(0.133 g, 10 mmoles). The soln was allowed to stand 12 hr and then poured into Et_2O. The solid was collected and washed with Et_2O (230 mg, mp 188–193°), recrystd from *n*-PrOH, mp 213–215° (80 mg); uv (abs EtOH) max 214, 284, min 263 mμ.

(Procedure D) 2,4-Diamino-5-(1-adamantyl)-6-methylpyrimidine ESA Salt (15b). DAMP (**15a**) (320 mg, 1.23 mmoles) was dissolved in abs EtOH (110 ml), $C_2H_5SO_3H$ (0.137 g, 1.24 mmoles) was added to this soln, the reaction mixt stirred at room temp for 0.5 hr, and the vol reduced to about 20 ml under vacuum, poured into Et_2O, and refrigerated for 4 hr. After collection and washing with Et_2O, the solid product (360 mg) was recrystd, PrOH (28 ml).

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Analogs of Phenothiazines. 4. Effect of Structure upon Neuropharmacological Activity of Some Chlorpromazine Analogs of the Diphenylmethane Type

Carl Kaiser,* Alex M. Pavloff, Eleanor Garvey, Philip J. Fowler, David H. Tedeschi, Charles L. Zirkle,

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

Edward A. Nodiff, and Andrew J. Saggiomo

Germantown Laboratories, Affiliated with the Franklin Institute, Philadelphia, Pennsylvania 19144.

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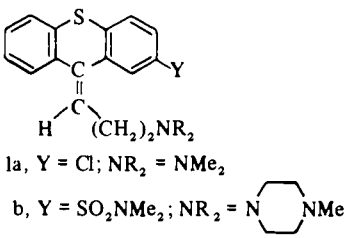
The synthesis of a series of chlorpromazine analogs of the diphenylmethane type, *i.e.*, aminoalkyl and aminoalkylidene derivatives of diphenylmethane, xanthene, thioxanthene, and dibenzocycloheptane, is described. These compounds, prepared as analogs of the tricyclic psychotropic agents, were investigated in several pharmacological tests for psychotropic activity. One of the geometric isomers (presumably, the cis isomer) of *N,N*-dimethyl-2-trifluoromethylthioxanthen-$\Delta^{9,\gamma}$-propylamine (**25**) and the related xanthene **38** were more potent than chlorpromazine in several animal tests in which many neuroleptic agents are active. Aminoalkyl derivatives **58** and **65**, the side-chain-reduced congeners of these olefins, were nearly equipotent with chlorpromazine in various pharmacological tests for neuroleptic activity. Some of the intermediate carbinols (V), congeners of the antiemetic agent, diphenidol, were examined for their ability to inhibit apomorphine-induced emesis in dogs. Two of these compounds, *p*-Cl (**14**) and *p*-CF_3 (**19**) congeners of diphenidol, were more potent than the parent. Structure-activity relationships of these series of compounds are discussed.

Of the many tricyclic analogs of the antipsychotic (neuroleptic) phenothiazines studied since the discovery of chlorpromazine [1-4] the thioxanthene derivative chlorprothixene (Ia) was the first reported to have potent chlorpromazine-like activity.[5] Research in several laboratories has produced other thioxanthenes of type I which are clinically effective neuroleptic agents. Two drugs of this class, Ia and thiothixene (Ib),[6,7] are currently marketed in the United States.

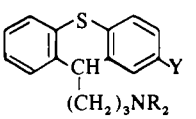
Although structure-activity studies suggest that the pharmacological activity of thioxanthenes and phenothiazines generally varies with structure in a similar way, the published data,[5,8-11] many of which have been obtained only in mice by procedures which do not reliably predict neuroleptic potency,[12,13] are difficult to interpret. Less information is available on the activity of the saturated thioxanthenes II which apparently have not been studied as much as the type I compounds. It was concluded from an early study of a few saturated derivatives in our laboratories and elsewhere[8] that they were considerably less potent than the unsaturated thioxanthenes. Even scantier data on the pharmacological activity of xanthene,[14,15] dibenzocycloheptene,[16-18] dihydroanthracene analogs of I and II, and of the "ring-opened" analogs, the diphenylmethane[14,19,20] derivatives, III and IV, have been published.

