdot}C_4H_4O_4$	217–219	NT	NT

[a] Analyses for C, H, and N for all compounds listed are within ±0.4% of the calculated values unless noted otherwise. All compounds were prepared by method A (Experimental Section). Compounds **17** and **61** were purified by crystallization from MeOH. All others were crystallized from EtOH. [b] The standard NCI protocols described in ref 17 were used. The dose listed was given once a day for 9 days. T/C = treated animal survival time/control animal survival time × 100. I = inactive, i.e., T/C ⩽125. [c] Fumarate salt. [d] Toxic means deaths occurred at this dose. [e] NT = not tested. [f] Blanz and French[10] reported mp 89–90 °C.

3-Methoxy- (**33**),[11] 5-methoxy- (**34**),[12] and 6-methoxyanthranilic acid (**35**)[13] were diazotized and converted to the corresponding dithiosalicyclic acids (**36–38**), and the unpurified acids were condensed with *p*-chlorotoluene to give the mixed thioxanthenones. The isomers **39–41**, which contained the more reactive 1-chloro substituent, were allowed to react with *N,N*-diethylethylenediamine and *N,N*-dimethylethylenediamine as described by Archer and Suter[9] to give the corresponding 1-[[(dialkylamino)alkyl]amino]thioxanthenones **42–47**.

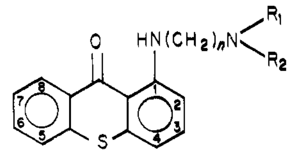
In the case of the preparation of **46**, chromatography of the crude acid-soluble fraction gave a mixture of the desired methoxythioxanthenone (**46**) and the corresponding 8-hydroxy compound (**52**). This result can be attributed to the presence of considerable amounts of 1-chloro-8-hydroxy-4-methylthioxanthenone in the mixture of methoxythioxanthenones. Demethylation during the H_2SO_4 cyclization step probably occurred during the preparation of **52** (see below). Demethylation of the methoxythioxanthenones **42–47** with 48% HI proceeded smoothly in each case to give the target compounds **48–53**, which were purified as the hydriodide salts.

Since the hydroxyethylaminoethylamino derivative **59** could not be prepared by HI demethylation of the corresponding methoxythioxanthenone, the sequence shown in Scheme III was used to prepare **59** and a few other 7-hydroxy analogues.

5-Methoxydithiosalicyclic acid (**37**) was reduced with zinc to give 5-methoxythiosalicyclic acid[14] (**54**), which was condensed with 2-bromo-4-chlorotoluene (**55**) to give the phenylthio acid **56** using the procedure of Laidlaw et al.[15] Ring closure with H_2SO_4 gave a mixture of the thioxanthenones **57** and **58**. NMR spectroscopy indicated that the demethylated compound **58** was present in substantial

(11) W. M. Stanley, E. McMahon, and R. A. Adams, *J. Am. Chem. Soc.*, **55**, 706 (1933).
(12) N. B. Chapman, G. M. Gibson, and F. G. Mann, *J. Chem. Soc.*, 890 (1947).
(13) H. Brockmann, H. Muxfeldt, and G. Haese, *Chem. Ber.*, **89**, 2174 (1956).
(14) A. H. Blatt, Ed., "Organic Syntheses", Collect. Vol. I, Wiley, New York, London, and Sydney, 1943, p 580.
(15) G. Laidlaw, J. Collins, S. Archer, D. Rosi, and J. W. Schulenberg, *J. Org. Chem.*, **38**, 1743 (1973).

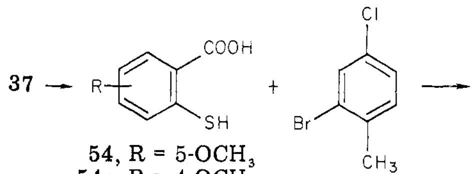
Table II. Chemical and Biological Data on Hydroxylucanthone Analogues



