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Analogues of Hycanthone and Lucanthone as Antitumor Agents

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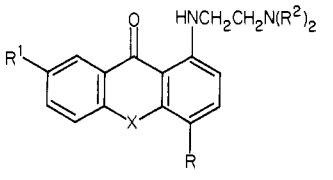
Hycanthone analogues (**5** and **6**) containing 7-substituted hydroxyl groups were prepared and evaluated as antitumor agents. These compounds were significantly more active than the corresponding unsubstituted derivatives. The 7-hydroxylated 4-(hydroxymethyl)-9*H*-xanthen-9-ones, **11** and **12**, were also active antitumor agents. However, the 7-hydroxy-9*H*-xanthen-9-one counterparts of the 7-hydroxylucanthones were totally devoid of antitumor activity. Results obtained thus far are consistent with the hypothesis that 4-hydroxymethyl substituents in the 9*H*-xanthen-9-one and 9*H*-thioxanthen-9-one series are required for antitumor activity.

In a previous paper[1] in which the synthesis and antitumor activity of some ring-hydroxylated analogues of lucanthone were described, it was mentioned that Hirschberg[2] found that hycanthone (**1**), the active metabolite of



X = S

1, R = CH_2OH; R^1 = H; R^2 = C_2H_5 (hycanthone)
2, R = CH_3; R^1 = H; R^2 = C_2H_5 (lucanthone)
3, R = CH_3; R^1 = OH; R^2 = C_2H_5
4, R = CH_3; R^1 = OH; R^2 = CH_3
5, R = CH_2OH; R^1 = OH; R^2 = C_2H_5
6, R = CH_2OH; R^1 = OH; R^2 = CH_3
7, R = CH_2OH; R^1 = H; R^2 = CH_3

X = O

8, R = CH_3; R^1 = H; R^2 = C_2H_5
9, R = CH_3; R^1 = OH; R^2 = C_2H_5
10, R = CH_3; R^1 = OH; R^2 = CH_3
11, R = CH_2OH; R^1 = OH; R^2 = C_2H_5
12, R = CH_2OH; R^1 = OH; R^2 = CH_3

lucanthone (**2**), was an antitumor agent in L-1210 mice. Just as in the case of lucanthone, the antitumor activity of **1** was abolished by pretreatment of the leukemic mice with SKF-525A. In the same paper,[1] it was reported that 7-hydroxylucanthone (**3**) and its dimethyl analogue (**4**) were more active than lucanthone in the NCI P-388 antitumor screening test. On the basis of this finding as well as for other reasons, we synthesized 7-hydroxyhycanthone (**5**) and its dimethylamino analogue (**6**) (Scheme I) and submitted them to the NCI for evaluation for antitumor activity. The dimethylamino analogue (**7**) of hycanthone was prepared for comparison with **6**.

Miracil A (**8**) exhibited schistosomicidal activity in mice.[3] Since this drug differs from lucanthone (**2**) only by having an oxygen substituted for a sulfur atom, it was expected that **8**, would be an intercalating agent also and show some antitumor activity. Since 7-hydroxylation of **2** markedly increased antitumor activity, it was thought desirable to prepare a group of 7-hydroxyxanthenones (**9–12**) and compare their antitumor activity with their sulfur analogues.

Chemistry. The synthesis of 7-hydroxyhycanthone (**5**) and its dimethylamino analogue (**6**) is shown in Scheme I.

5-Methoxythiosalicylic acid (**13**) was prepared by reduction of the corresponding 5-methoxydithiosalicyclic acid[1] with zinc dust in acetic acid. Condensation with **14** gave the (phenylthio)benzoic acid **15**, which, after cyclization with H_2SO_4 afforded a mixture of the methoxy-9*H*-thioxanthen-9-ones **16** and **17**. NMR spectroscopy revealed that **16** and **17** were contaminated with substantial quantities of their corresponding demethylated products. Methylation of the crude cyclization mixture converted the phenols to the methyl ethers **16** and **17**. Previously, we had observed that when 5-methoxydithiosalicylic acid was condensed with *p*-chlorotoluene in sulfuric acid, the chloromethoxy-9*H*-thioxanthen-9-ones were contaminated with appreciable amounts of phenolic thioxanthenones.[1] Treatment of the 9*H*-thioxanthen-9-ones, **16** and **17**, with *N*,*N*-diethylethylenediamine gave a mixture of 3-[[2-(diethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one (**18**) and 1-[[2-(diethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one (**19**) in which the latter predominated. These isomers were separated by means of column chromatography. When *N*,*N*-dimethylethylenediamine was used, only **20** was isolated, unaccompanied by the 3-substituted isomer. Treatment of either **19** or **20** with formaldehyde and dilute acetic acid according to the procedure of Rosi et al.[4] furnished the hydroxymethyl derivatives **21** and **22**. In view of the acid sensitivity of hycanthone,[5] it seemed unlikely that either **21** or **22** would survive an acidic demethylation procedure. These hydroxymethyl derivatives were oxidized with MnO_2 to the aldehydes **23** and **24**, which were demethylated with pyridine hydrochloride to the corresponding 7-hydroxy-9*H*-thioxanthen-9-one aldehydes **25** and **26**. These, in turn, reduced readily with $NaBH_4$ to give the desired hycanthone analogues **5** and **6**.

The demethylation that occurred during the H_2SO_4 cyclization complicated the workup in the synthesis, but more serious was the poor overall conversion of **19** to the target compound, **5**. A modified procedure, shown in Scheme II, was used first to synthesize the xanthenones **11** and **12** and then to prepare additional quantities of **5** and **6**.

Condensation of commercially available 5-methoxysalicylic acid (**27**) with *m*-chloroiodobenzene (**28**) gave the phenoxy acid **29**, cyclization of which with polyphosphoric acid furnished a mixture of the methoxy-9*H*-xanthen-9-ones **30** and **31**. Little, if any, demethylation occurred when this reagent was used for cyclization. Treatment of the mixture of chloromethoxy-9*H*-xanthen-9-ones with *N*,*N*-diethylethylenediamine or *N*,*N*-dimethylethylenediamine gave the amines **32** and **33**, respectively. None of the isomeric 3-[[(dialkylamino)alkyl]amino]-9*H*-

(1) Archer, S.; Miller, K. J.; Rej, R.; Perana, C.; Fricker, L. *J. Med. Chem.* **1982**, *25*, 220.
(2) Hirschberg, E. *Antibiotics* **1974**, *3*, 274.
(3) Kikuth, W.; Gonnert, R. *Ann. Trop. Med. Parasitol.* **1948**, *42*, 256. Mauss, H. *Chem. Ber.* **1948**, *81*, 19.
(4) Rosi, D.; Collins, J. C.; Miller, T. C. U.S. Patent 3711512, 1973.
(5) Rosi, D.; Perruzzotti, G.; Dennis, E. W.; Berberian, D. A.; Freele, H.; Archer, S. *J. Med. Chem.* **1967**, *10*, 867.