As part of an extensive study of structure-activity relationships in the phenothiazine series[21] we have investigated many diphenylamine and diphenylmethane derivatives, in-



Ia, Y = Cl; NR_2 = NMe_2

b, Y = SO_2NMe_2; NR_2 = N NMe



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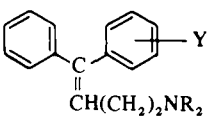
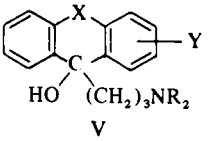


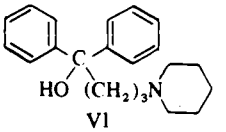
III

IV

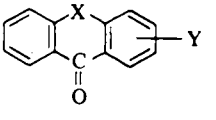


V

X = S, O, ——

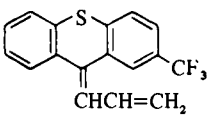


VI



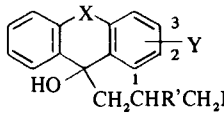
VII

X = S, O, ----



VIII

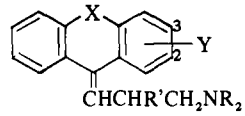
Table I. Aminoalkyl Derivatives of Thioxanthen-9-ols, Xanthen-9-ols, and Diphenylcarbinols



No.	X	Y	R'	NR_2	Salt	Mp, °C	Recrystn solvent	Yield, %	Formula[a]	Pharmacol data: Antiapomorphine activity, dogs[b] Dose, mg/kg (po)	Response, %
1[c]	S	2-CF_3	H	NMe_2		118–119	EtOH-H_2O	95	$C_{19}H_{20}F_3NOS$	*d*	
2	S	2-CF_3	H	4-methylpiperazin-1-yl		158–159	Et_2O	92	$C_{22}H_{25}F_3N_2OS$		
3	O	2-CF_3	Me	NMe_2		*e*		93	$C_{20}H_{22}F_3NO_2$[f]	*g*	
4	O	2-CF_3	H	NMe_2		132–133	EtOH-H_2O	93	$C_{19}H_{20}F_3NO_2$[f]	2(5)	25 (63)[h]
5	O	2-CF_3	H	4-methylpiperazin-1-yl		130–131	MeOH-H_2O	78	$C_{22}H_{25}F_3N_2O_2$	*i*	
6	O	2-CF_3	H	pyrrolidin-1-yl		144–146[j]	EtOH-H_2O	75	$C_{21}H_{25}NO_2$[f]	*k*	
7		H	H	4-methylpiperazin-1-yl		145–146	Et_2O	94	$C_{21}H_{28}N_2O$	25	56
8		H	Me	NMe_2	Maleate	139–140	EtOH-Et_2O	98	$C_{23}H_{29}NO_5$[f]		
9		H	Me	pyrrolidin-1-yl	Maleate	154–155	MeOH-Et_2O	86	$C_{26}H_{33}NO_5$[f]	3.7	17.4
10		H	H	4-(2-benzyloxyethyl)piperazin-1-yl		89–90	Hexane	54	$C_{29}H_{36}N_2O_2$		
11		2-Cl	H	4-methylpiperazin-1-yl	Dimaleate	198 dec	MeOH	91	$C_{29}H_{35}ClN_2O_9$	15.2	5.6[l]
12		3-Cl	H	4-methylpiperazin-1-yl	Dimaleate	204 dec	MeOH	98	$C_{29}H_{35}ClN_2O_9$	15.2	44.4[l]
13		2-Cl	H	pyrrolidin-1-yl	Citrate	181 dec	MeOH	98	$C_{27}H_{34}ClNO_8$[f]	ED_{50} *ca.* 2.8	
14		3-Cl	H	pyrrolidin-1-yl	Maleate	128–129	EtOH-Et_2O	73	$C_{25}H_{30}ClNO_5$	ED_{50} *ca.* 0.9 (0.4–1.9)	
15		2-CF_3	H	4-methylpiperazin-1-yl	Dimaleate	196–197	EtOH-H_2O	79	$C_{30}H_{35}F_3N_2O_9$	*l*	
16		3-CF_3	H	4-methylpiperazin-1-yl	Dimaleate	204 dec	MeOH	76	$C_{30}H_{35}F_3N_2O_9$[m]	9.3	39.7[n]
17		1-CF_3	H	pyrrolidin-1-yl	Maleate	133–135	EtOH-Et_2O	66	$C_{26}H_{30}F_3NO_5$[f]	11.5	8.1
18		2-CF_3	H	pyrrolidin-1-yl	Maleate	138–140	Me_2CO-Et_2O	90	$C_{26}H_{30}F_3NO_5$	3.8 (11.5)	23.8 (66.1)
19		3-CF_3	H	pyrrolidin-1-yl	Maleate	128–129	Me_2CO-Et_2O	88	$C_{26}H_{30}F_3NO$	ED_{50} 0.8 (0.6–1.2)[o]	
Diphenidol (VI)										ED_{50} 1.5 (0.4–2.9)[p]	