no.	ring substituents	*n*	R	R_1	emp formula[a]	mp, °C	method of preparation	solvent of recrystn	in vivo antitumor act. vs. P-388 lymphocytic leukemia[b] dose, mg/kg	T/C
1	(lucanthone)								100	158[b]
20	2-OH, 4-CH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S$	79–80	B	EtOH	200	100
									100	104
									50	99
21	2-OH, 4-CH_3	2	CH_3	CH_3	$C_{18}H_{20}N_2O_2S$[e]	119–120	B	MeOH	200	100
									100	101
									50	100
22	2-OH, 4-CH_3	3	C_2H_5	C_2H_5	$C_{21}H_{26}N_2O_2S$	84–85	B	EtOH	200	100
									100	94
									50	94
23	2-OH, 4-CH_3	3	CH_3	CH_3	$C_{19}H_{22}N_2O_2S{\cdot}H_2O$[c]	138–140	B	EtOH	200	115
									100	126
									50	108
30	4-OH	2	C_2H_5	C_2H_5	$C_{19}H_{22}N_2O_2S{\cdot}2HI$[e]	223–224	B	EtOH	50	103
									25	99
									12.5	89
31	4-OH	2	CH_3	CH_3	$C_{17}H_{18}N_2O_2S$[e]	179–180	B	MeOH	200	toxic[d]
									100	90
									50	94
32	4-OH	3	CH_3	CH_3	$C_{18}H_{20}N_2O_2S{\cdot}2HI$[e]	243–245	B	MeOH	200	toxic[d]
									100	toxic[d]
									3.13–50	<125
48	5-OH, 4-CH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S{\cdot}HI$	251–253	B	MeOH	200	104
									100	100
									50	104
49	5-OH, 4-CH_3	2	CH_3	CH_3	$C_{18}H_{20}N_2O_2S{\cdot}HI$	272–275	B	MeOH	200	97
									100	95
									50	100
50	7-OH, 4-CH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S{\cdot}HI$	254–255	B	MeOH	100	123
									50	188
									25	159
									12.5	142
51	7-OH, 4-CH_3	2	CH_3	CH_3	$C_{18}H_{20}N_2O_2S{\cdot}HI$	273–275	B	MeOH	128	toxic[d]
									64	265
									32	191
									16	170
									8	180
									4	141
									2	139
									1	130
52	8-OH, 4-CH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S{\cdot}HI$	242–244	B	MeOH	200	<125
									100	181
									50	143
53	8-OH, 4-CH_3	2	CH_3	CH_3	$C_{18}H_{20}N_2O_2S{\cdot}HI$	278–280	B	MeOH	200	<125
									100	<125
									50	166
59	7-OH, 4-CH_3	2	CH_2CH_2OH	H	$C_{18}H_{20}N_2O_3S$	193–195	C	EtOH	25	103
									12.5	169
									6.25	150
62	7-OH, 4-CH_3	2	H	H	$C_{16}H_{16}N_2O_2S{\cdot}HI$	277–278	B	MeOH	100	148
									50	135
									25	117
63	7-OH, 4-CH_3	2	CH_3	H	$C_{17}H_{18}N_2O_2S{\cdot}HI$	278–280	B	MeOH	100	toxic[d]
									50	toxic[d]
									25	93
70	6-OH, 4-CH_3	2	C_2H_5	C_2H_5	$C_{20}H_{24}N_2O_2S{\cdot}HI$	231–234	B	EtOH	200	106
									100	108
									50	107
71	6-OH, 4-CH_3	2	CH_3	CH_3	$C_{18}H_{20}N_2O_2S{\cdot}HI$	265–266	B	MeOH	200	126
									100	110
									50	110
72	6-OH, 4-CH_3	2	CH_2CH_2OH	H	$C_{18}H_{20}N_2O_3S$	193–195	C	EtOH	100	154
									50	146
									25	133
									12.5	130

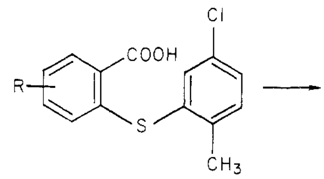
[a] Analyses for C, H, and N for all compounds listed are within ±0.4% of the calculated unless noted otherwise. [b] The standard NCI protocols were used. See Table I. See ref 18. [c] Anal. Calcd: C, 63.30; H, 6.70; N, 7.77. Found: C, 63.49; H, 6.12; N, 7.68. Prepared by 30-min reflux of **19** without purification of **19**. [d] Deaths occurred at this dose. [e] Prepared by refluxing the corresponding benzyl ether with 48% HI for 30 min.

Scheme III

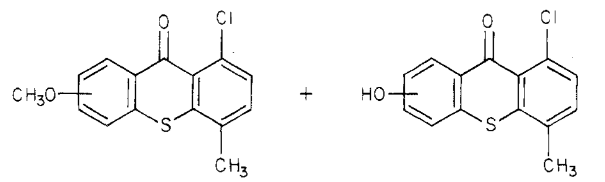


54, R = 5-OCH_3
54a, R = 4-OCH_3

55

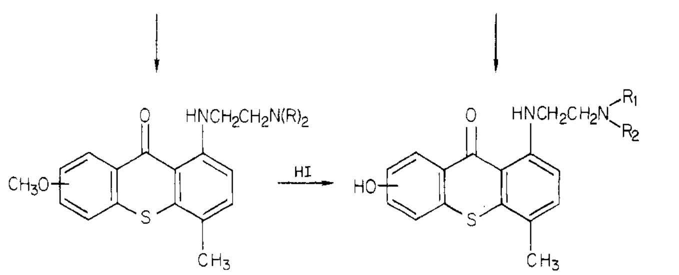


56, R = 5-OCH_3
56a, R = 4-OCH_3



57, 7-OCH_3
66, 6-OCH_3

58, 7-OH
67, 6-OH



60, 7-OCH_3; R = H
68, 6-OCH_3; R = C_2H_5
60, 6-OCH_3; R = CH_3

59, R = 7-OH; R_1 = H; R_2 = CH_2CH_2OH
62, R = 7-OH; R_1 = R_2 = H
63, R = 7-OH; R_1 = H; R_2 = CH_3
70, R = 6-OH; R_1 = R_2 = CH_3
71, R = 6-OH; R_1 = R_2 = CH_3
72, R = 6-OH; R_1 = H; R_2 = CH_2CH_2OH

amounts. Methylation of the crude mixture, followed by crystallization, proved to be the most convenient way to secure pure **57**, which in turn was demethylated smoothly with HI in acetic acid to give pure **58**. The latter was allowed to react with hydroxyethylaminoethylamine to give **59** accompanied by a high-melting, acetic acid-insoluble, unidentified byproduct.

