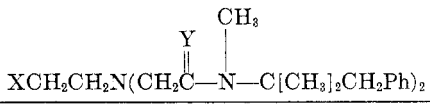
TABLE VI

MISCELLANEOUS DERIVATIVES



No.	X	Y	M.P.	Formula	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Duration of Activity, Min.	(% Soln.)
1	Cl	O	155–156[a]	$C_{28}H_{41}N_3O_2Cl_2$	13.50	13.16	8.04	7.75	43[b]	0.1
2	NH_2	O	231–232[a]	$C_{28}H_{44}N_4O_2Cl_2$	13.15	13.40	10.40	10.71	Neg.	0.1
3	$HO(CH_3I)$	O	122–123	$C_{29}H_{44}N_3O_3I$	20.85[c]	20.90	6.92	6.60	Neg.	0.1
4	HO	2H	239–240[a]	$C_{28}H_{43}N_3OCl_3$	19.40	19.47	7.66	7.70	Neg.	0.1

[a] Hydrochloride. [b] The compound *per se* may not be active; this degree of activity can be attributed to a trace of the highly active *N,N*-bis(*N*-methyl-*N*-ω-phenyl-*tert*-butylacetamido)-2-hydroxyethylamine present in the chloro compound either as an initial impurity or formed *in situ* by hydrolysis of the 2-chloroethylamine group. [c] Iodine.

A trimethiodide was prepared by heating the free base of the above trihydrochloride with methyl iodide in acetone. After crystallization from acetone it melted at 154–155°.

Anal. Calcd. for $C_{31}H_{54}IN_3O$: N, 4.85, I, 43.90. Found: N, 4.60; I, 43.82.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide methiodide. 2-Hydroxyethyliminobis[N-methyl-(α,α-dimethylphenethyl)acetamide], 5 g. (0.011 mole), was heated under reflux with 25 ml. of methyl iodide for 30 min. The solution was concentrated and the residue taken up in 30 ml. of ethyl acetate. On standing in the cold crystallization occurred and the product was collected on a filter, washed with ether, and dried; yield, 5.7 g. (86.4%), m.p. 122–123°.

Anal. Calcd. for $C_{29}H_{44}IN_3O_3$: N, 6.92, I, 20.85. Found: N, 6.60; I, 20.90.

PHILADELPHIA 1, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Tranquilizing Agents. Xanthen- and Thioxanthen-$\Delta^{9,\gamma}$-propylamines[1] and Related Compounds

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Received November 16, 1960

The Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with xanthen-9-ones and thioxanthen-9-ones gave a series of 9-(3-dialkylaminopropyl)xanthen-9-ols and thioxanthen-9-ols. Dehydration of these compounds gave the corresponding xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines, some of which were potent tranquilizers. Substantial differences in dehydration of the xanthen-9-ols and thioxanthen-9-ols were observed and are explained. The characteristic changes in the ultraviolet spectra, used to follow these reactions, are described. Several open chain analogs were prepared to study structure-activity relationships.

The well known efficacy of chlorpromazine in the treatment of neuropsychiatric disorders has led to the syntheses of a great number of 10-phenothiazinepropylamines,[2] many of which are new tranquilizing drugs. We wish to report the chemistry of a series of xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III) (Table II) with potent tranquilizing activity. Our basic idea for these compounds originated from consideration of the structures of azacyclonol[3] and chlorpromazine.[4] This suggested the preparation of 9-(3-dialkylaminopropyl)xanthen-9-ol and thioxanthen-9-ol analogs (I) (Table I) for pharmacological investigation as potential tranquilizing agents. Dehydration of these compounds yielded the unsaturated analogs (III).

The general method for the preparation of the tertiary alcohols of type I was the Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with a xanthen-9-one or thioxanthen-9-one. A modification of Marxer's procedure for 3-(dialkylaminopropyl)-diphenylcarbinols[5] was used. The reaction of the

(1) Since 1957, Chemical Abstracts numbering of the thioxanthene ring system has been changed to conform with that of the isosteric xanthene molecule. The current nomenclature is used throughout this paper.

(2) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061, 1072 (1958); **42**, 259 (1959).

(3) (a) Frenquel is the trademark of Wm. S. Merril Co. for azacyclonol—*i.e.*, α-(4-piperidyl)diphenylcarbinol hydrochloride; (b) F. Rinaldi, L. H. Rudy and H. E. Himwich, *Am. J. Psychiatry*, **112**, 343 (1955).

(4) Thorazine is the trademark of Smith Kline and French Laboratories for chlorpromazine—*i.e.*, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

(5) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

TABLE I. 9-(3-DIALKYLAMINOPROPYL)XANTHEN-9-OL AND -THIOXANTHEN-9-OL ANALOGS

No.	$N(R_2)$	R_1	R_2	X	Procedure[a]	M.P.,[b] °C.	Yield, %	Molecular Formula[b]	Carbon		Hydrogen		Halogen		Nitrogen		Sulfur	
									Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$(CH_3)_2$	H	H	O	A	109–111	70	$C_{18}H_{21}NO_2$	76.3	76.0	7.47	7.36			4.94	4.78		
2	$(CH_3)_2$	H	1-Cl	O	A	158–160	46	$C_{18}H_{20}ClNO_2$	68.0	68.0	6.34	6.50	11.2	11.0	4.41	4.52		
3	$(CH_3)_2$	H	2-OCH_3	O	A	103–104	92	$C_{19}H_{23}NO_3$	72.8	72.8	7.40	7.59			4.47	4.47		
4	$(CH_3)_2$	2-Cl	6-Cl	O	A	206–208[c]	55	$C_{18}H_{20}Cl_2NO_2$[c]	55.6	54.7	5.19	5.44	27.4	27.0	3.60	3.25		
5	$(CH_3)_2$	H	H	S	A	153–157	86	$C_{18}H_{21}NOS$	72.2	72.0	7.07	7.30			4.68	4.65	10.7	11.0
6	$(CH_3)_2$	H	2-Cl	S	A	152–153[d]	83	$C_{18}H_{20}ClNOS$	64.7	64.7	6.05	6.12	10.6	10.2	4.19	4.08	9.60	9.69
7	$(CH_3)_2$	H	2-OCH_3	S	A	123–125	89	$C_{19}H_{23}NO_2S$	69.3	69.1	7.04	7.09			4.25	4.16	9.74	9.72
8	$(CH_3)_2$	H[e]	4-CH_3	S	A	122–124	80	$C_{19}H_{23}NOS$	72.8	72.4	7.40	7.64	0.00	0.53[e]	4.47	4.50	10.2	10.4
9	$(CH_3)_2$	1-CH_3	4-Cl	S	A	162–166	55	$C_{19}H_{22}ClNOS$	66.5	66.4	6.38	6.13	10.2	11.1	4.02	3.99	9.20	9.26
10	CH_3N (N)	H	H	S	C	171–173	60	$C_{21}H_{26}N_2OS$	71.2	71.0	7.39	7.40			7.89	7.60	9.05	9.22

[a] See Experimental. [b] Free bases, except as noted. [c] The hydrochloride salt separated from a *N* hydrochloric acid solution of the product in an effort to dehydrate it according to Procedure D. It was recrystallized from hot water. [d] Lit.,[11] m.p. 153–154°. [e] From 1-chloro-4-methylthioxanthen-9-one. The 1-chlorine atom was reduced apparently during the Grignard reaction.

ketones with two moles of 3-chloro-*N*,*N*-dimethylpropylamine and two moles of magnesium, in a benzene-ether mixture, usually required twelve to twenty-four hours of heating under reflux. However, up to eighty hours were needed for the reactions with 1-(3-chloropropyl)-4-methylpiperazine under the same conditions. The latter reactions required only three to seven hours in tetrahydrofuran (THF) when the ethylene bromide procedure of Pearson *et al.*,[6,7] was used.