[a] All compds were analyzed for C, H, N and analytical values were within ±0.4% of calcd values unless otherwise noted. [b] See Exptl Section. [c] Ref 47, 48. [d] In the mouse rage test 25 mg/kg inhibited induced fighting behavior in 14.2% of the pairs. [e] Bp 142–145° (0.2 mm). [f] Analyzed for C, H. [g] In rats, 200 mg/kg produced no overt response. [h] In the conditioned avoidance response test 75 mg/kg produced specific blockade in 62% of the rats. [i] In the mouse rage test 25 mg/kg did not produce a response. [j] Bp 173–176° (0.2 mm). [k] In the mouse rage test 25 mg/kg inhibited fighting behavior in 43% of the pairs. [l] In rats 182 mg/kg produced no overt response. [m] H: calcd, 5.65; found, 6.33. [n] In rats 188 mg/kg produced no overt response. [o] In the rat dose range test 230 mg/kg produced decreased motor activity, ptosis, and low body posture. In the conditioned avoidance response test 230 mg/kg produced specific blockade in 50% of the rats. [p] Ref 22.

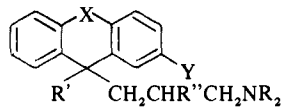
Table II. Aminopropylidene Derivatives of Thioxanthenes, Xanthenes, and Diphenylmethanes