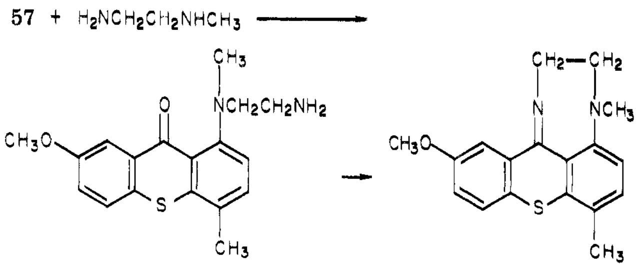
Condensation of **57** with ethylenediamine gave **60**, which on demethylation gave **62**. When the same reaction was carried out with *N*-methylethylenediamine, a mixture of bases was obtained; 1-[[(methylamino)ethyl]amino]-7-methoxy-4-methylthioxanthenone (**61**) was the minor component. Demethylation of **60** afforded **63**. The major product was tentatively assigned structure **65** on the basis of the spectroscopic and analytical data, which indicated that a mole of H_2O had been lost.

The formation of **65** can be rationalized by postulating that **57** reacted with *N*-methylethylenediamine at the secondary amine site to give **64**, which at the elevated temperature of the reaction cyclized to give the diazepine **65** (Scheme IV).

The 6-hydroxy analogues **70** and **71** were prepared by the sequence shown in Scheme III. 4-Methoxyanthranilic acid[16] was used as the starting material to prepare 4-methoxythiosalicylic acid (**54a**), which was converted to 2-[(5-chloro-2-methylphenyl)thio]-4-methoxybenzoic acid (**56a**). Cyclization in H_2SO_4 gave **66**, which, with the requisite *N,N*-dialkylethylenediamines, gave **68** and **69**, which were smoothly demethylated to give **70** and **71**.

Demethylation of **66** with HI in acetic acid furnished **67**, which was converted to **72** with the aid of *N*-(2-hydroxyethyl)ethylenediamine.

Scheme IV



64 **65**

Table III. Association Constants and ΔT_m of Some Drug-DNA Complexes

compd	ΔT_m, °C	K_{app}
lucanthone	20	2.2×10^6
20	6	2.3×10^6
48	20	2.2×10^6
42		2.7×10^6
50	20	4.3×10^6
44		1.8×10^7

Biological Results

The target thioxanthenones related to lucanthone were submitted to the National Cancer Institute for evaluation in the P-388 screen.[17] The results are recorded in Tables I and II. The historical data on lucanthone are included in Table II for comparative purposes.[18] None of the methoxy analogues in Table I was of sufficient biological interest to warrant further consideration. The 7-methoxy analogue (**44**) showed a T/C = 147 at 100 mg/kg and **45** was weakly active (T/C = 135 at 100 mg/kg). The others were either ineffective, toxic, or both.

The hydroxy analogues reported in Table II are of greater interest. The results in the 2-hydroxy and 5-hydroxy series were uniformly disappointing. However, in the 7-hydroxy series at least two compounds, **50** and **51**, are of considerable biological interest; the former showed T/C = 188 at 50 mg/kg and the latter showed T/C = 265 at 64 mg/kg. Activities for both compounds were confirmed in repeated tests. It should be noted that **59**, which has the same side chain as **6**, was less active (possibly more toxic) than **50** and **51**, whereas in the dihydroxyanthracenedione series, Cheng found the reverse to be true.[6]

Compounds in the 6-hydroxy (e.g., **19**, T/C = 154 at 100 mg/kg) and 8-hydroxy series (e.g., **52**, T/C = 181 at 100 mg/kg) were active in the P-388 screen, but no other compounds in this series were as active as **51**.

The ΔT_m and K_{app} values for some of the lucanthone analogues are recorded in Table III.

(16) J. M. L. Stephen, I. M. Tonkin, and J. Walker, *J. Chem. Soc.*, 1034 (1947).
(17) R. L. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3(2), 1 (1972).
(18) We thank Drs. Harry Wood and B. J. Abbott of the NCI for furnishing these data.

It should be noted that all of the compounds listed in Table III have K_{app} values equal to or greater than lucanthone. The 7-methoxy analogue (**44**) appears to bind better to DNA than lucanthone yet is no more active as an antitumor agent and far less active than **50**. Compound **48** has a ΔT_m value and a K_{app} approximately the same as lucanthone yet is completely devoid of antitumor activity. It is apparent from these few examples that there is no quantitative correlation between the ability of these thioxanthenones to bind to DNA and their antitumor activity. On the other hand, compound **50** is more active than lucanthone as an antitumor agent and has a somewhat better K_{app} also. If the data in Table III may be interpreted to indicate that, like lucanthone, these compounds are intercalating agents, then it may be concluded that in this series, intercalation is a necessary but not sufficient condition for antitumor activity.