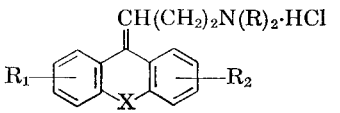
Generally, isolation of the desired tertiary alcohols (I) was dependent on whether or not mineral acids were used during the purification procedure. This was evident when 9-(3-dimethylaminopropyl)-xanthen-9-ol (Table I, No. 1) very readily dehydrated during its isolation on treatment with dilute hydrochloric acid. The isolated product was *N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine, characterized as the hydrochloride, giving the first member of the xanthen-$\Delta^{9,\gamma}$-propylamine series (III. X = O). The desired alcohol (Table I, No. 1) was easily obtained as the free base, however, by decomposing the Grignard complex with ammonium chloride solution. Generally, the use of mineral acids must be assiduously avoided for the decomposition of this complex and for subsequent purification. This facile dehydration to the unsaturated series (III) was a general characteristic of the oxygen series (I. X = O). Dehydration in the sulfur series (I. X = S) required more drastic conditions. The *tert*-alcohols were insolable as mineral acid addition salts as well as the free bases. Furthermore, the use of dilute mineral acid was a distinct advantage for their purification.

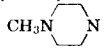
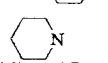
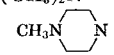
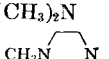
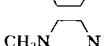
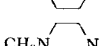
(6) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

(7) The purpose of the ethylene bromide was to activate the magnesium surfaces and thus improve the formation of the Grignard reagent. The reaction of ethylene bromide and magnesium is: $Mg + BrCH_2CH_2Br \rightarrow CH_2{=}CH_2 + MgBr_2$ as described by Pearson *et al.*[6]

TABLE II

XANTHEN- AND THIOXANTHEN-$\Delta^{9,\gamma}$-PROPYLAMINE ANALOGS



No.	N(R$_2$)	R$_1$	R$_2$	X	Procedure[a]	M.P.[b]	Yield, %[c]	Molecular Formula[b]	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
1	$(CH_3)_2$	H	H	O	D	201.5–203	60	$C_{18}H_{20}ClNO$	71.6	71.4	6.68	6.65	11.8	11.6	4.64	4.63		
2	$(C_4H_9)_2$	H	H	O	D	203–205[d]	25	$C_{24}H_{32}ClNO$	74.7	74.2	8.36	8.47	9.19	9.27	3.63	3.57		
3		H	H	O	D	251–253	32	$C_{21}H_{26}Cl_2N_2O$	64.1	63.6	6.66	7.01	18.0	17.9	7.12	7.33		
4		H	H	O	D	213–214.5	20	$C_{21}H_{24}ClNO$	73.8	73.9	7.07	7.43	10.4	10.5	4.10	3.99		
5	$(CH_3)_2N$	H	1-Cl	O	D	173–177	21	$C_{18}H_{19}Cl_2NO$	64.3	64.3	5.70	5.87	21.1	21.1	4.17	4.43		
6	$(CH_3)_2N$	H	2-Cl	O	D	193–195	36	$C_{18}H_{19}Cl_2NO$	64.3	64.2	5.70	5.85	21.1	20.9	4.17	3.92		
7	$(CH_3)_2N$	H	2-Br	O	D	174–176	50	$C_{18}H_{19}BrClNO$	56.8	56.9	5.03	5.28	9.33	9.57[e]	3.68	3.95		
8	$(CH_3)_2N$	H	3-Cl	O	F[f]	170–172	30	$C_{18}H_{19}Cl_2NO$	64.3	64.0	5.70	5.39	21.1	20.7	4.17	4.23		
9	$(CH_3)_2N$	H	4-Cl	O	D	162–164	45	$C_{18}H_{19}Cl_2NO$	64.3	63.9	5.70	5.98	21.1	20.8	4.17	4.10		
10	$(CH_3)_2N$	2-Cl	6-Cl	O	E[f]	215–217	58	$C_{18}H_{18}Cl_3NO$	58.3	58.0	4.89	5.16	28.7	28.7	3.78	3.82		
11	$(CH_3)_2N$	2-Cl	4-CH_3	O	D	219–222	75	$C_{19}H_{21}Cl_2NO$	65.1	65.2	6.04	6.18	20.2	20.0	4.00	4.20		
12	$(CH_3)_2N$	2-Cl	7-OCH_3	O	D	170–172	50	$C_{19}H_{21}Cl_2NO_2$	62.3	62.0	5.80	6.09	19.4	19.3	3.83	3.93		
13	$(CH_3)_2N$	H	2-OCH_3	O	D	196–198	80	$C_{19}H_{22}ClNO_2$	68.8	68.8	6.68	6.84	10.7	10.6	4.22	4.13		
14	$(CH_3)_2N$	H	2-OCH_3	O	g	170–172[g]	15[g]	$C_{23}H_{25}NO_6$[g]	67.1	67.0	6.12	6.26			3.41	3.46		
15	$(CH_3)_2N$	H	2-OCH_3	O	h	151–153.5[h]	89[h]	$C_{23}H_{25}NO_6$[h]	67.1	66.9	6.12	6.46			3.41	3.46		
16	$(CH_3)_2N$	H	2-OH	O	i	219–221	57[j]	$C_{18}H_{20}ClNO_2$	68.0	67.6	6.34	6.26	11.2	11.2	4.41	4.41		
17		H	2-OCH_3	O	D	211–213	25	$C_{22}H_{28}Cl_2N_2O_2$	62.4	62.2	6.67	6.82	16.8	16.8	6.62	6.59		
18	$(CH_3)_2N$	H	H	S	F	181–183	48	$C_{18}H_{20}ClNS$	68.0	67.8	6.34	6.55	11.2	11.1	4.41	4.29	10.1	10.2
19	$(CH_3)_2N$	H	2-Cl	S	E	191–193[k]	89	$C_{18}H_{19}Cl_2NS$	61.4	61.3	5.44	5.67	20.1	19.8	3.98	4.33	9.10	9.01
20	$(CH_3)_2N$	H	2-OCH_3	S	F	168–170	61	$C_{19}H_{22}ClNOS$	65.6	65.4	6.37	6.68	10.2	10.2	4.03	3.86	9.21	9.17
21	$(CH_3)_2N$	H	4-CH_3	S	F	174–176	75	$C_{19}H_{22}ClNS$	68.7	68.3	6.69	6.82	10.7	10.3	4.22	4.22	9.64	9.40
22	$(CH_3)_2N$	1-CH_3	4-Cl	S	F	187–190	64	$C_{19}H_{21}Cl_2NS$	62.3	62.0	5.78	6.03	19.4	19.2	3.83	4.00	8.75	8.52
23		H	H	S	F	248–249	83	$C_{21}H_{26}Cl_2N_2S$	61.6	61.3	6.40	6.74	17.3	17.6	6.84	7.01	7.83	7.83
24		H	2-Cl	S	F	247–249	85	$C_{21}H_{25}Cl_3N_2S$	56.8	56.8	5.68	5.92	24.0	23.6	6.31	6.26	7.22	6.81
25		H	2-OCH_3	S	E	212–215[l]	44	$C_{22}H_{30}Cl_2N_2O_2S$[l]	57.8	57.6	6.61	6.92	15.5	15.4	6.12	6.39	7.01	6.58

[a] See Experimental. [b] Hydrochlorides except as noted. [c] Yields of the oxygen analogs were calculated from the xanthen-9-ones, except as noted. Yields of the sulfur analogs were calculated from the thioxanthen-9-ols (Table I), except as noted. [d] Lit.,[9] m.p. 204–205°. [e] Bromine: Calcd.: 21.0. Found: 21.4. [f] Procedure D was not satisfactory for these compounds. More drastic conditions were necessary for dehydration. [g] *cis* (or *trans*) fumarate (Va); see Experimental. [h] *trans* (or *cis*) fumarate (Vb); see Experimental. [i] Prepared by hydrolysis of compound No. 13; see Experimental. [j] From compound No. 13. [k] Lit.,[11] m.p. 189–190°. [l] Monohydrate, H_2O; Calcd.: 3.09. Found: 3.08. The anhydrous dihydrochloride, m.p. 225–226°, also gave a satisfactory analysis.