No.	X	Y	R'	NR_2	Salt	Mp, °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
20[c]	S	H	H	NMe_2						
21[c]	S	H	H	N◠NMe						
22	S	H	H	N◡	Citrate	105–108[d]	$EtOH-Et_2O$	A–B	55	$C_{26}H_{29}NO_7S$[e]
23	S	H	H	NHMe	HCl	223–224	$EtOH-Et_2O$	I	70	$C_{17}H_{18}ClNS$[e]
24[c,f]	S	2-Cl	H	NMe_2						
25[g]	S	2-CF_3	H	NMe_2	HCl	199–200	$EtOH-Et_2O$	C[h]	30	$C_{19}H_{19}ClF_3NS$
26[i]	S	2-CF_3	H	NMe_2	HCl	212–213	$EtOH-Et_2O$	C[h]	32	$C_{19}H_{19}ClF_3NS$
27[j]	S	2-CF_3	H	NHMe	HCl	169–171	Me_2CO-Et_2O	I	73	$C_{18}H_{17}ClF_3NS$[e,k]
28[l]	S	2-CF_3	H	NHMe	HCl	177–178	Me_2CO-Et_2O	I	68	$C_{18}H_{17}ClF_3NS$
29	S	2-CF_3	H	N◠NMe	2HCl[m]	243 dec	Me_2CO-Et_2O	B, D	93, 52	$C_{22}H_{25}Cl_2F_3N_2S$
30[n,o]	S	2-CF_3	H	N◡	HCl	251–252	$EtOH-Et_2O$	D[h]	36	$C_{22}H_{23}ClF_3NS$
31[p,q]	S	2-CF_3	H	N◡	Cyclohexyl-sulfamate	155–157	Me_2CO-Et_2O	D[h]	35	$C_{28}H_{35}F_3N_2O_3S$
32[r]	S	2-CF_3	H	N◡	HCl	219–221	$EtOH-Et_2O$	D	33	$C_{21}H_{21}ClF_3NS$
33[s]	S	2-CF_3	H	N◠N$(CH_2)_2OH$	2HCl	227–230	$MeOH-Et_2O$	D	36	$C_{23}H_{27}Cl_2F_3N_2OS$
34	O	H	H	N◡	HCl	182–184	$EtOH-Et_2O$	A–B	70	$C_{20}H_{22}ClNO$[e]
35[n]	O	2-Cl	H	NMe_2	Maleate	175–177	*i*-PrOH	C[h]	27	$C_{22}H_{22}ClNO_5$
36[p]	O	2-Cl	H	NMe_2	Maleate	156–158	*i*-PrOH	C[h]	22	$C_{22}H_{22}ClNO_5$
37	O	2-Cl	H	N◠NMe	2HCl	246 dec	$EtOH-Et_2O$	A–B	74	$C_{21}H_{25}Cl_3N_2O$[t]
38[n]	O	2-CF_3	H	NMe_2	HCl	191–192	Me_2CO	C[h]	28	$C_{19}H_{19}ClF_3NO$[e]
39[p]	O	2-CF_3	H	NMe_2	HCl	192–193	Me_2CO	C[h]	40	$C_{19}H_{19}ClF_3NO$[e]
40[n]	O	2-CF_3	Me	NMe_2	HCl	215–216	$MeCN-Et_2O$	C[h]	32	$C_{20}H_{21}ClF_3NO$[e]
41[p]	O	2-CF_3	Me	NMe_2	HCl	203–204	$MeCN-Et_2O$	C[h]	28	$C_{20}H_{21}ClF_3NO$[e]
42[n]	O	2-CF_3	H	N◠NMe	2HCl	241 dec	EtOH	C[h]	30	$C_{22}H_{25}Cl_2F_3N_2O$[k]
43	O	2-CF_3	H	N◠N$(CH_2)_2OCH_2Ph$	2HCl	219–222	$EtOH-Et_2O$	A, C	80, 85	$C_{23}H_{27}Cl_2F_3N_2O_2$[e]
44		H	H	N◠N$(CH_2)_2OCH_2Ph$	2HCl[u]	259–262	*i*-PrOH-Et_2O	B	79	$C_{21}H_{28}Cl_2N_2$[v]
45		H	H	N◠N$(CH_2)_2OH$	2HCl	240–241	EtOH	B	59	$C_{22}H_{30}Cl_2N_2O$[k]
46		H	Me	NMe_2	HCl	178–179	$EtOH-Et_2O$	B	78	$C_{19}H_{24}ClN$[e]
47		H	Me	N◡	HCl	184–185	$EtOH-Et_2O$	B	72	$C_{22}H_{28}ClN$
48		2-Cl	H	N◠NMe	2HCl[w]	216–218	$EtOH-Et_2O$	B	72	$C_{21}H_{27}Cl_3N_2$[t]
49[n]		3-Cl	H	N◠NMe	2HCl[x]	250 dec	EtOH	B	53	$C_{21}H_{27}Cl_3N_2$[t]
50[p,y]		3-Cl	H	N◠NMe	2HCl	213–215	$EtOH-Et_2O$	B	40	$C_{21}H_{27}Cl_3N_2$[t]
51		2-CF_3	H	N◠NMe	2HCl	215–217[z]	$EtOH-Et_2O$	B	53	$C_{22}H_{27}Cl_2F_3N_2$
52		3-CF_3	H	N◠NMe	Dimaleate	198 dec[aa]	MeOH	B	72	$C_{30}H_{33}F_3N_2O_8$

[a] See Exptl Section, General Procedures. [b] Footnote *a* in Table I. [c] Ref 9. [d] Base, bp 230° (2.5 mm). [e] Analyzed for C, H, [f] Trans isomer. [g] Isomer A. Ref 9 reports mp 199–200° for trans isomer. [h] See Exptl Section for sepn of isomers. [i] Isomer B. Ref 9 reports mp 218–220° for cis isomer. [j] Isomer A. Prepd from **25**. [k] *Anal.* calcd for 0.5 mole of H_2O. [l] Isomer B. Prepd from **26**. [m] A dipicrate was crystd from Me_2CO–EtOH; mp 247° dec. *Anal.* ($C_{34}H_{29}F_3N_8O_{14}S$) C, H, N. [n] Isomer A. [o] Glpc of the base using a 2% GF-1 on Gas Chrom Z Column at 195° gave a single peak with a shorter retention time than that of base isolated from 31. [p] Isomer B. [q] Glpc of base using same conditions as in footnote *o* gave a single peak of longer retention time than that of 30. [r] Glpc of the base using conditions described in footnote *o* gave a single peak, 15-min retention time. The mixture from which **32** was isolated under similar glpc conditions gave two peaks of retention times 14.7 min (54.6%) and 15.0 min (42.5%). [s] Ref 9 reports mp 235–237° for this compd or its isomer. [t] *Anal.* calcd for 1 mole of H_2O. [u] A dipicrate was crystd from Me_2CO, mp 251° dec. *Anal.* ($C_{33}H_{32}N_8O_{14}$) C, H, N. [v] C, calcd, 66.98; found, 66.30. [w] Only one isomer was isolated. A dipicrate crystd from Me_2CO, mp 249° dec. *Anal.* ($C_{33}H_{31}ClN_8O_7$) C, H, N. [x] A dipicrate was crystd from Me_2CO, mp 254° dec. *Anal.* ($C_{33}H_{31}ClN_8O_7$) C, H, N. [y] This isomer was isolated from the mother liquors from isolation of 49. A dipicrate was crystd from Me_2CO–EtOH, mp 244.5° dec. *Anal.* ($C_{33}H_{31}ClN_8O_7$) C, H, N. [z] Base, bp 184–188° (0.5 mm). [aa] Base, bp 160–163° (0.2 mm).