It is important to note that the antitumor activity of lucanthone was increased significantly by hydroxylation at C-7, a possible site of metabolism by a mixed-function oxidase which is susceptible to inhibition by SKF-525-A. Work in progress indicates that **50** may not be the ultimate biotransformation product which is responsible for the antitumor activity of lucanthone but that 7-hydroxylation is an essential step in the metabolic pathway.

Experimental Section

Melting points were taken on a laboratory device Mel-Temp apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrometer, and NMR spectra were run on a Varian T-60A spectrometer in either $CDCl_3$ or $(CD_3)_2SO$ solution with Me_4Si as an internal standard. Elementary analyses were determined by Instranal Laboratories, Rensselaer, NY, and Spang Microanalytical Laboratory, Eagle Harbor, MI.

1-[[2-(Diethylamino)ethyl]amino]-2-methoxy-4-methylthioxanthenone (14). Method A. A mixture of 31.3 g (0.2 mol) of 4-chloro-3-methoxytoluene, 15.4 g (0.1 mol) of thiosalicylic acid, and 250 mL of concentrated H_2SO_4 was stirred at room temperature for 16 h and then at 60 °C for 2 h before being poured onto ice. During the early stages of the reaction the solution turned dark red and SO_2 was evolved. The yellow solid that separated was filtered and suspended in 7% NH_4OH. The suspension was warmed on the steam bath for about 30 min and filtered. The solid was washed with H_2O, EtOH, and acetone and dried. After crystallization from pyridine, the 1-chloro-2-methoxy-4-methylthioxanthenone weighed 11.0 g (38%), mp 177–178 °C.

A mixture of 21.75 g (0.075 mol) of the thioxanthenone, 10 mL of *N*,*N*-diethylethylenediamine, and 3.0 mL of dry pyridine was heated under reflux for 20 h. The dark mixture was cooled, treated with 5.0 mL of 50% KOH solution, and steam distilled. The mixture was allowed to cool and the aqueous supernatant was carefully decanted. The residue was heated to boiling with 10% acetic acid solution and filtered. The dark filtrate was made alkaline and the base was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and concentrated to leave an oil, which did not crystallize. In most of the cases listed in Table I, crystallization occurred at this point, and the bases were purified by recrystallization from the solvents indicated in Table I. In other instances when the base did not crystallize readily, it was converted to a crystalline salt.

In this case, the base (**14**) readily formed a fumarate salt in absolute EtOH. After two recrystallizations from the same solvent, there was obtained 15.0 g (41%) of analytically pure material.

1-[[2-(Diethylamino)ethyl]amino]-2-hydroxy-4-methylthioxanthenone (20). Method B. A suspension of 18.5 g of the 2-methoxythioxanthenone (**14**) and 50 mL of 48% HI was refluxed under N_2 for 20 h and cooled. The HI salt which separated was collected. In most cases the salt was recrystallized. The properties of these compounds are recorded in Table II. In some instances the hydroxythioxanthenones were obtained as free bases as described in the present instance. The crude HI salt was suspended in H_2O, and the suspension was made alkaline with K_2CO_3 and shaken thoroughly with $CHCl_3$. The organic layer was separated, washed with H_2O, dried, and concentrated to furnish an oil, which crystallized. Recrystallization from EtOH gave the pure base: yield 11.6 g (65%).

1-Chloro-2-hydroxy-4-methylthioxanthenone (12). A solution of 20 g (0.13 mol) of thiosalicylic acid and 35.7 g (0.25 mol) of 2-chloro-5-methylphenol in 1500 mL of concentrated H_2SO_4 was stirred overnight and then poured into a large volume of ice–water. The yellow solid was collected and then suspended in 7% NH_4OH. The suspension was heated with stirring to 90 °C and filtered hot. The thioxanthenone was crystallized from MeOH: mp 188–189 °C; yield 9.0 g (25%). Anal. ($C_{14}H_9ClO_2S$) C, H, N.

1-Chloro-2-(benzyloxy)-4-methylthioxanthenone (13). A suspension of 5.5 g (0.02 mol) of the 2-hydroxythioxanthenone (**12**), 2.5 mL (0.02 mol) of benzyl chloride, and 1.52 g (0.011 mol) of K_2CO_3 in 300 mL of MeOH was refluxed for 16 h. The cooled mixture was filtered. The solid that was collected was washed with H_2O, dried, and recrystallized from MeOH to give 4.0 g (55%) of the benzyl ether, mp 141–143 °C. Anal. ($C_{21}H_{15}ClO_2S$) C, H, N.

1-Chloro-4-hydroxythioxanthenone (25). A solution of 52.0 g (0.30 mol) of thiosalicylic acid, 65.0 g (0.50 mol) of *p*-chlorophenol, and 750 mL of concentrated H_2SO_4 was stirred overnight and poured into a large volume of ice–water. The solid that separated was washed with H_2O and then suspended in 7% NH_4OH. The suspension was heated with stirring on the steam bath and filtered hot. The solid was washed with H_2O and recrystallized from pyridine to give 30.4 g (39%) of the thioxanthenone, mp, 260–262 °C. Anal. ($C_{13}H_7ClO_2S$) C, H, Cl.