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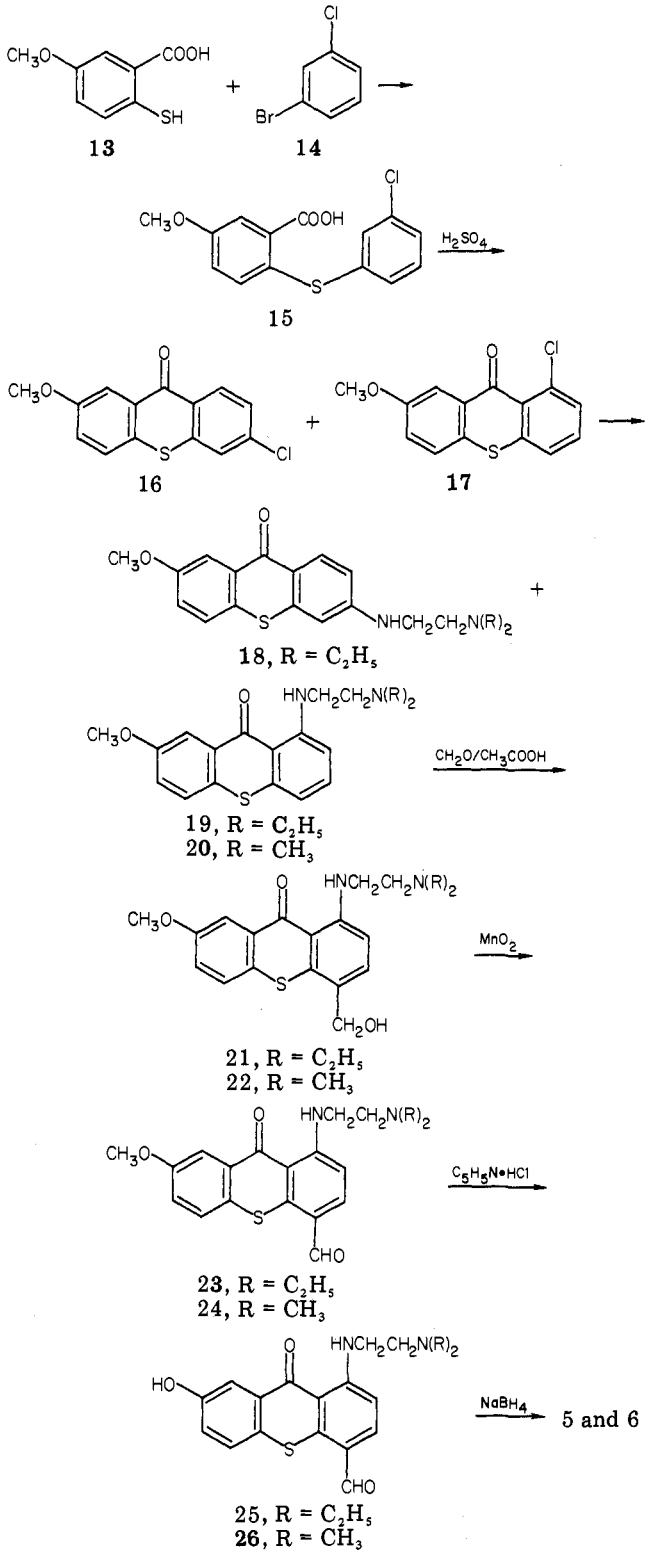
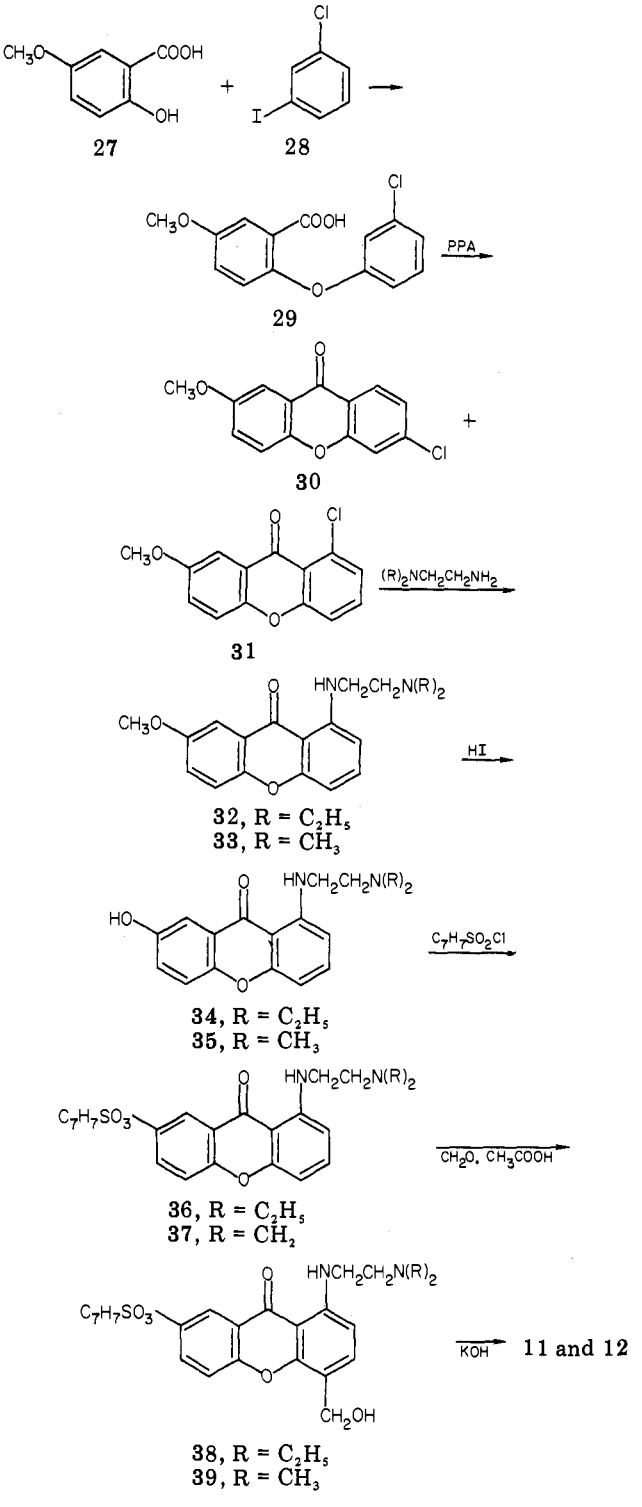
Scheme I



xanthen-9-ones was obtained. Demethylation with HI proceeded in high yield to give **34** and **35**, which were converted to the tosylates **36** and **37**. Hydroxymethylation with formalin–dilute acetic acid afforded the benzylic alcohols **38** and **39**, which were hydrolyzed to give xanthenones **11** and **12**. This sequence resulted in a marked improvement in overall yield and was employed to prepare **5** and **6** as described in the Experimental Section.