The dehydration appeared to be a two-step process. First, an acid-catalyzed dehydroxylation produced the "onium" salt (IIa, b), indicated by characteristic changes in the visible region of the absorption spectrum (*vide infra*). This was followed by a base-catalyzed deprotonization of the α-carbon (IIa → III). Dehydration of the oxygen-series *tert*-alcohols generally took place immediately at room temperature upon the addition of 0.5-1*N* aqueous hydrochloric acid as evidenced by the rapid development of a red color in the solution. The sulfur-series *tert*-alcohols were dehydrated by several procedures: treatment with (a) glacial acetic and concentrated hydrochloric acids, (b) anhydrous hydrogen chloride in benzene or ether, and (c) acetic anhydride–glacial acetic acid mixtures. Addition of base then gave the dehydrated products. The interesting differences in ease of dehydration between the oxygen and sulfur series may be explained by a greater resonance stabilization of the oxonium ion (IIb. X = O and its equivalent ions) compared to the sulfonium ion (IIb. X = S). This is due to the greater tendency of oxygen to "increase its covalency" described by Ingold.[8] 2,6-Dichloro-9-(3-dimethylaminopropyl)-xanthen-9-ol was an exception to the facile dehydration of the oxygen series, and required the more vigorous conditions used for the sulfur series.

The facile dehydration of a xanthen-9-ol derivative (I) was actually first observed by Perrine[9] in 1953. He obtained *N,N*-di-*n*-butylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (when he used hydrochloric acid to decompose the Grignard complex) instead of the desired *tert*-alcohol.

After our work was well underway it became evident that other laboratories were also investigating the tranquilizing activity of the xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines.[10-12] Other routes to these compounds have since been reported: (a) the Grignard reaction of allyl bromide with xanthen-9-ones and thioxanthen-9-ones followed by subsequent dehydration and amination[13]; (b) 9-cyanoethylation of the xanthen-9-ols and thioxanthen-9-ols followed by reduction and dehydration[13]; (c) reaction of 3-dimethylaminopropyne-1 derivatives with xanthen-9-one and thioxanthen-9-one followed by reduction and dehydration.[14]

When unsymmetrically substituted ketones are used, stereoisomers are possible in both the *tert*-alcohol series (I) and the unsaturated series (III).

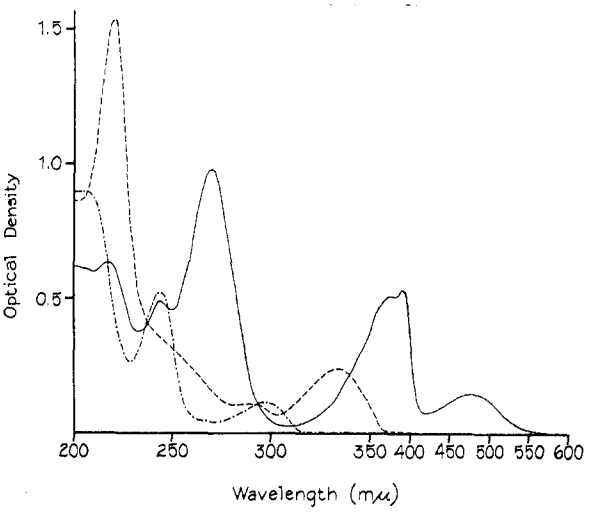
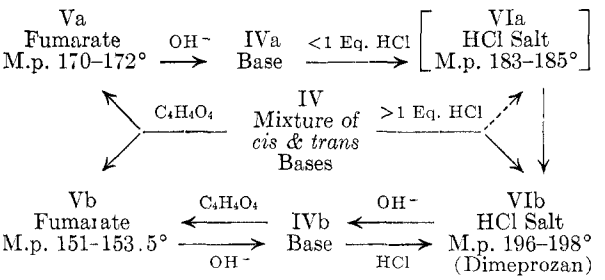


Fig. 1. Ultraviolet absorption spectra of oxygen series (concn. 10 μg./ml)
(a) -·—·—, 2-methoxy-9-[3-dimethylaminopropyl)xanthen-9-ol in methanol
(b) — — — —, 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride in methanol
(c) ————, the "onium" salt from (a) in 6*N* hydrochloric acid[15]

Separation of enantiomorphs in the *tert*-alcohol series was not attempted. Investigation of the geometrical isomers (*cis* and *trans*) in the unsaturated series was carried out with 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. Neutralization of red oxonium salt (IIa, b; devoid of stereoisomers), formed when 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol was dissolved in hydrochloric acid, produced a mixture of *cis* and *trans* bases (IV). This was demonstrated by isolation of a mixture of fumarates (Va and Vb), m.p. 143–152°, from IV, and fumaric acid in ethanol. Repeated



fractional crystallization from ethanol afforded the less soluble fumarate (Va), m.p. 170–172°. The more soluble fumarate (Vb) could be isolated from the mother liquors, but was more readily obtained from VIb. The isomeric bases, IVa and IVb, liberated from the purified fumarates Va and Vb, respectively, gave different infrared absorption spectra. The spectrum of IV was consistent with its formulation as a mixture of IVa and IVb. When the mixture of bases (IV) was treated with slightly more than

(8) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 75.
(9) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).
(10) P. V. Petersen, N. Lassen, T. Holm, R. Kopf, and I. Møller Nielsen, *Arzneimittel Forsch.*, **8**, 395 (1958).
(11) J. M. Sprague and E. L. Engelhardt, U. S. Pat. **2,951,082** (1960).
(12) Hoffmann-La Roche AG, Belg. Pat. **558,171** (1957).
(13) Kefalas A/S, Belgian Pat. **585,338** (1960).
(14) W. Ried and J. Schönherr, *Ber.*, **93**, 1870 (1960).
(15) Before the spectrum was taken the solution was allowed to stand at room temperature for 1.75 hr. to insure complete transformation to the "onium" salt.

TABLE III

SUMMARY OF ULTRAVIOLET ABSORPTION MAXIMA

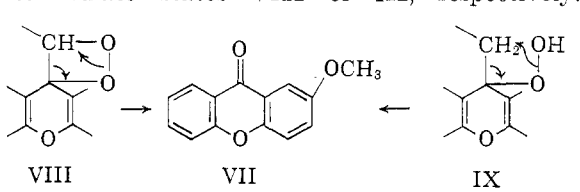
	Oxygen Series (X = O)		Sulfur Series (X = S)	
	$M\mu$	$\epsilon \times 10^{-3}$	$M\mu$	$\epsilon \times 10^{-3}$
Xanthen- and thioxanthen-9-ols (I)[a]; in methanol	208–212	28.3–33.4	210–214	26.7–28.7
	240–245	10.1–15.4	268–271	12.2–14.5
	280–290	2.50–3.50 broad band		
"Onium" forms (II); in 6*N* HCl	217	20.9[b]	212	24.5[c]
	244	17.3	229	20.6
	269	32.5	293	49.1
	375	16.9	395	9.74
	390	17.6	520	3.65
	480	4.81		
Xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III)[d]; in methanol	215–222	44.8–56.5	208–210	32.0–42.0[e]
	315–338	7.70–8.90	228–230	31.4–56.0
			268–270	13.1–24.5
			325–335	3.15–5.30

[a] Determined as bases. [b] 2-Methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol was dissolved in 6*N* hydrochloric acid and allowed to stand at room temperature for 1.75 hr. to insure complete transformation before the spectrum was taken. [c] 2-Methoxy-*N*,*N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride was dissolved in 6*N* hydrochloric acid and allowed to stand at room temperature for 1.75 hr. to ensure complete transformation before the spectrum was taken. [d] Determined as hydrochlorides. [e] The sulfur compounds (III. X = S) containing the methylpiperazine moiety lacked this maximum.

one equivalent of alcoholic hydrochloric acid, one isomeric salt (VIb) was isolated in excellent yield (80% or better), m.p. 196–198°. This was demonstrated by liberating the base IVb (from VIb) and converting it to the lower melting fumarate (Vb) in 89% yield, m.p. 151–153.5°. The base IVb was also reconverted to VIb. The isomeric base IVa, obtained from the higher-melting fumarate (Va), was treated with slightly less than one equivalent of alcoholic hydrochloric acid. The isolated salt (VIa) melted at 183–185° and was more soluble than VIb in ethanol. Characterization of this material (VIa) as the geometric isomer of VIb was difficult since it completely changed to VIb on standing for two weeks. Alternately, treatment of base IVa with more than one equivalent of alcoholic hydrochloric acid yielded VIb directly in 70% yield. These findings suggest that equilibration of the *cis* and *trans* forms occurs through the oxonium salt (IIa, b) in the presence of mineral acid. This allows preferential crystallization of the less soluble isomer in good yield.