4-(Benzyloxy)-1-chlorothioxanthenone (26). A suspension of 9.48 g (0.04 mol) of (**25**), 5.0 mL (0.04 mol) of benzyl chloride, and 0.45 g (0.025 mol) of K_2CO_3 in 50 mL of MeOH was refluxed with stirring for 20 h. The cooled mixture was filtered, and the solid that was collected was washed with H_2O, dried, and crystallized from pyridine to afford 8.3 g (59%) of the benzyl ether, mp 140–141 °C. Anal. ($C_{20}H_{13}ClO_2S$) C, H, Cl.

1-[[2-(Dimethylamino)ethyl]amino]-4-hydroxythioxanthenone (31). Method B. A suspension of 5.0 g (0.014 mol) of 4-(benzyloxy)-1-chlorothioxanthenone, 15 mL of *N*,*N*-dimethylethylenediamine, and 5 mL of pyridine was refluxed overnight and worked up as described above. The crude base (**28**) melted at 174–175 °C after recrystallization from EtOH: yield 1.71 g (30%). A solution of 1.616 g (0.004 mol) of **28** and 10 mL of 48% HI was refluxed for 30 min, cooled, and filtered. The crude HI salt was suspended in H_2O and treated with K_2CO_3 and $CHCl_3$. The organic phase was separated, dried, and concentrated to give the free base, which melted at 177–178 °C after crystallization from MeOH: yield 430 mg (34%).

3-Methoxydithiosalicyclic Acid (36). A solution of 37.2 g (0.26 mol) of 2-amino-3-methoxybenzoic acid[11] (**33**) in 45 mL of concentrated HCl and 112 mL of H_2O was cooled to 5 °C and diazotized with a solution of 18.0 g of $NaNO_2$ in 63 mL of H_2O. The diazonium solution was filtered and added slowly to a cold solution of Na_2S_2 prepared from 58 g of $Na_2S \cdot 9H_2O$ dissolved in 65 mL of H_2O to which was added 7.6 g of S and 9.0 g of NaOH in 23 mL of H_2O. The mixture was left overnight, filtered, and cautiously acidified with 35 mL of concentrated HCl, whereupon 33.5 g (80%) of the dithio acid, suitable for the next step, was obtained. A small sample was recrystallized twice from EtOH, mp 200–205 °C. Anal. Calcd for $C_{16}H_{14}O_6S_2$: C, 52.46; H, 3.83. Found: C, 52.34; H, 4.32.

1-[[2-(Dimethylamino)ethyl]amino]-5-methoxy-4-methylthioxanthenone (43). A mixture of 32.2 g of 3-methoxydithiosalicylic acid (**36**), 89 mL of *p*-chlorotoluene, and 340 mL of concentrated H_2SO_4 was stirred overnight at room temperature and then at 60 °C for 2 h before being poured into ice–water. The neutral fraction which was a mixture of isomeric 5-methoxythioxanthenones was used directly in the next step.

A suspension of 1.5 g of the above thioxanthenones and 5 mL of *N*,*N*-dimethylethylenediamine was refluxed overnight and then worked up as usual to give the crystalline base, mp 176–177 °C after crystallization from EtOH: yield 300 mg.

5-Methoxydithiosalicylic Acid (37). Ten grams of 5-methoxyanthranilic acid[12] (**34**) was converted to the corresponding dithio acid as described above. There was obtained 8.5 g (78%)

of the desired dithio acid, mp 302–305 °C after two crystallizations from 2-methoxyethanol. Anal. ($C_{16}H_{14}O_6S_2$·$0.5H_2O$) C, H.

1-[[2-(Dimethylamino)ethyl]amino]-7-methoxy-4-methylthioxanthenone (45) and 1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-methylthioxanthenone (51). A mixture of 12.3 g of 5-methoxydithiosalicylic acid (**37**), 34 mL of *p*-chlorotoluene, and 130 mL of concentrated H_2SO_4 furnished 9.0 g of a mixture of isomeric 7-methoxythioxanthenones. A suspension of 3.2 g of this mixture in 8 mL of *N,N*-dimethylethylenediamine was refluxed overnight. The excess diamine was removed by distillation with steam. The residue was dissolved in glacial acetic acid, diluted with H_2O, and filtered to remove the unreacted 4-chloro-7-methoxy-1-methylthioxanthenone. Basification of the filtrate furnished the desired product (**45**): mp 141–143 °C after crystallization from EtOH; yield 1.55 g.

A suspension of 1.55 g of **45** in 12 mL of 48% HI was refluxed for 3 h, cooled, and filtered. Recrystallization from MeOH gave 1.7 g of the HI salt of **51**, mp 273–275 °C.

1-Chloro-7-methoxy-4-methylthioxanthenone (57). A solution of 28.3 g of 5-methoxyanthranilic acid[12] (**34**) in 34.0 mL of concentrated HCl and 85 mL of H_2O was diazotized with a solution of 11.8 g of $NaNO_2$ in 48 mL of H_2O. The filtered diazonium solution was added to a solution of Na_2S_2 prepared from 45 g of Na_2S·$9H_2O$, 5.8 g of S, 6.9 g of NaOH, and 70 mL of H_2O. The crude dithio acid (26.7 g) was suspended in 140 mL of glacial acetic acid and stirred under reflux with 6.5 g of Zn dust. During the course of the reduction, which took 5 h, two additional portions of 6.0 g of Zn dust in 20 mL of acetic acid were added. The suspension was cooled and filtered. The filter cake was washed with H_2O and then suspended in hot H_2O and treated with a solution of 10.0 g of NaOH in H_2O. The suspension was filtered through a bed of Celite, and the filtrate on acidification with HCl gave the crude thiosalicylic acid:[19] mp 172–175 °C after recrystallization from aqueous EtOH; yield 17.3 g.