The 7-hydroxy-9*H*-xanthen-9-ones **9** and **10** were prepared according to the reaction sequence shown in Scheme III.

Scheme II

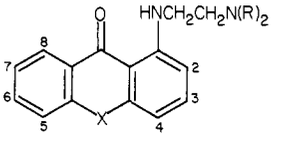


Condensation of **27** with 3-iodo-4-methyl-1-chlorobenzene[6] (**40**) gave **41**, which on cyclization in H_2SO_4 furnished **42**. Treatment of the latter with either *N,N*-diethylethylenediamine or *N,N*-dimethylethylenediamine gave **43** and **44**, respectively. Demethylation with HI proceeded smoothly to give the desired 9*H*-xanthen-9-ones **9** and **10**, which were isolated as their HI salts.

The dimethylamino analogue, **7**, of hycanthone was prepared as follows: thiosalicylic acid was condensed with *m*-bromochlorobenzene to give 2-[(3-chlorophenyl)thio]-benzoic acid, which was cyclized in H_2SO_4 to a mixture of

(6) Long, R.; Dains, M. *Univ. Kans. Sci. Bull.* **1930**, *19*, 205.

Table I. Chemical and Biological Data of the 9*H*-Xanthen-9-one and 9*H*-Thioxanthen-9-one Analogues



no.	ring substituents	X	R	emp formula[a]	mp, °C	in vivo antitumor act. vs P-388 lymphocytic leukemia[b] dose, mg/kg	T/C
1	(hycanthone)	S	C_2H_5			60	165
2	(lucanthone)	S	C_2H_5			100	158
5	4-CH_2OH, 7-OH	S	C_2H_5	$C_{20}H_{24}N_2O_3S$	182–184	75.0	207[c]
						37.5	179
						18.75	207
						9.88	163
6	4-CH_2OH, 7-OH	S	CH_3	$C_{18}H_{20}N_2O_3S$	>350 dec	200	222
						100	194
						50	175
						25	160
7	4-CH_2OH	S	CH_3	$C_{18}H_{20}N_2O_2S$	192–194	100	150
						50	114
						25	94
9	4-CH_3, 7-OH	O	C_2H_5	$C_{20}H_{24}N_3O_3 \cdot HI$	240–242 dec	50	117[d]
						25	106
						12.5	106
10	4-CH_3, 7-OH	O	CH_3	$C_{18}H_{20}N_3O_3 \cdot HI$	285–288 dec	50	108[d]
						25	106
						12.5	99
11	4-CH_2OH, 7-OH	O	C_2H_5	$C_{20}H_{24}N_2O_4$	186–187	200	163
						100	214
						50	181
12	4-CH_2OH, 7-OH	O	CH_3	$C_{18}H_{20}N_2O_4$	144 dec	200	128
						100	198
						50	170

[a] Analyses for C, H, and N for all compounds listed are within ±0.3% of the calculated values. All compounds listed were purified by crystallization from MeOH. [b] Standard NCI protocols were used (see ref 7). The medication schedule for hycanthone and lucanthone was once a day for 9 days. For all others, the mice were treated once a day for 5 days. No deaths were noted at the doses listed. [c] The drug was administered for only 2 days. On day 1 and day 4, postinoculation. [d] Deaths occurred in the groups treated with 100 and 200 mg/kg.

1-chloro- (**45**) and 3-chloro-9*H*-thioxanthen-9-one (**46**). Condensation with *N*,*N*-dimethylethylenediamine furnished 1-[[2-(dimethylamino)ethyl]amino]-9*H*-thioxanthen-9-one (**47**). Treatments with formalin in dilute acetic acid give **7**.[12] Treatment with MnO_2 gave the corresponding aldehyde, which on reduction with $NaBH_4$ gave **7**.

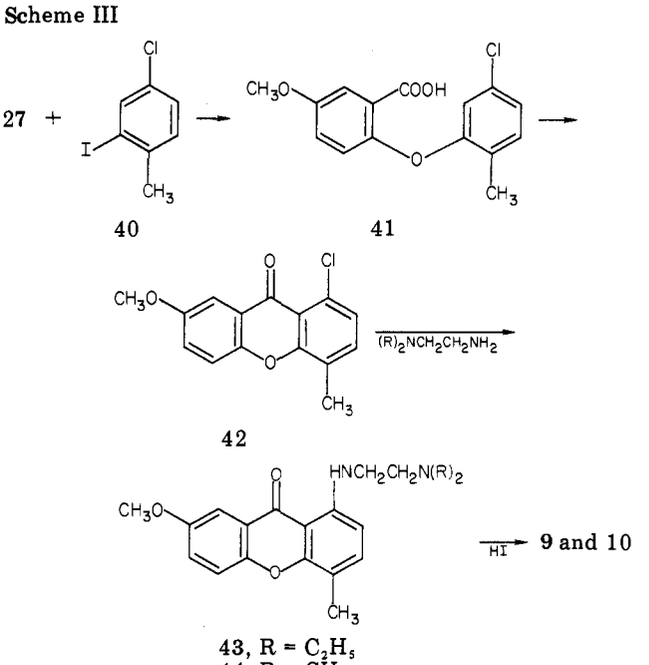
The mixed chloro-9*H*-thioxanthen-9-ones **45** and **46** were treated with *N*,*N*-dimethylethylenediamine to furnish **47**, which was hydroxymethylated to give **7**. Oxidation with MnO_2 gave the corresponding aldehyde, which on reduction with $NaBH_4$ gave **7**.

The physical properties and antitumor activity of the target compounds are summarized in Table I.

Biological Results

All compounds listed in Table I were submitted to the National Cancer Institute for evaluation in the P-388 antitumor screen.[7] The historical data on lucanthone and hycanthone are included for comparative purposes.[8] Comparisons between the current data and those obtained previously were complicated by the fact that a modification of the standard NCI protocol was introduced in October, 1980. At that time the medication period was shortened from 9 days to 5 days. Nevertheless, it is clear from inspection of the data in Table I that 7-hydroxyhycanthone (**5**) is more active than hycanthone (**1**) and that the di-

Scheme III



(7) Geran, R. L.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2), 1.

(8) We thank Drs. Harry Wood and Betty J. Abbott of the NCI for furnishing these data.

methylamino compound, **6**, is more active than the corresponding nonhydroxylated analogue, **7**. It should be noted that just as in the lucanthone series, 7-hydroxylation increased antitumor activity.