The ultraviolet absorption spectra of these compounds show characteristic changes between the *tert*-alcohols (I), the "onium" forms (II) and the unsaturated derivatives (III). These changes are very useful for following the dehydration reactions and are summarized in Table III. Figures 1 and 2 illustrate these transformations (I → II → III) for a typical member of the oxygen and sulfur series, respectively. The development of low intensity maxima in the 315–340 mμ region was particularly characteristic for the formation of the unsaturated compounds (III. X = O or S). The corresponding *tert*-alcohols (I. X = O or S) were transparent in this region and this band was used for estimation of purity. Additionally, the unsaturated compounds (III. X = O) showed a particularly sharp and intense maximum in the 215–222 mμ region. The spectral bands particularly characteristic of the "onium" salts (II. X = O or S) were those above 350 mμ (red color).

In the course of working with 2-methoxy-*N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine base over a period of several months, oxidative decomposition of this material was observed. After standing for two months at room temperature an ethereal solution deposited 13% of 2-methoxyxanthen-9-one (VII). This change was more rapid in air in the absence of solvent; about 65% of the ketone (VII) was obtained in three to five days. Suspecting that the decomposition in ether might be due to peroxides, an alcoholic solution of this base was treated with hydrogen peroxide. After nine days, 10–23% of the ketone (VII) was isolated. Dry air, aspirated through an alcoholic solution for twenty-four days did not appreciably affect the free base, as determined by infrared and ultraviolet spectra. The carbonyl absorption of 2-methoxy-xanthen-9-one at 6.03–6.05 μ was particularly diagnostic for the presence of this decomposition product in mixtures. The hydrochloride (VIb) was stable for extended periods, however. These air and peroxide oxidations may be considered as taking place through the intermediate states VIII or IX, respectively.



VIII VII IX

These oxidations may be surprising but are not without literature precedents.[16,17]

(16) R. Q. Brewster, *Organic Chemistry*, 2nd ed., Prentice-Hall, New York, 1953, p. 236.

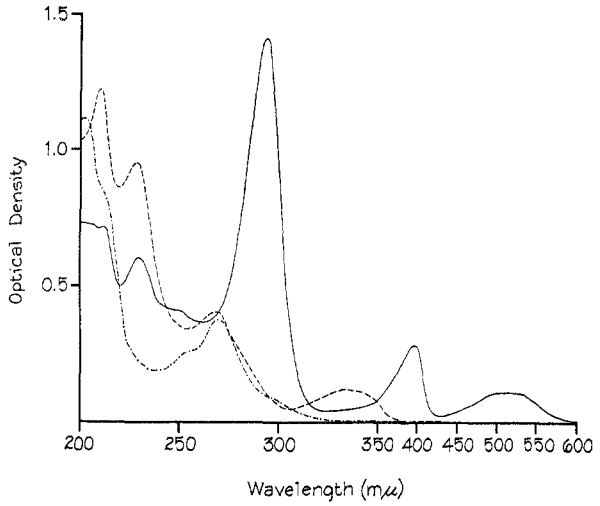
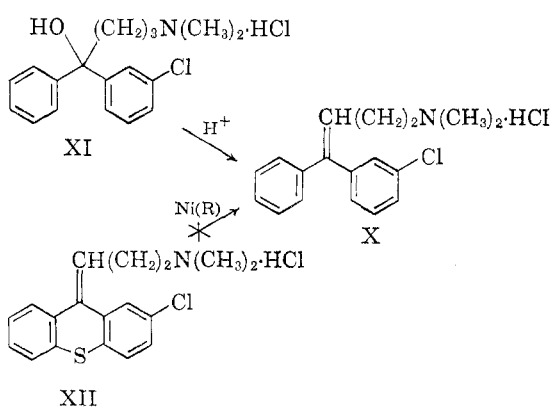


Fig. 2. Ultraviolet absorption spectra of sulfur series (concn. 10 μg./ml.)
(a) — · — · —, 2-methoxy-9-(3-dimethylaminopropyl)thioxanthen-9-ol in methanol
(b) — — — —, 2-methoxy-N,N-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride in methanol
(c) ————, the "onium" salt from (b) in 6N hydrochloric acid[15]

Additional structural modifications were investigated to determine those features necessary for good tranquilizing activity. Catalytic hydrogenation of N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride saturated the $\Delta^{9,\gamma}$-double bond yielding N,N-dimethylxanthene-9-propylamine hydrochloride with markedly reduced tranquilizing activity. 4-(*m*-Chlorophenyl)-N,N-dimethyl-4-phenyl-3-butenylamine hydrochloride (X), an open chain analog of active xanthene or thioxanthene derivatives, was prepared. The Grignard reaction of 3-



chloro-N,N-dimethylpropylamine with *m*-chlorobenzophenone yielded 3-chloro-α-(3-dimethylaminopropyl)benzhydrol, isolated as the stable hydrochloride (XI). Dehydration of this *tert*-alcohol required the vigorous conditions necessary for the thioxanthen-9-ol analogs (I. X = S). An attempt to prepare X by Raney nickel desulfurization[18] of 2-chloro-N,N-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (XII)[10-13] was unsuccessful; only starting material was recovered. The corresponding open chain analog of chlorpromazine, N-*m*-chlorophenyl-N',N'-dimethyl-N-phenyl-1,3-propanediamine hydrochloride (XIII), was also prepared for comparative testing. This was accomplished by treating *m*-chlorodiphenylamine with 3-chloro-N,N-dimethylpropylamine. As these derivatives lacked the hetero-atom, it seemed interesting to prepare an open chain analog containing an *o*-methoxyl group. This oxygen atom is situated in the same relative position as that occupied by the hetero-atom (O or S) of the "xanthene" or "thioxanthene" series, and at the same time the molecule retains the flexible characteristics of X. The preparation of 4-(*o*-methoxyphenyl)-N,N-dimethyl-4-phenyl-3-butenylamine was attempted but ether cleavage occurred during the Grignard reaction. *o*-Methoxybenzophenone treated with magnesium and 3-chloro-N,N-dimethylpropylamine gave α-(3-dimethylaminopropyl)-*o*-hydroxybenzhydrol (XIV) which required vigorous conditions for dehydration to *o*-(4-dimethylamino-1-phenyl-1-butenyl)phenol hydrochloride (XV). All of these open chain analogs were inactive indicating the need for maintaining the dibenzoheterocyclic system intact. The fluorene analog, N,N-dimethylaminofluoren-$\Delta^{9,\gamma}$-propylamine hydrochloride (XVI) was obtained from the vigorous dehydration of 9-(3-dimethylaminopropyl)-9-fluorenol (XVII) and had markedly reduced activity.