A suspension of 14.0 g of the above acid, 17.3 g of 2-bromo-4-chlorotoluene, 16.2 g of K_2CO_3, 700 mg of KI, and 750 mg of Cu bronze in 190 mL of DMF was stirred under reflux for 18 h, cooled, and poured onto ice. The cold suspension was filtered (Celite) and extracted with ether. The aqueous phase was acidified to give 18.5 g of 2-[(5-chloro-2-methylphenyl)thio]-5-methoxybenzoic acid (**56**), mp 143–145 °C after two recrystallizations from aqueous EtOH. Anal. Calcd for $C_{15}H_{13}ClO_3S$: C, 58.34; H, 4.24. Found: C, 58.77; H, 4.13.

A solution of 1.0 g of the acid **56** in 5.0 mL of concentrated H_2SO_4 was heated with stirring on the steam bath for 1.5 h. It was poured into ice–water to give a solid, which melted at 230–265 °C after treatment with warm 7% NH_4OH. After recrystallization from acetic acid it melted at 280–287 °C: yield 320 mg. The NMR and IR spectra indicated that it was 1-chloro-4-methyl-7-hydroxythioxanthenone (**58**) prepared as described below. Concentration of the filtrate furnished 200 mg of 1-chloro-7-methoxy-4-methylthioxanthenone (**57**), mp 155–157 °C after recrystallization from EtOH. The NMR spectrum showed a signal for CH_3O. Anal. Calcd for $C_{15}H_{11}ClO_2S$: C, 61.96; H, 3.81. Found: C, 62.70; H, 3.80.

In another experiment 12.4 g of the crude thioxanthenone mixture was added to a suspension of 12.0 g of K_2CO_3 in 300 mL of MeOH. The suspension was stirred under reflux while a total of 25 mL of CH_3I was added over a period of 6 h. At the end of this time, the solvent was removed and the residue was washed with H_2O and crystallized from ethanol: mp 155–157 °C: yield 11.1 g. This material was used in the preparation of **60** and **61** (Table I).

1-[[2-(Methylamino)ethyl]amino]-7-methoxy-4-methylthioxanthenone (61). A suspension of 3.0 g of 1-chloro-7-methoxy-4-methylthioxanthenone (**57**) in 10 mL of *N*-methylethylenediamine was refluxed for 14 h. The mixture was cooled, diluted with 100 mL of H_2O, and distilled until about 50 mL of H_2O was collected. The residue was treated with a few milliliters of 50g KOH, and the gummy solid that separated was taken up in $CHCl_3$. The extract was dried and then chromatographed on silica gel. The $CHCl_3$ eluates were combined and evaporated to leave a crystalline substance, mp 152–155 °C after recrystallization from EtOH; yield 1.6 g. The diazepine structure (**65**) was tentatively assigned to this compound. Anal. ($C_{18}H_{18}N_2OS$) C, H, N.

On further elution using $CHCl_3$–3% MeOH, another crystalline substance was obtained: yield 518 mg; mp 94–98 °C. This is the desired product (**61**). It formed a fumarate, mp 217–219 °C after crystallization from MeOH. Refluxing the 7-methoxythioxanthenone (518 mg) with 3 mL of 48% HI for 3 h gave the corresponding 7-hydroxy derivative (**63**) as the HI salt, mp 278–280 °C after crystallization from MeOH: yield 550 mg.

1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-7-hydroxy-4-methylthioxanthenone (59). Method C. A suspension of 1.0 g of 1-chloro-7-methoxy-4-methylthioxanthenone (**57**) in 10 mL of acetic acid and 10 mL of 48% HI was refluxed for 2 h, cooled, and filtered. The solid was crystallized from 2-methoxyethanol to give 650 mg of 1-chloro-7-hydroxy-4-methylthioxanthenone (**58**), mp 297–299 °C dec. Anal. ($C_{14}H_9ClO_2S$) C, H.

A solution of 300 mg of **58**, 3.0 mL of *N*-(hydroxyethyl)ethylenediamine, and 3.0 mL of dry pyridine was refluxed for 16 h. It was diluted with H_2O and distilled until about 20 mL of distillate was collected. The cooled suspension was filtered, and the collected crystals were washed with H_2O, dried, and crystallized from EtOH: mp 189–191 °C; yield 200 mg.