It is not completely clear that compounds of the hycanthone series are more active than their counterparts in the lucanthone series. It appears that 7-hydroxyhycanthone (**5**) (T/C = 207 at 18.75 mg/kg for 2 days) is more active than 7-hydroxylucanthone (**3**) (T/C = 188 at 50 mg/kg for 9 days),[1] but the results with the dimethylamino analogues are equivocal [compound **6** T/C = 222 at 200 mg/kg for 5 days vs. 1-[[2-(dimethylamino)ethyl]-amino]-7-hydroxy-4-methyl-9*H*-thioxanthen-9-one (**4**) T/C = 265 at 64 mg/kg for 9 days).[1] The link between the two series cannot be established on the basis of these data. The connection was established from the antitumor results in the xanthenone series. It can be seen from Table I that the hycanthone analogues **11** and **12** are active antitumor agents with T/C values of 214 (100 mg/kg) and 198 (100 mg/kg), respectively. These values compare favorably with the antitumor results found for their sulfur counterparts **5** and **6**. On the other hand, the 4-methyl-9*H*-xanthen-9-ones **9** and **10**, which are the oxygen analogues of 7-hydroxylucanthones, are totally inactive! The simplest interpretation of these findings is that the 4-hydroxymethyl group is essential for antitumor activity and, in contrast to their corresponding lucanthone analogues, the 4-methyl-7-hydroxy-9*H*-xanthen-9-ones are not substrates for murine mixed-function oxidase(s) required to effect this biooxidation. This substrate specificity has been encountered previously. For example, it was found that mice convert 6-chlorolucanthone to 6-chlorohycanthone, whereas this biooxidation does not occur in monkeys.[9]

Our results to date in the 9*H*-thioxanthen-9-one series are best rationalized in the following way. In order for either lucanthone (**2**) or hycanthone (**1**) to exhibit antitumor activity, they must be biotransformed to **5**. In the case of **1**, there is a direct hydroxylation pathway to **5**. Lucanthone may either be oxidized first to **3**, which is then transformed to **5**, or, alternately, it may be oxidized first to hycanthone, which is then converted to **5**. Aromatic and methyl group hydroxylations can be effected by mixed-function oxidases and are susceptable to inhibition by SKF-525A.[10] If the biooxidation of **1** and **2** to **5** is obligatory for these drugs to exert their antitumor action, then Hirschberg's observation[2] that SKF-525A abolishes the antitumor action of **1** and **2** can be accounted for. Work in progress in our laboratory suggests that rather than being the ultimate biotransformation product responsible for the antitumor activity of **1** and **2**, **5** is instead an essential stage in the metabolic pathway to the proximate active antitumor metabolite.

Experimental Section

Melting points were taken on a 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-61A spectrometer in either $CDCl_3$ or $(CD_3)_2SO$ solution with Me_4Si as an internal standard. Elementary analyses were determined by Spang Microanalytical Laboratory Eagle Harbor, MI.

5-Methoxythiosalicyclic Acid (13). A suspension of 1.0 g of 5-methoxydithiosalicylic acid[1] and 500 mg of Zn dust in 10.0 mL of acetic acid was vigorously stirred under reflux for 4 h. During this time an additional 500 mg of Zn dust and 5.0 mL of acetic acid were added. The mixture was cooled and filtered. The solid was washed with water, air-dried, and suspended in 40 mL of boiling H_2O. A solution of 4.0 g of NaOH in 10 mL of H_2O was added carefully while the suspension was kept under reflux. The warm suspension was filtered, and the filtrate was acidified to precipitate the desired acid: yield 600 mg (60%); mp 170–175 °C. After two crystallizations from C_2H_5OH–H_2O, a sample melted at 173–178 °C. Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 51.62; H, 4.33. When run on an 11.0-g scale, there was obtained, after one crystallization from EtOH–H_2O, 7.0 g of the acid (64%), mp 174–178 °C.

2-[(3-Chlorophenyl)thio]-5-methoxybenzoic Acid (15). A suspension of 3.50 g (19 mmol) of 5-methoxythiosalicylic acid, 4.03 g of 3-chloro-1-bromobenzene, 186 mg of Cu-bronze, and 4.05 g of K_2CO_3 in 45 mL of DMF was stirred under reflux for 18 h. The cooled mixture was poured onto ice–water and then filtered through a bed of Celite. The filtrate was extracted with ether, and after the layers were separated, the aqueous portion was acidified carefully with 3 N HCl. The crystalline solid that separated was collected and dried: yield 4.3 g (77%); mp 140–148 °C. After two recrystallizations from C_2H_5OH–H_2O, the acid melted at 150–153 °C. Anal. ($C_{14}H_{11}ClO_3S$) C, H.

1-Chloro- (17) and 3-Chloro-7-methoxy-9*H*-thioxanthen-9-one (16). A suspension of 3.2 g (10.8 mmol) of 2-[(3-chlorophenyl)thio]-5-methoxybenzoic acid in 20 mL of H_2SO_4 was heated on a steam bath at 90 °C with stirring for 90 min, cooled, and poured onto ice. The solid was filtered, sucked as dry as possible, and suspended in hot 7% NH_4OH. The suspension was filtered to give 2.7 g of crude 9*H*-thioxanthen-9-ones. The NMR spectrum indicated that the signal for OCH_3 was not as strong as expected. The solid was suspended in 50 mL of acetone, to which 5.4 g of K_2CO_3 and 4.0 mL of CH_3I were added. The mixture was heated with stirring under reflux for 6 h. At the end of this time, it was evaporated to dryness in vacuo. The residue was shaken with H_2O and filtered, and the solid was dried. After recrystallization from 2-methoxyethanol, the solid weighed 2.06 g. After one more crystallization, it melted over the range of 125–180 °C. Anal. ($C_{14}H_9ClO_2S$) C, H.

Ten grams (34 mmol) of 2-[(3-chlorophenyl)thio]-5-methoxybenzoic acid was added portionwise to 40 mL of 50% polyphosphoric acid, which was being stirred at 130 °C. After 4 h, the solution was cooled and poured onto ice–water. The suspension was filtered, and the solid was washed with hot H_2O and dried to give 8.2 g (87%) of the mixed 9*H*-thioxanthen-9-ones. NMR spectroscopy indicated that no demethylation had occurred. After crystallization from 2-methoxyethanol, the solid melted at 155–171 °C.

1-[[2-(Diethylamino)ethyl]amino]- (19) and 3-[[2-(Diethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one (18). A mixture of 360 mg (1.3 mmol) of the mixed 9*H*-thioxanthen-9-ones **16** and **17** and 3.0 mL of *N*,*N*-diethylethylenediamine was heated under reflux for 18 h while protected from moisture. The suspension was cooled and poured into H_2O, and 10 mL of 20% KOH was added. The apparatus was set for downward distillation, and 20 mL of distilate was collected. The cooled suspension was made acidic with acetic acid, diluted to 75 mL, and filtered. The filtrate was made basic, and the oil that separated was extracted with $CHCl_3$. The dried extracts were evaporated to dryness to leave an oil, which was chromatographed on a column of 20 g of silica gel. The desired product was eluted with $CHCl_3$: yield 120 mg; mp 71–73 °C, which after crystallization from C_2H_5OH melted at 71–72 °C. Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N.

The next fraction was eluted with $CHCl_3$–CH_3OH (19:1). The NMR indicated that it was the 3-isomer. It formed a fumarate, mp 172–174 °C, after crystallization from absolute EtOH. Anal. ($C_{20}H_{24}N_2O_2S \cdot C_4H_4O_4$) C, H, N.