Table III. Aminoalkyl Derivatives of Diphenylmethanes and Related Compounds



No.	X	Y	R'	R''	NR_2	Salt	Mp, °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
53[c]	S	H	H	H	NMe_2						
54	S	H	H	H	NHMe	HCl	192-193	EtOH-Et_2O	F	93	$C_{17}H_{20}ClNS$[d]
55	S	H	Me	H	NMe_2	HCl	183-184	EtOH-Et_2O	H	67	$C_{19}H_{24}ClNS$[e]
56[c]	S	Cl	H	H	NMe_2						
57	S	MeS	H	H	NMe_2		[f]		G	72	$C_{19}H_{23}NS_2$[d]
58	S	CF_3	H	H	NMe_2	Maleate	143-145	EtOH-Et_2O	G, F[g]	52, 76	$C_{23}H_{24}F_3NO_4S$[d]
59	S	CF_3	H	H	N◯NMe	2HCl[h]	271 dec	EtOH	G, F	79, 66	$C_{22}H_{27}Cl_2F_3N_2S$[d]
60	S	CF_3	H	H	NHMe	HCl	161-163	EtOH-Et_2O	I	64	$C_{18}H_{19}ClF_3NS$
61	S	CF_3	Me	H	NMe_2	HCl[i]	164-168	EtOH-Et_2O	H	19	$C_{20}H_{23}ClF_3NS$
62[j]	O	H	H	H	NMe_2						
63	O	H	H	H	N◯	HCl	143-144[k]	EtOH-Et_2O	G	53	$C_{20}H_{24}ClNO$[d]
64	O	Cl	H	H	NMe_2	Citrate	96-97[l]	EtOH-Et_2O	G	53	$C_{24}H_{28}ClNO_4$[d]
65	O	CF_3	H	H	NMe_2	HCl	154-155	EtOAc	E	57	$C_{19}H_{21}ClF_3NO$
66	O	CF_3	H	H	N◯NMe	2HCl	225 dec	EtOH-Et_2O	E	83	$C_{22}H_{27}Cl_2F_3NO$[d,m]
67	O	CF_3	H	H	N◯N$(CH_2)_2OAc$	Dimaleate	189-191 dec	MeOH	*n*	67	$C_{33}H_{37}F_3N_2O_{11}$
68	O	CF_3	H	H	N◯N$(CH_2)_2OH$	2HCl	154-155	EtOAc	E	57	$C_{19}H_{21}ClF_3NO$
69	O	CF_3	H	H	NHMe	HCl	136-137	EtOAc-Et_2O	I	72	$C_{18}H_{19}ClF_3NO$[d,o]
70		H	H	H	N◯NMe	2HCl	271-272	*i*-PrOH-Et_2O	E	59	$C_{21}H_{30}Cl_2N_2$[o]
71		H	H	Me	NMe_2	HCl	189-190	EtOH-Et_2O	E	89	$C_{19}H_{26}ClN$[d]
72		H	H	Me	N◯	HCl	154-155	EtOH-Et_2O	E	87	$C_{23}H_{30}ClN$[d]
73		CF_3	H	H	N◯NMe	Dimaleate	193-194	EtOH-Et_2O	E	88	$C_{30}H_{35}F_3N_2O_8$[d]
74	CMe_2	H	H	H	NMe_2	HCl	196-198	EtOH-Et_2O	E[p]	83	$C_{21}H_{28}ClN$[d]
75	$(CH_2)_2$	H	Me	H	NMe_2	HCl[q]	191-193	EtOH-Et_2O	H	12	$C_{21}H_{28}ClN$