1-[[2-(Diethylamino)ethyl]amino]-8-methoxy-4-methylthioxanthenone (46). A solution of 8.7 g of 6-methoxyanthranilic acid[13] (**35**) in 10.5 mL of concentrated HCl and 25.0 mL of H_2O was converted to the corresponding diazonium salt with a solution of 3.6 g of $NaNO_2$ in 15.0 mL of H_2O. The filtered solution was converted to the dithiosalicylic acid (**38**) by addition to a solution of Na_2S_2 prepared from 13.8 g of Na_2S·$9H_2O$, 2.1 g of NaOH, and 1.5 g of S in 20 mL of H_2O, followed by cautious acidification. The crude acid, **38**, so obtained[14] weighed 7.0 g, of which 5.4 g was converted to a mixture of 8-methoxythioxanthenones by stirring overnight with 19 mL of *p*-chlorotoluene and 64 mL of H_2SO_4. After the customary workup, there was obtained 3.5 g of a mixture of thioxanthenones.

A suspension of 5.7 g of the above mixture of thioxanthenones and 15 mL of *N,N*-diethylethylenediamine was refluxed for 17 h, cooled, diluted with H_2O, and subjected to distillation. After about 25 mL was collected, the cooled suspension was filtered. The gummy solid was dissolved in glacial acetic with warming, diluted with H_2O, and filtered. The basified filtrate yielded an oil, which was taken up in $CHCl_3$, dried, and chromatographed on silica gel using $CHCl_3$ and $CHCl_3$–MeOH as the eluates. The first crystalline fraction weighed 300 mg after crystallization from EtOH, mp 73–75 °C. The NMR spectrum showed all the expected signals except for a CH_3O group. The elementary analyses were those expected for the corresponding 8-hydroxy analogue **52**. Anal. ($C_{20}H_{24}N_2O_2S$·$0.25H_2O$) C, H, N.

The major fraction was eluted with $CHCl_3$ and $CHCl_3$–2% MeOH: yield 1.45 g; mp 93–96 °C after crystallization from EtOH. The NMR spectrum and elementary analyses were in agreement with the assigned structure (**46**).

1-[[2-(Dimethylamino)ethyl]amino]-6-methoxy-4-methylthioxanthenone (69). A suspension of 20.2 g of 4-methoxythiosalicylic acid[20] (**54a**), 25.0 g of 2-bromo-4-chlorotoluene, 23.4 g of K_2CO_3, 1.0 g of KI, and 1.1 g of Cu bronze in 275 mL of DMF was refluxed for 18 h. The mixture was cooled, diluted with H_2O, and extracted with ether. The aqueous phase was acidified to give the desired acid (**56a**), which, after crystallization from acetic acid, melted at 192–194 °C: yield 25.3 g.

A solution of 8.0 g of the above acid in 44 mL of concentrated H_2SO_4 was heated with stirring on the steam bath for 90 min. It was cooled and poured into ice–water, and the solid was collected. It was warmed with 7% NH_4OH, filtered, and dried: yield 5.0 g; mp 186–190 °C. Material of this quality was used to prepare the thioxanthenones **71** and **68** and 1-chloro-6-hydroxy-4-methylthioxanthenone (**67**).

A mixture of 400 mg of the above 6-methoxythioxanthenone (**66**) and 2.5 mL of *N,N*-dimethylethylenediamine was refluxed for 18 h and worked up in the usual way to give 300 mg of the

(19) F. O. Bennett, J. Johnson, and J. Tramondozzi, *Org. Prep. Proced. Int.*, **6**, 287 (1947).

(20) L. Katz, U.S. Patent 2 767 173 (Oct 16, 1956); *Chem. Abstr.*, **51**, P6704*b* (1957).

desired base, mp 130–133 °C. After recrystallization from EtOH, the base (**69**) melted at 130–132 °C.

1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-6-hydroxy-4-methylthioxanthenone (72). A solution of 1.0 g of 1-chloro-6-methoxy-4-methylthioxanthenone in 10 mL of acetic acid and 10 mL of 48% HI was refluxed for 2 h and then allowed to stand overnight. After two crystallizations from acetic acid, the 6-hydroxythioxanthenone (**67**) melted at 229–231 °C. Anal. ($C_{14}H_9ClO_2S$) C, H.

A suspension of 1.3 g of the above 6-hydroxythioxanthenone in 13.0 mL of *N*-(2-hydroxyethyl)ethylenediamine and 13.0 mL of pyridine was refluxed for 16 h. H_2O was added to the cooled mixture, which was then set up to distill, and about 35 mL of distillate was collected. After cooling, the solid was collected by filtration and crystallized three times from EtOH to give the desired base: yield 1.0 g; mp 193–195 °C.

Determination of Melting Temperatures of Drug–DNA Complexes. All solutions used were prepared in a low ionic strength buffer of 3.3×10^{-4} M Na_2HPO_4, 10^{-4} M sodium ethylenediaminetetraacetate, and 3×10^{-3} M NaCl at pH 6.8. The DNA solution concentration was approximately 20 μg/mL of calf thymus DNA (Sigma type 1). The exact concentration was determined spectrophotometrically.[21] Several milligrams of the drugs to be tested were weighed accurately and dissolved in 10 mL of the buffer solution. Varying volumes of the drug solutions ranging from 20 to 200 μL were added to 2.0-mL aliquots of the DNA solution so that the final drug concentrations ranged from 2 to 20 μmol/L.