When run on a 2.06-g scale, there was obtained 1.08 g of **19** (41%), mp 71–73 °C after chromatography on silica gel.

1-[[2-(Dimethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one (20). A suspension of 5.0 g (18 mmol) of the mixed 9*H*-thioxanthen-9-ones **16** and **17**, 17.0 mL of dry pyridine, and 3.0 mL of *N*,*N*-dimethylethylenediamine was refluxed for 18 h, protected from moisture, and worked up as in the above experiment. Chromatography on silica gel with $CHCl_3$–CH_3OH gradients as the elution solvent furnished 1.80 g (30.5%), mp 109–112 °C. After crystallization from C_2H_5OH it melted at 113–114 °C. Anal. ($C_{18}H_{20}N_2O_2S$) C, H, N.

(9) Archer, S.; Yarinsky, A. *Prog. Drug Res.* **1972**, *16*, 11.
(10) Testa, B.; Jenner, P. "Drug Metabolism"; Marcel Dekker: New York and Basel, 1976.

1-[[2-(Diethylamino)ethyl]amino]-4-(hydroxymethyl)-7-methoxy-9*H*-thioxanthen-9-one (21). A solution of 2.70 g (7.5 mmol) of 1-[[2-(diethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one (**19**) in 135 mL of 37% formalin containing 2.7 mL of 5 N acetic acid was heated on the steam bath for 4 h, cooled, and made alkaline with 10 N NaOH solution. The suspension was taken up in $CHCl_3$. The extract was evaporated to dryness and covered with C_2H_5OH. The "dimer" separated: yield 400 mg. It was recrystallized from 2-methoxyethanol.[10] The filtrate was evaporated to dryness to leave an oil, which, after chromatography on silica gel with $CHCl_3$–CH_3OH as the eluant, furnished 1.30 g (44.5%) of the desired product, mp 103–105 °C after crystallization from ethyl acetate–petroleum ether. Anal. ($C_{21}H_{26}N_2O_3S$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-4-(hydroxymethyl)-7-methoxy-9*H*-thioxanthen-9-one (22). A solution of 100 mg (0.30 mmol) of 1-[[2-(dimethylamino)ethyl]amino]-7-methoxy-9*H*-thioxanthen-9-one in 5 mL of 37% formalin and 0.1 mL of 5 N acetic acid was heated on a steam bath for 4 h as in the case of the diethylamino analogue (**21**). The reaction mixture was worked up as directly above. Little, if any, of the "dimer" was isolated. Chromatography on silica gel with $CHCl_3$–CH_3OH as the eluting solvent gave 7.0 mg of starting material and 37 mg (35%) of the desired product, **22**, which melted at 153–156 °C after crystallization from C_2H_5OH. Anal. ($C_{19}H_{22}N_2O_3S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-methoxy-9-oxo-9*H*-thioxanthene-4-carboxaldehyde (23). A solution of 1.25 g (0.32 mmol) of the (hydroxymethyl)thioxanthenone **21** in 300 mL of dry ether was treated with 2.60 g of activated MnO_2 and stirred under reflux for 2 h in a vessel protected from moisture. The suspension was stirred overnight at room temperature and filtered. The filtrate was evaporated to dryness, and the residue was chromatographed on 40 g of silica gel with $CHCl_3$–CH_3OH as the eluting solvent. The aldehyde **23** was eluted in the $CHCl_3$–3% CH_3OH fraction: yield 0.8 g (64%); mp 125–127 °C. The analytical sample (melting point unchanged) crystallized from C_2H_5OH. Anal. ($C_{21}H_{24}N_2O_3S$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-methoxy-9-oxo-9*H*-thioxanthene-4-carboxaldehyde (24). The same procedure as described directly above was used. A total of 1.20 g (3.0 mmol) of **22** furnished the aldehyde **24**, which was eluted from the silica gel column with $CHCl_3$–2% CH_3OH: yield 600 mg (50%). The analytical sample, mp 170–172 °C, was prepared by recrystallization from C_2H_5OH. Anal. ($C_{19}H_{20}N_2O_3S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-9-oxo-9*H*-thioxanthene-4-carboxaldehyde (25). A mixture of 600 mg (1.56 mmol) of the methoxyaldehyde **23** and 6.0 g of pyridine hydrochloride was heated at 140 °C for 3.5 h in a vessel protected from moisture. The mixture was cooled and treated with H_2O. The clear aqueous solution was made alkaline by the cautious addition of solid K_2CO_3. The suspension was extracted with $CHCl_3$, and the solvent was removed by evaporation. The residue was chromatographed on a column of silica gel (30 g). The eluant solvent was $CHCl_3$–CH_3OH. There was recovered the starting material in the $CHCl_3$/1–2% CH_3OH. The $CHCl_3$/4–7% CH_3OH fractions furnished 100 mg of a crude product, which, after crystallization from 95% C_2H_5OH, furnished 77 mg (13% as the hydrate) of the hydroxy aldehyde, mp 85–90 °C. Anal. Calcd for $C_{20}H_{22}N_2O_3S \cdot H_2O$: C, 61.83; H, 6.23; N, 7.21. Found: C, 62.31; H, 5.77; N, 7.09.