Preliminary evaluation of the tranquilizer activity of these compounds was carried out by determining the doses which produced ataxia, 50% reduction of spontaneous motor activity, loss of righting reflex and lethality in mice.[19] In these experiments, several of the xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III) showed activity qualitatively and quantitatively similar to chlorpromazine. Chlorine and methoxyl groups in the 2-position were particularly desirable. Dimethylamino or methylpiperazino groups were the basic moieties present in the active compounds. The structure-activity relationships in this series generally paralleled those of the phenothiazine series. The xanthen- and thioxanthen-9-ol precursors (I) showed no significant activity. 2-Methoxy-N,N-dimethyl-$\Delta^{9,\gamma}$-xanthenpropylamine hydrochloride (VIb), *dimeprozan*, is the same *cis*- or *trans*-isomer as the lower melting fumarate (Vb), and both of these were equally potent, active compounds comparing favorably with chlorpromazine. The higher melting fumarate (Va), on the other hand, was less

(17) (a) J. Fishman, *J. Am. Chem. Soc.*, **80**, 1213 (1958); (b) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).

(18) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(19) Pharmacological screening and evaluation studies were carried out by A. C. Osterberg *et al.*, of the Experimental Therapeutics Research Section of these laboratories. Details will be reported elsewhere.

than one-tenth as potent and about one-half as toxic. Dimeprozan was one of several compounds considered for trial in man. Preliminary clinical results suggest it is less effective than chlorpromazine as a tranquilizer for hospitalized psychotic patients. Pharmacological[10,20] and extensive clinical investigations[21] of 2-chloro-*N*,*N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, *chlorprothixene*, have been reported. It is interesting to note that the xanthen-$\Delta^{9,\gamma}$-propylamines (oxygen series; III. X = 0) cannot be oxidized to the 10-oxide in the fashion that phenothiazine tranquilizers have been reported to be partially metabolized.[22,23] 10-Oxide formation is a potential metabolic route for the thioxanthen-$\Delta^{9,\gamma}$-propylamines (sulfur series; III. X = S).

EXPERIMENTAL[24]

Preparation of salts. The hydrochloride salts were prepared by treating a weighed quantity of the bases, in the minimum volume of absolute alcohol, with the equivalent quantity of standardized alcoholic hydrogen chloride determined by the number of basic groups in the molecules.

Procedure A: 9-(3-Dialkylaminopropyl)xanthen-9-ol analogs (Table I). The preparation of 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol is an example of this general procedure. Magnesium metal, 43.7 g. (1.8 g.-atoms), in a 12-l. three-necked flask fitted with stirrer, condenser and a 1-l. addition funnel, was activated with a crystal of iodine and 2 ml. of methyl iodide. With gentle heating and stirring, a mixture of 1.8 moles of 3-chloro-*N*,*N*-dimethylpropylamine[5] in 900 ml. of anhydrous ether was added over a 45-min. period. The mixture was heated to reflux and 0.9 mole of 2-methoxyxanthen-9-one, dissolved in 3 l. of dry benzene, was added dropwise over 1.5 hr. The mixture was stirred and heated under reflux for 20 hr. (almost no magnesium metal remained). After cooling, the Grignard complex was decomposed by the addition of 2.2 l. of 10% ammonium chloride solution followed by 2.2 l. of water. The organic phase was separated and the aqueous phase was extracted with 2 l. of ether. The organic phases were combined and washed with water [Fraction (a)]. This ethereal solution was dried over magnesium sulfate and evaporated. Treatment of the residue with 2 parts of ethanol caused crystallization of the crude material as an almost white solid, m.p. 103–104°, 275 g. (92% yield). Recrystallization from alcohol did not change the melting point. For analysis see Table I, No. 3. The thioxanthen-9-ol analogs were isolated according to Procedure B. Dehydration of the xanthen-9-ol analogs was accomplished according to Procedure D, and the thioxanthen-9-ol analogs were dehydrated according to Procedure E or F.

Procedure B. 9-(3-Dialkylaminopropyl)thioxanthen-9-ol analogs (Table I). 2-Chloro-9-(3-dimethylaminopropyl)thioxanthen-9-ol is an example of this general method. 2-Chlorothioxanthen-9-one, 38 g. (0.15 mole) reacted with 38 g. (0.31 mole) of 3-chloro-*N*,*N*-dimethylpropylamine and 7.5 g. (0.31 g.-atom) of magnesium in an ether-benzene mixture as described in Procedure A. The combined organic phases corresponding to Fraction (a), (Procedure A), were extracted with three 200-ml. portions of *N* hydrochloric acid. The acidic aqueous extracts were combined and made alkaline with 20% sodium hydroxide, and extracted with several portions of ether. The combined ether extracts were washed free of alkali with water, dried over magnesium sulfate, and evaporated. The crude residue, on recrystallization from 3 A alcohol, afforded 43 g. (83% yield) of crystalline product, m.p. 152–153°, (lit.,[11] m.p. 153–154°). For analysis see Table I, No. 6.

Procedure C. 9-(3-Dialkylaminopropyl)xanthen-9-ol or -thioxanthen-9-ol analogs (Table I). *A modification of procedure A.* The preparation of 2-chloro-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthen-9-ol is an example of this general procedure. Freshly ground magnesium metal, 22.9 g. (0.94 g.-atom), and 250 ml. of anhydrous tetrahydrofuran,[25] in a 3-l. four-necked flask fitted with stirrer, condenser, 1-l. and 250-ml. addition funnels was treated with 1 ml. of ethylene bromide. The mixture was warmed to start the reaction. 1-(3-Chloropropyl)-4-methylpiperazine,[26] 82.7 g. (0.47 mole), was added in one portion, and a solution of 88.4 g. (0.47 mole) of ethylene bromide in 200 ml. of tetrahydrofuran was added dropwise until the reaction with magnesium was again evident. This generally required only a small portion of the ethylene bromide solution; the reaction may become vigorously exothermic at this point. Therefore, a cooling bath should be ready for use if necessary. When the exothermic reaction subsided, a suspension of 2-chlorothioxanthen-9-one, 57.9 g. (0.24 mole) in 700 ml. of tetrahydrofuran was added portionwise (15 min.). The reaction mixture was heated under reflux for 7 hr. while the remainder of the ethylene bromide was added dropwise. The reaction mixture was then decomposed as described in Procedure A. The crude product, 88.9 g. (97% yield), was isolated as described in Procedure B and was converted to 1-[3-(2-chlorothioxanthen-9-ylidene)propyl]-4-methylpiperazine dihydrochloride as described in Procedure F.

Procedure D. N,N-Dialkylxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 2-methoxy-*N*,*N*-dimethylxanthen-$\Delta^{9,\gamma}$ propylamine hydrochloride (VIb) is an example of this procedure generally used for the dehydration of the xanthen-9-ol analogs. A solution of 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol, prepared as described in Procedure A [Fraction (a)], was extracted with five 1-l. portions of *N* hydrochloric acid. The dark red, acidic extracts were combined and made alkaline with potassium carbonate under a layer of ether. The yellow aqueous layer and the ether layer were separated, and the aqueous layer was extracted with three 250-ml. portions of ether. The combined ether layers, after drying with magnesium sulfate, were concentrated *in vacuo* to a viscous oil on a steam bath; yield 250 g. (95% from xanthone). All efforts to crystallize this base were unsuccessful. It was dissolved in 675 ml. of ethanol and treated with anhydrous hydrogen chloride (with stirring) until a faint red tinge persisted. This solution was seeded and stirred for 16 hr. The heavy crystalline slurry was cooled to 10° and the product was collected by filtration. After vacuum drying (40°) 240 g. (80% yield, based on 2-methoxyxanthen-9-one) of product was obtained, m.p. 194–198°. Two recrystallizations from ethanol raised the melting point slightly, m.p. 196–198°, and gave analytically pure material (See Table II, No. 13).