The drug–DNA solutions were degassed at 50 °C under vacuum (20 torr) and placed in a water-jacketed cuvette of a Beckmann DB-G grating spectrophotometer. The temperature of the solution was raised at a rate of 1 °C/min, while absorbance was being read at 2 °C intervals at 260 nm. The results were plotted (A_{260nm} vs. temperature), and the T_m was taken as the midpoints of the curve between the high and low temperature constant–absorbance regions. Under these conditions the T_m of the uncomplexed DNA was 57.2 °C. Assuming that maximum intercalation occurs at a ratio of one drug molecule for every two base pairs, then at DNA concentrations of 20 μg/mL the maximum drug concentration for intercalation is 14.4 μmol/L. Beyond this limiting value, the drug does not intercalate but may bind electrostatically to phosphate residues. The secondary binding may cause a slight increase in the T_m of the drug–DNA complex. A series of T_m determinations were made at different drug–DNA ratios, and the T_m values were plotted vs. drug concentration (μmol/L). The T_m values reported in Table III are those read off at drug concentrations of 14.4 μmol/L or the point where the slope of the curve changed abruptly below this concentration.

Determination of Drug–DNA Association Constants. All solutions were prepared in a 0.009 M Tris–0.01 M NaCl buffer at pH 7.0. A crude DNA solution was prepared by dissolving 100 mg of the calf thymus DNA in 50 mL of buffer and dialyzing against 200-mL quantities of 4, 3, 2, and 1 M NaCl buffer and 0.1 M NaEDTA, and finally four times against the Tris buffer. After dialysis, the DNA solution was diluted to 100 mL with Tris buffer and frozen. Each week a new DNA portion was thawed, and the concentration was determined spectrophotometrically.[21]

Aliquots, 10 to 200 μL, of the DNA solution were added sequentially to 5 mL of a 5×10^{-5} M drug solution at room temperature. After equilibration, absorption at 448 nm was determined on a Gilford 240 single-beam spectrophotometer. Approximately 15 aliquots were added per run so that about 1 mL of DNA solution was added per 5 mL of drug solution. The results were plotted and K_{app}'s calculated as described by Double and Brown[7] and are recorded in Table III.

Acknowledgment. We are indebted to the National Cancer Institute of the National Institutes of Health for a grant (CA-19674) which supported most of the work reported here and also for the results of the antitumor tests.

(21) L. M. Angerer and E. M. Mourdrianakis, *J. Mol. Biol.*, **63**, 505 (1972).

Synthesis and Peripheral Cardiovascular Action of *cis*- and *trans*-2-(3,4-Dimethoxybenzyl)cyclopentylamine Hydrochlorides

Sonia R. Teller* and Charles H. Jarboe

Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, Louisville, Kentucky 40292.
Received July 24, 1981

The hydrochlorides of *cis*- and *trans*-2-(3,4-dimethoxybenzyl)cyclopentylamine have been synthesized. They are transient hypotensive agents with early and delayed depressor effects and antagonists of dopamine-induced vasodepression. In the atropinized and phenoxybenzamine-treated dog, the threshold dose for hypotension was 3–5 μmol/kg. The early depressor phases were attenuated variably by different types of antagonists, suggesting a nonspecific interaction with blood pressure regulation mechanisms. Cimetidine blocked the delayed depressor phases, consistent with endogenous histamine release. The cis amine hydrochloride was three to four times more potent than its trans isomer as a peripheral dopamine blocking agent. Cimetidine but not diphenhydramine interfered with this effect.

Dopamine cardiovascular pharmacology is of particular interest. The compound causes vasodepression in response to action at specific vascular receptors.[1,2] Vasodilation from inhibition of autonomic ganglionic transmission is attributed to specific dopamine receptors in sympathetic ganglia and postganglionic nerves.[3–5] The interaction of dopamine with α- and β-adrenergic receptors is also well documented,[1–3] and it has been postulated that there is a composite dopamine–serotonin receptor in the canine vasculature.[6]

In the central nervous system, dopamine is of significant importance in modulating motor, behavioral, and neuroendocrine functions. Dopamine agonists and antagonists have been used therapeutically in those diseases that involve either its apparent deficiency or superabundance.[7] Several types of dopamine-sensitive sites and receptors have been identified by specific radioligand binding assays and by correlation with biological response patterns to dopaminergic drugs.[8] Evidence favors the existence of

(1) L. I. Goldberg, *Pharmacol. Rev.*, **24**, 1 (1972).
(2) P. E. Setler, R. G. Pendleton, and E. Finlay, *J. Pharmacol. Exp. Ther.*, **192**, 702 (1975).
(3) L. I. Goldberg, P. H. Volkman, and J. D. Kohli, *Annu. Rev. Pharmacol. Toxicol.*, **18**, 57 (1978).
(4) S. Z. Langer, *Br. J. Pharmacol.*, **60**, 481 (1977).
(5) M. F. Lokhandwala and B. S. Jandhyala, *J. Pharmacol. Exp. Ther.*, **210**, 120 (1979).
(6) J. C. Gilbert and L. I. Goldberg, *J. Pharmacol. Exp. Ther.*, **193**, 435 (1975).
(7) J. R. Bianchine, G. M. Shaw, J. E. Greenwald, and S. M. Dandalides, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2434 (1978).

0022-2623/82/1825-0227$01.25/0