Increasing the temperature to 165 °C caused extensive decomposition. Increasing reaction times beyond 3.5 h at 140 °C did not materially increase the yield of **25**.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-9-oxo-9*H*-thioxanthene-4-carboxaldehyde (26). A mixture of 4.13 g (12 mmol) of the methoxyaldehyde **24** and 55 g of pyridine hydrochloride was heated at 185 °C for 1.5 h in a vessel protected from moisture. The cooled mixture was diluted with H_2O, and the crystals were collected by filtration. These were dissolved in H_2O, and the solution was made alkaline with K_2CO_3. The crop of crystals that separated was set aside. The filtrate from the original filtration was made alkaline with K_2CO_3 and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract left a crystalline residue, which was combined with the first crop of crystals: yield 3.4 g (83%); mp 219–220 °C. After two crystallizations from C_2H_5OH, the compound melted at 223–225 °C. Anal. ($C_{18}H_{18}N_2O_3S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (5). To a solution of 85 mg (0.23 mmol) of the aldehyde **25** in 20 mL of CH_3OH was added 40 mg of $NaBH_4$ in one portion. After the solution was stirred at room temperature for 1.0 h, the solvent was evaporated in vacuo, and H_2O was added to the residue. The suspension was adjusted to pH 8 by careful addition of dilute acetic acid, and the crystals that separated were collected and recrystallized from CH_3OH: yield 46 mg (54%); mp 182–184 °C.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (6). The above procedure was used. A solution of 650 mg (1.9 mmol) of **26** in 400 mL of CH_3OH was reduced with 400 mg of $NaBH_4$. The crystals that were obtained were purified by crystallization from CH_3OH: yield 500 mg (77%); mp >350 °C dec.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-9*H*-thioxanthen-9-one. A solution of 1.50 g (4.2 mmol) of **19** in 15 mL of 56% HI solution was refluxed for 3 h and cooled. The crystals that separated were collected, washed with ether, and dried. They were dissolved in 10% NaOH, the solution was filtered, and the filtrate was neutralized with dilute acetic acid. The suspension was extracted with $CHCl_3$, and the dried extract was evaporated to leave 1.22 g (83%) of the phenol, which melted at 157–158 °C after crystallization from 70% aqueous methanol. Anal. ($C_{19}H_{22}N_2O_2S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one. To a stirred solution of 1.40 g (4.1 mmol) of the above 9*H*-thioxanthen-9-one and 15.0 mL of dry pyridine there was added 0.95 g (5.0 mmol) of toluenesulfonyl chloride. The reaction mixture was stirred at room temperature in a flask protected from moisture for 1 h. The contents were then poured into cold water, and the suspension was extracted with ether. The extract was washed with water, dried, and evaporated to dryness to leave an oil: yield 2.0 g (99%). It was characterized as a crystalline fumarate, mp 127–128 °C after crystallization from CH_3OH. Anal. ($C_{26}H_{28}N_2O_4S_2 \cdot C_4H_4O_4$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one. A suspension of 4.0 g (12 mmol) of the methoxythioxanthenone **20** in 40 mL of 56% HI was refluxed for 3 h and worked up as described above to give 2.70 g (71%) of the phenol, mp 175–177 °C after crystallization from C_2H_5OH. A stirred solution of 2.3 g (7.3 mmol) of the crude phenol in 20 mL of dry pyridine was treated with 1.6 g (8.3 mmol) of *p*-toluenesulfonyl chloride. The reaction mixture was worked up as described above to give 1.95 g (86%) of the tosylate, mp 118–119 °C after crystallization from C_2H_5OH. Anal. ($C_{24}H_{24}N_2O_4S_2$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-4-(hydroxymethyl)-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one. A solution of 1.48 g (2.98 mmol) of the oily (toluenesulfonyloxy)-9*H*-thioxanthen-one, 3 mL of 5 N acetic acid, and 150 mL of 37% formalin was stirred while being heated at 60–70 °C for 48 h. The cooled mixture was made alkaline with Na_2CO_3 solution and extracted with $CHCl_3$. The dried extract was evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$/CH_3OH as the eluant. Some starting material was recovered from the early fractions. Later fractions yielded the desired hydroxymethyl derivative: yield 0.58 g (37%); mp 129–130 °C after crystallization from CH_3OH. Anal. ($C_{27}H_{30}N_2O_5S_2$) C, H. N.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (5) from the Toluenesulfonate. A solution of 0.51 g (0.096 mmol) of the above ester in 15 mL of C_2H_5OH containing 1.5 mL of 5 N KOH was refluxed for 1 h. The solvent was evaporated, and the residue was dissolved in 50 mL of H_2O and filtered (Celite). The clear filtrate was neutralized, and the precipitate was collected and crystallized from CH_3OH: yield 0.26 g (72%); mp 181–182 °C.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (6). A solution of 2.5 g (5.3 mmol) of the toluenesulfonate in 400 mL of 37% formaldehyde containing 20 mL of 20% acetic acid was heated at 70–80 °C for 72 h. The reaction mixture was worked up as above. Elution of the silica gel column with $CHCl_3$/1% CH_3OH removed some starting material. The product was eluted with $CHCl_3$/3–6%

CH_3OH: yield 1.7 g (64%); mp 175–176 °C after crystallization from absolute C_2H_5OH. Anal. ($C_{25}H_{26}N_2O_5S_2$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (6) from the Toluenesulfonate. Two grams (4.0 mmol) of the above ester was dissolved in 20 mL of C_2H_5OH, and 5 mL of 5 N KOH was added. After the solution was refluxed for 30 min, the solvent was evaporated and worked up as described above to leave 1.3 g (92%) of **6**, which after crystallization from absolute C_2H_5OH melted indefinitely with decomposition. It was identical in all respects with the sample prepared by the method outlined in Scheme I.

1-[[2-(Dimethylamino)ethyl]amino]-4-(hydroxymethyl)-9*H*-thioxanthen-9-one (7). A suspension of 26.8 g of a mixture of 1-chloro- and 3-chloro-9*H*-thioxanthen-9-ones **45** and **46**, 17.9 mL of *N,N*-dimethylethylenediamine, and 100 mL of dry pyridine was refluxed for 18 h and worked up in the usual way[11] to give 11 g of 1-[[2-(dimethylamino)ethyl]amino]-9*H*-thioxanthen-9-one (**47**). Five grams of this base was dissolved in 250 mL of 37% formalin and 10 mL of 5 N acetic acid. The mixture was heated on the steam bath for 3 h and worked up in the usual way. After the $CHCl_3$ extracts were evaporated to dryness, the residue was covered and warmed with a $CHCl_3/CH_3OH$ solution. The insoluble residue, mp 191–196 °C, yield 2.4 g, was filtered, and the filtrate was taken to dryness and chromatographed to give an additional 1.4 g of material: total yield 3.8 g (69%) of slightly impure material.

A solution of 1.2 g of the above compound was dissolved in 200 mL of CH_2Cl_2, and 2.4 g of activated MnO_2 was added. The mixture was stirred under reflux for 2 h, and stirring was continued overnight. The solution was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel with $CHCl_3/CH_3OH$ as the eluting solvent mixture. There was obtained 0.5 g (42%) of the desired aldehyde, mp 160–162 °C after crystallization from ethanol. Anal. ($C_{18}H_{20}N_2O_2S$) C, H, N.

A solution of 50 mg of the above aldehyde in 20 mL of CH_3OH was treated with 50 mg of $NaBH_4$. After 30 min, the mixture was evaporated to dryness, and the residue was covered with H_2O. The pH was adjusted to 8, and the crystals were filtered. After recrystallization from CH_3OH, the hydroxymethyl compound **7** melted at 192–194 °C.

2-(3-Chlorophenoxy)-5-methoxybenzoic Acid (29). A suspension of 18.0 g (0.11 mol) of 5-methoxysalicylic acid (**27**) and 28 g of dry K_2CO_3 in 200 mL of dry DMF was heated at 120 °C for 10 min. Then, 25 g (0.11 mol) of *m*-chloroiodobenzene, 0.5 g of Cu powder, and 0.3 g of CuI were added. The mixture was heated and stirred under reflux for 50 h. The cooled suspension was filtered, and the filtrate was concentrated in vacuo to a small volume. The residue was treated with H_2O and then acidified with HCl. The oil that separated soon solidified. The solid was filtered, and the residue was washed with warm H_2O and dried: yield 18 g (61%). After recrystallization from 70% aqueous CH_3OH, the crystals melted at 142–143 °C. Anal. ($C_{14}H_{11}ClO_4$) C, H.