(20) (a) I. Møller-Nielsen and K. Neuhold, *Acta Pharmacol. Toxicol.*, **15**, 335 (1959); (b) B. Pellmont, F. A. Steiner, H. Besendorf, H. P. Bächtold, and E. Läuppi, *Helv. Physiol. Acta*, **18**, 241 (1960).

(21) H. Hoffet and F. Cornu, *Schweiz. Med. Wochschr.*, **90**, 602 (1960); these authors also review earlier pertinent references.

(22) N. P. Salzman, N. C. Moran, and B. B. Brodie, *Nature*, **176**, 1122 (1955).

(23) L.-G. Allgén, B. Jönsson, A. Rappe, and R. Dahlbom, *Experientia*, **15**, 318 (1959).

(24) All melting points are uncorrected and were taken in a Hershberg melting point apparatus.

(25) Anhydrous tetrahydrofuran was prepared by drying commercially available material over sodium hydroxide pellets followed by distillation. The distilled product was then refluxed for 1 hr. in the presence of lithium aluminum hydride and finally redistilled.

(26) O. Hromatka, I. Grass, and F. Sauter, *Monatsh.*, **87**, 701 (1956); *Chem. Abstr.*, **51**, 8109h (1957).

Procedure E. N,N-Dialkylthioxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 2-chloro-*N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine is an example of this general procedure for the dehydration of thioxanthen-9-ol analogs. Five grams (0.015 mole) of 2-chloro-9-(3-dimethylaminopropyl)thioxanthen-9-ol, isolated according to Procedure B, was dissolved in 100 ml. of anhydrous benzene, and hydrogen chloride was bubbled through the solution at room temperature for 15 min. During this time the solution turned dark red and a dark red gum separated (thioxanthonium salt). About 100 ml. of anhydrous ethanol was then added and the resultant, virtually colorless solution was evaporated on a steam bath *in vacuo*. The residue, a white glass, was dissolved in 25 ml. of absolute ethanol and diluted with anhydrous ether to the cloud point. On standing, the colorless hydrochloride crystallized and was collected, m.p. 181–193°. Recrystallization from ethanol by the addition of ether afforded 4.7 g. (89% yield) of product (Table II, No. 19), m.p. 191–193° (lit.,[11] m.p. 189–190°). No effort was made to separate the *cis* and *trans* isomers. The free base was obtained from the hydrochloride and distilled; b.p. 210–215°/0.5 mm.

Anal. Calcd. for $C_{18}H_{18}ClNS$ (315.86): C, 68.4; H, 5.74; Cl, 11.2; N, 4.43; S, 10.2 Found: C, 68.5; H, 5.91; Cl, 11.3; N, 4.26; S, 10.3.

Procedure F. N,N-Dialkylthioxanthen-$\Delta^{9,\gamma}$-propylamine analogs (Table II). The preparation of 1-[3-(2-chlorothioxanthen-9-yliden)propyl]-4-methylpiperazine dimaleate (and other salts) is an example of this general method. 2-Chloro-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthen-9-ol, 83.9 g. (0.22 mole) (Procedure C), in 250 ml. of concd. hydrochloric acid and 500 ml. of glacial acetic acid, was heated under reflux for 2 hr. The dark red solution (presumably the thioxanthonium cation) was made alkaline with 20% sodium hydroxide and extracted several times with ether. The combined ether extracts (yellow solution), after being washed free of alkali, were dried over magnesium sulfate and evaporated to dryness. The yield of the crude base[27] was 66.4 g. (76%) which could not be crystallized. This base, 61.4 g. (0.16 mole) in 300 ml. of ethanol, was treated with 38.2 g. (0.34 mole) of maleic acid in 300 ml. of ethanol. The crystalline salt was collected after 1 hr.; yield, 93 g. (94% from the crude base), m.p. 185–187° dec. Recrystallization from 85% alcohol yielded 80 g. (78% recovery) of pure dimaleate, m.p. 190–192°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2C_4H_4O_4$ (603.09): C, 57.8; H, 5.18; Cl, 5.88; N, 4.65; S, 5.32. Found: C, 57.6; H, 5.53; Cl, 5.17; N, 4.91; S, 5.47.

Using the above procedure, from 5.0 g. (0.013 mole) of crude base in 30 ml. of ethanol and 3.1 g. (0.027 mole) of fumaric acid in 100 ml. of ethanol, 7.2 g. (92% yield) of the difumarate salt was isolated, m.p. 220–222° dec. Recrystallization from ethanol afforded 6.0 g.(77% yield) of product, m.p. 219–221° dec.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2C_4H_4O_4$ (603.09): C, 57.8; H, 5.18; Cl, 5.88; N, 4.65; S, 5.32. Found: C, 57.1; H, 5.18; Cl, 5.68; N, 4.87; S, 5.68.

To 12.9 g. of crude base, in 15 ml. of ethanol, was added 50 ml. of 2.5*N* aqueous nitric acid and the mixture was allowed to stand for 0.5 hr. The precipitated dinitrate was collected, washed with water and dried. The yield was 14.9 g. (86% from crude base). A sample was recrystallized from boiling water, and the pure dinitrate decomposed instantly at 181°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2HNO_3$ (496.97): C, 50.8; H, 5.07; Cl, 7.13; N, 11.3; S, 6.45. Found: C, 50.8; H, 5.02; Cl, 7.47; N, 11.2; S, 6.69.

The dinitrate, 13.5 g. (0.027 mole) was suspended in 100 ml. of water and 100 ml. of 20% aqueous sodium hydroxide was added. The mixture was extracted with three 100-ml. portions of ether, the combined ether extracts were washed free of alkali and dried over magnesium sulfate. Evaporation of the ether yielded 9.0 g. (0.024 mole) of the purified base. It was dissolved in 15 ml. of ethanol and treatment with 17 ml. of 2.9*N* alcoholic hydrogen chloride (two equivalents) precipitated the dihydrochloride. Approximately 100 ml. of ethanol was added, and the mixture heated until complete solution was attained. The hot solution was decolorized with charcoal, filtered and allowed to cool. The crystalline dihydrochloride hydrate, 8.7 g. (85% from purified base), melted with decomposition at 235–236°.

Anal. Calcd. for $C_{21}H_{23}ClN_2S \cdot 2HCl \cdot H_2O$ (461.89): C, 54.6; H, 5.89; Cl, 23.0; N, 6.06; S, 6.96. Found: C, 54.7; H, 6.05; Cl, 23.0; N, 6.07; S, 7.35.

This salt was hygroscopic. However the anhydrous dihydrochloride, m.p. 247–249° (Table II, No. 24), was obtained when the atmospheric humidity was low.

trans (or *cis*) *2-Methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine fumarate* (Vb; Table II, No. 15). The hydrochloride (VIb) (Procedure D), 112 g. (0.34 mole), was added to a mixture of 700 ml. of water, 700 ml. of ether, and 70.5 g. (0.51 mole) of potassium carbonate. The mixture was shaken until two clear phases were present. The ether layer was removed and the aqueous layer extracted with three 100-ml. portions of ether. The combined ether layers were dried over magnesium sulfate and clarified. Fumaric acid, 39.5 g. (0.34 mole), was dissolved in 700 ml. of ethanol with heating. This solution, at 40–45°, was then poured into the ether solution above. An immediate precipitate appeared and was separated by filtration after cooling. The yield of the fumarate (dried in an oven at 45°) was 125 g. (89%), m.p. 151–153.5°. Recrystallization from 12 parts of ethanol gave 100 g. of analytically pure product, m.p. 151–153.5°. For analysis see Table II, No. 15.

This fumarate (Vb) was converted to its base (IVb) as described above. An alcoholic solution of this base, upon treatment with one equivalent of alcoholic hydrogen chloride, immediately deposited the hydrochloride (VIb) in 75–90% yield. The melting points, microanalyses, infrared and ultraviolet spectra were identical with those of this hydrochloride (VIb) from the mixture of *cis* and *trans* bases (IV).

cis (or *trans*) *2-Methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine fumarate* (Va; Table II, No. 14). A sample of crude 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine (IV, base), obtained directly from the dehydration of the xanthen-9-ol analog (Procedure D), was treated with an equimolar amount of fumaric acid (as described for the preparation of the lower melting isomer Vb). A mixture of fumarates, m.p. 143–152°, was obtained (90% yield). Repeated fractional crystallization of this product from the minimum amount of ethanol afforded the higher-melting, less soluble fumarate (Va) in about 15% yield, m.p. 170–172° (for analysis see Table II, No. 14). The lower-melting fumarate isomer (Vb) could be isolated from the mother liquors but was best obtained from the hydrochloride (VIb).

A sample of the higher-melting fumarate (Va) was converted to its base (IVa) (see preparation of Vb from VIb). An alcoholic solution of this base was treated with slightly less than one equivalent of alcoholic hydrogen chloride, and concentration of the solution deposited the hydrochloride (VIa), m.p. 183–185° (precipitation of VIa did not begin immediately as VIb did from IVb).

(27) Generally, the analogous xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamine bases were high boiling viscous oils. The dimethylaminopropyl derivatives were readily purified as the hydrochloride salts, since any residual 3-chloro-*N,N*-dimethylpropylamine or by-products from the Grignard reagent could be removed by washing an ethereal solution of the crude reaction product (Procedure A or C) with water. However, the (1-methyl-4-piperazino)propyl derivatives could not be purified this way. In these cases the excess Grignard reagent, or by-products derived from it, could not be removed by washing with water. Accordingly these compounds were isolated as dimaleates, difumarates or dinitrates which could be converted (*via* the free bases) to the desired hydrochlorides.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$ (331.84): C, 68.8; H, 6.68; Cl, 10.7; N, 4.22. Found: C, 68.0; H, 6.81; Cl, 10.7; N, 4.45.

The melting point of this hydrochloride changed to 190–194° on standing for 2 weeks. A mixed melting point with a sample of VIb, prepared from Vb, was not depressed.

2-Methoxyxanthen-9-one (VII). *Isolation from the decomposition of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine.* An ethereal solution of the free base (IV), 5.0 g. (00.017 mole), in a glass-stoppered flask, was allowed to stand for 2 months at room temperature. During the latter part of this period a large cluster of crystals formed, 0.6 g., m.p. 126–129°, which did not dissolve in 2*N* hydrochloric acid. Recrystallization from methanol yielded 0.5g. (13%) of 2-methoxyxanthen-9-one, m.p. 131–132° (lit.,[28] m.p. 130–131°). Its mixture melting point, infrared and ultraviolet spectra ($\lambda_{max}^{CH_3OH}$ 234 mμ, ε 39,100; 247 mμ, ε 33,200; 298 mμ, ε 4,290; 358 mμ, ε 6,550) were identical with those of an authentic sample.

Anal. Calcd. for $C_{14}H_{10}O_3$ (226.22): C, 74.4; H, 4.46. Found: C, 74.1; H, 4.54.

Hydrogen peroxide oxidation of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. A 50-ml. methanol solution of 4.0 g. (0.014 mole) of 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$ propylamine (from VIb) was divided into two 25-ml. portions. Fraction A was treated with 1.0 ml. of 30% hydrogen peroxide (approx. 1 equivalent) and fraction B received 2.0 ml. of 30% hydrogen peroxide (approx. 2 equivalents). Both fractions were kept in glass-stoppered flasks at room temperature. After 48 hr. no changes in the ultraviolet spectra were noticed. Fraction A was then treated with an additional equivalent of hydrogen peroxide while fraction B received two additional equivalents. Fraction B, 24 hr. later, deposited 100 mg. (6.6% yield) of 2-methoxyxanthen-9-one, m.p. 131-132°. Nine days later, fraction A deposited 150 mg. (10% yield) of 2-methoxyxanthen-9-one, while fraction B deposited an additional 250 mg. (16.6% yield) of this compound.

Air-oxidation of 2-methoxy-N,N-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine. A steady stream of air was passed through a solution of 4.0 g. (0.014 mole) of 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine in 40 ml. of ethanol for 12 days. A 10-ml. aliquot was removed and the solvent was evaporated. The residue, 1.0 g., was essentially unchanged starting material, shown by its infrared spectrum. A slight shoulder at 6.0 μ was apparent. 2-Methoxyxanthen-9-one shows a strong absorption peak at 6.03–6.05 μ, and 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine has no absorption in this region. After 12 more days of air oxidation, no further change in the infrared spectrum was observed. It may be concluded, therefore, that under the above conditions, 2-methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine was not oxidized to any appreciable extent. On the other hand, when 1.0 g. (3.4 mmoles) of the oily base was streaked on a glass slide and allowed to stand for several days exposed to air, a solid product was formed. On recrystallization from methanol 0.5 g. (65% yield) of 2-methoxyxanthen-9-one, m.p. 130–131°, was obtained.

9-(3-Dimethylaminopropylidene)xanthen-2-ol hydrochloride. 2-Methoxy-*N,N*-dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, 9.3 g. (0.028 mole) was heated under reflux for 18 hr. in 50 ml. of 48% hydrobromic acid. The resultant dark red solution was diluted with 100 ml. of water, and made slightly alkaline with potassium carbonate. The mixture was then extracted with three 75-ml. portions of ether, and the combined ether extracts were washed with water. The dried (magnesium sulfate) ethereal extract was treated with anhydrous hydrogen chloride and evaporated. The residue was dissolved in 300 ml. of hot ethanol, and decolorized with charcoal. On standing, the white crystalline product separated. It was collected by filtration and recrystallized from 200 ml. of 95% ethanol-dimethylformamide (3:1); yield, 3.5 g. (57%) of pure product, m.p. 219–221° dec. (for analysis see Table II, No. 16).

N,N-Dimethylxanthene-9-propylamine hydrochloride. *N,N*-Dimethylxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride, 4.83 g. (0.016 mole), was dissolved in 75 ml. of absolute ethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 250 mg. of platinum oxide. The reduction proceeded very rapidly, and the theoretical amount of hydrogen was absorbed in about 15 min. At the end of 35 min. the reduction was discontinued. The actual uptake of hydrogen was 457 ml. (theoretical was 445 ml. including the 50 ml. taken up by the platinum oxide). The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was a clear viscous oil. A sample was triturated in petroleum ether (b.p. 90–100°) and then in benzene. The semisolid gum was then dissolved in a few drops of hot acetone and cooled. The crystalline material, so obtained, was used to seed the crystallization of the rest of the product. When the oil had solidified, recrystallization from hot acetone yielded 4.35 g. (90% yield) of product, m.p. 108–110°. A second recrystallization raised the m.p. to 136–138°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$ (303.83): C, 71.2; H, 7.30; Cl, 11.7; N, 4.61. Found: C, 70.7; H, 7.38; Cl, 11.5; N, 4.46.

3-Chloro-α-(3-dimethylaminopropyl)benzhydrol hydrochloride (XI). The Grignard reagent from 6.95 g. (0.286 g.-atom) of magnesium and 34.8 g. (0.286 mole) of 3-chloro-*N,N*-dimethylpropylamine in 250 ml. ether was prepared according to Procedure A. A solution of 31 g. (0.143 mole) of *m*-chlorobenzophenone[29] in 200 ml. of anhydrous benzene was added in portions and the reaction mixture was heated under reflux for 12 hr. The reaction mixture was decomposed with 20% aqueous ammonium chloride solution, and the organic phase separated. It was washed with water and extracted with two 150-ml. portions of *N* hydrochloric acid. On standing at room temperature for 3 hr. the crystalline product separated from the acidic extract. Recrystallization from alcohol-ether afforded 32 g. (66% yield) of product, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{22}ClNO \cdot HCl$ (340.28): C, 63.5; H, 6.81; Cl, 20.8; N, 4.12. Found: C, 63.4; H, 7.21; Cl, 20.9; N, 4.11.