1-Chloro- (31) and 3-Chloro-7-methoxy-9*H*-xanthen-9-one (30). Eighteen grams (0.065 mol) of the above acid was added in one portion to 50 mL of 50% polyphosphoric acid preheated to 120 °C. The mixture was stirred at this temperature for 3 h. It was cooled, poured into ice–water, and filtered. The filter cake was washed with H_2O, 10% NaOH solution, and again wtih H_2O. The dried mixture weighed 14 g (83%). After crystallization from CH_3OH it melted at 139–140 °C. Anal. ($C_{14}H_9ClO_3$) C, H.

1-[[2-(Diethylamino)ethyl]amino]-7-methoxy-9*H*-xanthen-9-one (32). A mixture of 10.0 g (38.3 mmol) of the above chloro-9*H*-xanthen-9-one mixture, 6.0 mL of *N,N*-diethylethylenediamine, and 20 mL of dry pyridine was heated under reflux for 16 h. The reaction mixture was worked up in the usual way to give 6.5 g of the desired amine, which melted at 135–136 °C after crystallization from petroleum ether–ether. Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-methoxy-9*H*-xanthen-9-one (33). The above procedure was employed. A mixture of 18.0 g (0.069 mol) of the chloro-9*H*-xanthen-9-one mixture **31** and **32**, 12.0 mL of *N,N*-dimethylethylenediamine, and 40 mL of pyridine gave 10.0 g of the desired product, mp 122–123 °C after crystallization from CH_3OH/H_2O. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-9*H*-xanthen-9-one (34). A solution of 8.0 g (23.5 mmol) of the methoxy-9*H*-xanthen-9-one (**32**) in 60 mL of 56% HI was heated under reflux for 4 h. The mixture was cooled, and the HI salt of **34** was collected on a filter and washed with ether. It was dissolved in 400 mL of H_2O and made alkaline with NaOH. The solution was clarified by filtration through a bed of Celite, and then the filtrate was carefully neutralized with dilute acetic acid. The yellow crystals were filtered, washed with H_2O, and dried: yield 6.6 g (86%). After crystallization from CH_3OH, the yellow needles melted at 178–179 °C. Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-9*H*-xanthen-9-one (35). A suspension of 9.0 g (29.0 mmol) of **33** in 70 mL of 56% HI furnished 7.5 g (87%) of the phenol **35**. After crystallization from CH_3OH, the yellow needles melted at 199–200 °C. Anal. ($C_{17}H_{18}H_2O_3$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-xanthen-9-one (36). Four grams (20 mmol) of *p*-toluenesulfonyl chloride was slowly added to a stirred solution of 6.0 g (18.0 mmol) of the hydroxy-9*H*-xanthen-9-one (**34**) in 30 mL of dry pyridine. The stirred mixture was kept at 50 °C for 1.5 h and then poured onto ice–water. The mixture was made strongly alkaline with Na_2CO_3 solution, and the crystals that separated were filtered, washed thoroughly with H_2O, and dried: yeild 7.5 g (85%). After crystallization from ether–petroleum ether, the ester melted at 74–75 °C. Anal. ($C_{26}H_{28}N_2O_5S$) C, H, N.

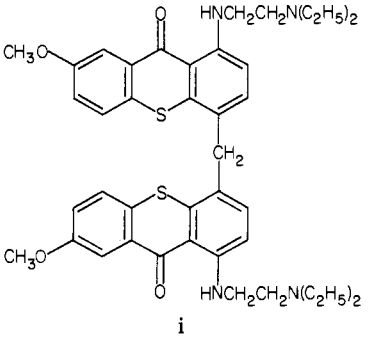
1-[[2-(Dimethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-xanthen-9-one (37). A mixture of 7.5 g (25.0 mmol) of the hydroxy-9*H*-xanthen-9-one (**35**) and 5.6 g (29.0 mmol) of *p*-toluenesulfonyl chloride in 45 mL of dry pyridine furnished 10.5 g (92%) of the ester **37**, mp 139–140 °C after crystallization from benzene–petroleum ether. Anal. ($C_{24}H_{24}N_2O_5S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-4-(hydroxymethyl)-9*H*-xanthen-9-one (38). A solution of 6.0 g (12.5 mmol) of the (toluenesulfonyloxy)-9*H*-xanthen-9-one **36** in 700 mL of 37% formalin and 10 mL of 5 N acetic acid was stirred at 70 °C for 72 h. The cooled mixture was made basic with Na_2CO_3 solution, and extracted with $CHCl_3$. The dried extract was evaporated to dryness in vacuo at 30 °C. The residue was chromatographed on silica gel. The desired product was eluted with $CHCl_3$/2–4% CH_3OH to give 3.8 g (60%) of the hydroxymethyl compound **38**, mp 145–146 °C after crystallization from absolute C_2H_5OH. Anal. ($C_{27}H_{30}N_2O_6S$) C, H, N.

1-[[2-(Dimethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-4-(hydroxymethyl)-9*H*-xanthen-9-one (39). A solution of 10.0 g (22.1 mmol) of the xanthenone **37** in 1200 mL of 37% formalin and 30 mL of 5 N acetic acid gave 4.86 g (46%) of the hydroxymethyl analogue **39**, mp 176–178 °C after crystallization from CH_3OH. Anal. ($C_{25}H_{26}N_2O_6S$) C, H, N.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-xanthen-9-one (11). A solution of 1.0 g (2.0 mmol) of the (toluenesulfonyloxy)-9*H*-xanthen-9-one **38** in 20 mL of

(11) This ethanol-insoluble material is the dimeric product, i,



i

formed by the condensation of 2 mol of **19** with 1 mol of CH_2O. Anal. Calcd for $C_{41}H_{48}N_4O_4S_2$: C, 67.92; H, 6.67; N, 7.73. Found: C, 68.02; H, 6.72; N, 7.68.

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C_2H_5OH containing 3 mL of 5 N KOH was heated on the steam bath for 30 min. The solvent was evaporated, and the residue was dissolved in H_2O. The solution was clarified by filtration and then neutralized. The base, 11, that separated was left overnight and then filtered, and the filtrate was dried: yield 0.63 g (90%).

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-(hydroxymethyl)-9*H*-xanthen-9-one (12). Two grams (4.0 mmol) of the 9*H*-xanthen-9-one **39** gave, after treatment by the method used for 11, 1.2 g (88%) of the desired phenolic product **12**, mp 199 °C dec after crystallization from CH_3OH.

2-(5-Chloro-2-methylphenoxy)-5-methoxybenzoic Acid (41). A mixture of 45 g (0.267 mol) of 5-methoxysalicyclic acid, 67.6 g (0.268 mol) of 4-chloro-2-iodotoluene, 50.3 g of dry K_2CO_3, and 3.0 g of Cu–bronze in 100 mL DMF was heated under reflux for 3 days. The cooled mixture was poured into a large volume of H_2O and extracted with ether. The layers were separated, and the aqueous phase was carefully acidified to furnish 51.1 g of the acid (65.4%), mp 185–187 °C after crystallization from acetic acid. Anal. ($C_{15}H_{13}ClO_4$) C, H.