4-(m-Chlorophenyl)-N,N-dimethyl-4-phenyl-3-butenylamine hydrochloride (X). Five grams (0.015 mole) of 3-chloro-α-(3-dimethylaminopropyl)benzhydrol hydrochloride (XI) was dehydrated with 10 ml. of concd. hydrochloric acid and 30 ml. of glacial acetic acid by heating under reflux for 3 hr. The reaction mixture was cooled, diluted with 100 ml. of water, and made alkaline with an excess of potassium carbonate. The free base was extracted with ether and converted to the hydrochloride in the usual way. Recrystallization of the crude product from 10 ml. alcohol and ether (to the cloud point) yielded 3.4 g. (70% yield) of product, m.p. 132–134°.

Anal. Calcd. for $C_{18}H_{20}ClN \cdot HCl$ (322.27): C, 67.1; H, 6.56; Cl, 22.0; N, 4.35. Found: C, 67.0; H, 6.83; Cl, 21.8; N, 4.28.

Attempted desulfurization of 2-chloro-N,N-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride. 2-Chloro-*N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine hydrochloride (prepared by Procedures A and E), 5.0 g. (0.014 mole), and 15 g. of Raney nickel were heated under reflux, with stirring, for 24 hr. The mixture was filtered, and the filtrate evaporated to dryness. The residue was recrystallized from alcohol-ether to give unchanged starting material, 4.0 g. (80% yield), m.p. 191–193°. A mixed melting point was unchanged.

N-m-Chlorophenyl-N',N'-dimethyl-N-phenyl-1,3-propanediamine hydrochloride (XIII). A mixture of 18.0 g. (0.09 mole of *m*-chlorodiphenylamine[30] and 5.9 g. (0.15 mole) of sodium

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amide in 300 ml. of anhydrous benzene was heated under reflux for 3 hr. 3-Chloro-*N,N*-dimethylpropylamine, 16.5 g. (0.13 mole), in 50 ml. of anhydrous benzene was added dropwise over a 30-min. period and the mixture was heated under reflux with stirring for an additional 5 hr. The excess sodium amide was decomposed with 25 ml. of ethanol followed by 50 ml. of water. The aqueous phase was separated and extracted with ether. The benzene and ether phases were combined, washed with water and then extracted with two 100-ml. portions of *N* hydrochloric acid. The acidic extracts were made alkaline with excess sodium carbonate, and extracted several times with ether. The ether extracts were dried and evaporated. Distillation of the residue yielded 21.0 g. (73% yield) of product, b.p. 152–155°/0.5 mm.

Anal. Calcd. for $C_{17}H_{21}ClN_2$ (288.82): C, 70.7; H, 7.33; Cl, 12.3; N, 9.70. Found: C, 69.9; H, 7.58; Cl, 12.3; N, 9.84.

The hydrochloride melted at 138–139°.

Anal. Calcd. for $C_{17}H_{21}ClN_2 \cdot HCl$ (325.28): C, 62.8; H, 6.81; Cl, 21.8; N, 8.61. Found: C, 62.4; H, 6.93; Cl, 22.1; N, 8.36.

α-(3-Dimethylaminopropyl)-o-hydroxybenzhydrol (XIV). The Grignard reagent was prepared according to Procedure A from 5.75 g. (0.236 g.-atom) of magnesium and 28.7 g. (0.236 mole) of 3-chloro-*N,N*-dimethylpropylamine in 250 ml of ether. *o*-Methoxybenzophenone,[31] 25 g. (0.118 mole), in 200 ml. of ether was added in small portions. The reaction mixture was heated under reflux for 16 hr., cooled and decomposed with 250 ml. of a cold 10% aqueous ammonium chloride solution. The organic phase was separated and extracted with 250 ml. of 0.5*N* hydrochloric acid. The acidic aqueous phase was made alkaline with potassium carbonate and extracted with ether. The dried ether extract was evaporated to a solid residue. Recrystallization from ethanol yielded 20 g. (56.5%) of product, m.p. 116–117°.

Anal. Calcd. for $C_{18}H_{23}NO_2$ (385.37): C, 75.8; H, 8.12; N, 4.91. Found: C, 75.0; H, 8.06; N, 4.90.

o-(4-Dimethylamino-1-phenyl-1-butenyl)phenol hydrochloride (XV). A mixture of 5 g. (0.018 mole) of α-(3-dimethylaminopropyl)-*o*-hydroxybenzhydrol (XIV), 10 ml. of concd. hydrochloric acid, and 30 ml. of glacial acetic acid was heated under reflux for 3 hr., cooled, diluted with 75 ml. of water, and made alkaline with an excess of potassium carbonate. The free base was extracted with ether and converted to the hydrochloride in the usual way. The yield of the hydrochloride was 4.0 g. (70%), m.p. 184–185°.

Anal. Calcd. for $C_{18}H_{21}NO \cdot HCl$ (303.83): C, 71.2; H, 7.30; Cl, 11.7; N, 4.61. Found: C, 71.0; H, 7.22; Cl, 12.2; N, 4.57.

9-(3-Dimethylaminopropyl)fluoren-9-ol (XVII). The Grignard reagent was prepared from 4.9 g. (0.2 g.-atom) of magnesium and 24.3 g. (0.2 mole) of 3-chloro-*N,N*-dimethylpropylamine in 150 ml. of ether as described in Procedure A. Fluoren-9-one, 18.1 g. (0.1 mole), in 150 ml. of benzene was added and the reaction mixture (a yellow suspension) was heated under reflux until all the magnesium was consumed (30 hr.). The reaction was worked up according to Procedure B, and the fluoren-9-ol derivative was isolated as the free base. Recrystallization from alcohol afforded 8.0 g. (30% yield) of product, m.p. 101–103°.

Anal. Calcd. for $C_{18}H_{21}NO$ (267.36): C, 80.9; H, 7.92; N, 5.24. Found: C, 80.6; H, 7.95; N, 5.37.

N,N-Dimethylfluoren-Δ$^{9,\gamma}$-propylamine hydrochloride (XVI). Six grams (0.02 mole) of 9-(3-dimethylaminopropyl)-fluoren-9-ol in 100 ml. of ether was dehydrated by passing hydrogen chloride through the solution for 15 min. The reaction mixture was evaporated and the residue was dissolved in water. The aqueous solution was made alkaline with 10% sodium hydroxide and extracted with ether. The product was isolated as the hydrochloride from the ethereal solution by the addition of alcoholic hydrogen chloride. Recrystallization from alcohol-ether afforded 4.5 g. (71% yield) of product, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{19}N \cdot HCl$ (285.81): C, 75.6; H, 7.05; Cl, 12.4; N, 4.90. Found: C, 75.4; H, 7.35; Cl, 12.5; N, 5.18.

Acknowledgment. We are indebted to N. Q. Quinones, L. H. Yogodzinski, and Miss B. A. Carpentier for their technical assistance; J. H. Clark and his group for the preparation of some of the intermediates; L. Brancone and associates for the microanalyses; and W. Fulmor and associates for the spectral data.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. IX. Lawsone Derivatives Containing an Alkylating Function[1,2]

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Received July 8, 1960

The Mannich reaction involving lawsone (2-hydroxy-1,4-naphthoquinone) and certain amines with formaldehyde and acetaldehyde has been carried out using modifications of a published procedure. In addition, the condensation product of lawsone with 4-bis(2-chloroethyl)aminobenzaldehyde is described.

It has been reported that lawsone (2-hydroxy-1,4-naphthoquinone) undergoes the Mannich reaction with a variety of primary and secondary amines including ethanolamine and morpholine, but not with diethylamine.[3] With the latter the reaction affords instead what appeared to be the diethylamine salt of 3,3′-methylenebis(2-hydroxy-1,4-naphthoquinone) (I).

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