1-Chloro-7-methoxy-4-methyl-9*H*-xanthen-9-one (42). A solution of 47.9 g (0.164 mol) of crude 41 in 240 mL of H_2SO_4 was heated on the steam bath for 1.5 h. The cooled solution was poured into ice–water and filtered, and the filter cake was washed with H_2O. The cyclization product was stirred with hot 8% NaOH solution, cooled, and filtered. The filter cake was washed with H_2O and dried: yield 20.3 g (45%). After two crystallizations from Me_2SO, the 9*H*-xanthen-9-one melted at 179–179.5 °C. Anal. ($C_{14}H_{11}ClO_4$) C, H.

1-[[2-(Diethylamino)ethyl]amino]-7-hydroxy-4-methyl-9*H*-xanthen-9-one (9). A solution of 3.72 g (13.5 mmol) of the chloro-9*H*-xanthen-9-one **42** and 25 mL of *N,N*-diethylethylenediamine was refluxed overnight in a flask protected from moisture. The cooled reaction mixture was diluted with H_2O and made strongly alkaline with KOH solution. The apparatus was set for downward distillation. A total of 100 mL of the solvent was distilled off, and the cooled reaction mixture was extracted with ether, which was concentrated to leave 4.55 g (95%) of crude **43**, mp 85.5–86.5 °C after crystallization from CH_3OH. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

A solution of 1.38 g (3.9 mmol) of crude **43** in 15 mL of 56% HI solution was heated under reflux for 2.5 h. The cooled solution was filtered, and the solid was washed with ether. Upon recrystallization from CH_3OH–ether, there was obtained 0.8 g (44%) of the HI salt, mp 240–242 °C dec.

1-[[2-(Dimethylamino)ethyl]amino]-7-hydroxy-4-methyl-9*H*-xanthen-9-one (10). A solution of 4.38 g (15.9 mmol) of crude **42** in 30 mL of *N,N*-dimethylethylenediamine was refluxed overnight. After the usual workup as described in the preceding section, there was obtained 3.80 g (73%) of crude **43**. A solution of 1.30 g (4.0 mmol) of this compound in 15 mL of 56% HI was refluxed for 3.5 h. The mixture was left overnight, and the salt was collected on a filter, washed with ether, and dried. After crystallization from CH_3OH, there was obtained 0.70 g (40%) of the pure HI salt.

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Registry No. 1, 3105-97-3; **2**, 479-50-5; **5**, 86455-90-5; **6**, 86455-91-6; **7**, 86455-92-7; **9**, 86455-93-8; **9**·HI, 86455-94-9; **10**, 86455-95-0; **10**·HI, 86455-96-1; 11, 86455-97-2; **12**, 86455-98-3; **13**, 16807-37-7; 14, 108-37-2; **15**, 86455-99-4; **16**, 86456-00-0; **17**, 86456-01-1; **18**, 86456-02-2; **18** fumarate, 86456-03-3; **19**, 86456-04-4; **20**, 86456-05-5; **21**, 86456-06-6; **22**, 86456-07-7; **23**, 86456-08-8; **24**, 86456-09-9; **25**, 86456-10-2; **26**, 86456-11-3; **27**, 2612-02-4; **28**, 625-99-0; **29**, 86456-12-4; **30**, 86456-13-5; **31**, 86456-14-6; **32**, 86456-15-7; **33**, 86456-16-8; **34**, 86456-17-9; **35**, 86456-18-0; **36**, 86456-19-1; **37**, 86456-20-4; **38**, 86456-21-5; **39**, 86456-22-6; **40**, 33184-48-4; 41, 86456-23-7; **42**, 86456-24-8; **43**, 86456-25-9; 44, 86456-26-0; **45**, 38605-72-0; **46**, 6469-87-0; **47**, 19058-08-3; i, 86456-27-1; 5-methoxydithiosalicylic acid, 19532-69-5; *N,N*-diethylethylenediamine, 100-36-7; *N,N*-dimethylethylenediamine, 108-00-9; 1-[[2-(diethylamino)ethyl]amino]-7-hydroxy-9*H*-thioxanthen-9-one, 86456-28-2; 1-[[2-(diethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one, 86456-29-3; 1-[[2-(diethylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one fumarate, 86456-30-6; 1-[[2-(dimethylamino)-ethyl]amino]-7-hydroxy-9*H*-thioxanthen-9-one, 86456-31-7; 1-[[2-(diemthylamino)ethyl]amino]-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one, 86456-32-8; 1-[[2-(diethylamino)ethyl]-amino]-4-(hydroxymethyl)-7-(toluenesulfonyloxy)-9*H*-thioxanthen-9-one, 86456-33-9; 1-[[2-(dimethylamino)ethyl]-amino]-9-oxo-9*H*-thioxanthene-4-carboxyaldehyde, 86470-89-5.

Structural Studies of Metyrapone: A Potent Inhibitor of Cytochrome P-450

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The crystal and molecular structure of metyrapone, a powerful inhibitor of certain cytochromes P-450, is described. Cytochrome P-450 enzymes are involved in metabolic processes, including those activating insecticides, drugs, and carcinogens. Metyrapone inhibits both the adrenal cytochrome P-450 catalyzing 11-β-hydroxylation in steroid biosynthesis and most microsomal cytochromes P-450 induced by phenobarbital pretreatment. Crystal data are as follows: a = 11.828 (1), b = 6.268 (6), c = 18.269 (3) Å, β = 115.27 (1)°, V = 1224.9 (3) Å^3, space group $P2_1/c$, d_{calcd} = 1.227 g cm^{-3}, Z = 4. No intermolecular interactions are apparent in the solid state other than van der Waals forces. The torsion angle about the C(7)–C(10) bond to which the two 3-pyridyl groups are attached is 59.4 (1)°. The three negatively charged heteroatoms form a triangle; the nitrogen atoms are anti to the exocyclic oxygen and are 4.347 (1) Å apart. The N5–O11 distance is 5.850 (1) Å; the N14–O11 intramolecular distance is 4.750 (1) Å. The "twisted butterfly" conformation found for metyrapone is found in other molecules that are substrates and inducers of the specific cytochrome P-450 inhibited by metyrapone. The availability of nucleophilic functional groups is a feature common to most directly acting inhibitors of cytochrome P-450 enzymes and is manifested in metyrapone by the presence of the basic nitrogens. These factors may be necessary for interaction with the protein.

The literature on metyrapone suggests a bifunctional role for this clinically active drug.[1,2] It is an inhibitor of two classes of cytochrome P-450 enzymes: adrenal steroid 11-β-hydroxylase and most phenobarbital-inducible forms of cytochrome P-450 ($P\text{-}450_{PB}$) found in various tissues. Cytochromes P-450 are a group of inducible enzymes responsible for the oxidation of lipophilic compounds including drugs, steroids, and polycyclic aromatic hydrocarbons.[3] The different cytochrome P-450 enzymes cat-

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