[a] See Exptl Section, General Procedures. [b] Footnote *a*, Table I. [c] Ref 9. [d] Analyzed for C, H. [e] C: calcd, 68.35; found, 67.75. [f] Bp 185-187° (0.5 mm). [g] Also prepd in 85% yield by hydrogenation of mixture of isomers **25** and **26** in EtOH in presence of Raney Ni at 25°. [h] Dimaleate, mp 204° dec, from MeOH. *Anal.* ($C_{30}H_{33}F_2N_2O_4S$) C, H. [i] Nmr peak ($CDCl_3$) at δ 1.9 ppm (s, 3 H, CCH_3). Base, bp 155-158° (0.5 mm). [j] Ref 14. [k] Base, bp 170-175° (0.2 mm). [l] Base, bp 158-160° (0.3 mm). [m] C: calcd, 57.02; found, 56.48. [n] See Exptl Section. [o] *Anal.* calcd for 0.5 mole H_2O. [p] Prepd from *N,N*,9,9-tetramethyl-9,10-dihydroanthracen-$\Delta^{9,\gamma}$-propylamine.[55] [q] Nmr peak ($CDCl_3$) at δ 2.0 ppm (s, 3 H, CCH_3).

cluding types I-IV, as well as several xanthenes, a dihydroanthracene (**74**), and a dibenzocycloheptane (**75**). In this paper we present the results of our pharmacological evaluation of some compounds of these four types. Included are data on some diphenylcarbinols V, the precursors of I-IV, which are analogs of diphenidol (VI), a potent antiemetic agent which lacks most of the pharmacological properties of the antipsychotic drugs.[22] The synthesis and characterization of some compounds not previously reported or not adequately described in the literature are also presented.

Synthesis. The diphenylcarbinol derivatives V (**1-19**, Table I) were prepared by addition of an aminoalkylmagnesium chloride[23] in THF to a benzophenone, thioxanthone, or xanthone (VII). Dehydration of diphenylcarbinols (V) to olefins (**20-28**, **34-52**, Table II) was accomplished with HCl or Ac_2O. Several thioxanthen-$\Delta^{9,\gamma}$-propylamines (**29-33**, Table II) were obtained by addition of amines[24] to the methiodide[25] derived from either *cis*- or *trans*-I (Y = CF_3; NR_2 = NMe_2)[26] or to 9-(2-propenylidene)-2-trifluoromethylthioxanthene (VIII) which likewise was obtained from either methiodide[25] *via* the Hofmann elimination reaction. By all of these routes olefins were obtained as mixtures of trans and cis isomers. Several mixtures were separated, but the stereochemistry of the isomers was not established.

One of the isomeric xanthenes (**42**) was isolated; however, attempts to isolate the other isomer were complicated by the rapid equilibration of the cis and trans forms, probably *via* an oxonium salt,[14] in the presence of mineral acid. Some propylamine derivatives (Table III) were prepared by catalytic hydrogenation or P-HI reduction of the corresponding olefinic compound; others (Table III) were obtained by alkylation of the appropriate diphenylmethane with an aminoalkyl halide in PhMe or DMSO.

Secondary N-methylated amines (**23**, **27**, **28**, **60**, **69**) were prepared from corresponding dimethylamines by hydrolysis of intermediate substituted cyanamides obtained by the von Braun cyanamide reaction.[27]

Syntheses of various intermediates, a 5-oxide (**76**) prepared from **26**, and a succinamide derivative (**77**) obtained from **60** are also described in the Experimental Section.

Pharmacology. Results and Discussion. The pharmacological data on some unsaturated (type I) and saturated (type II) thioxanthenes and their xanthene analogs are collected in Tables IV and V. From a study of a large number of thioxanthenes, including some of those in Tables IV and V, administered ip to mice, Møller Nielsen and coworkers[9] concluded that potent central depressant activity in this series depends on ring substitution at C-2, presence

Table IV. Pharmacological Activity of Thioxanthene- and Xanthene-$\Delta^{9,\gamma}$-propylamines[a]

No.	Dose range,[b] rat	Conditioned avoidance, rat	Ptosis production, rat	Rage, mouse	Depression of spontaneous motor activity, mouse	Antiapomorphine, dog
20			22.2 = 0%			
21	–	ED_{50} *ca.* 115.0	20.6 = 28%	20.6 = 14%		
22		123.0 = 40%	25 = 0%			ED_{50} 23.4
Chlorprothixene	++	11.2 (4.8–25.6)	ED_{50} *ca.* 25.5	ED_{50} *ca.* 4.3	3.4 (1.9–5.3)	2.8 (1.4–13.8)
24		44.8 = 33%			DD_{50} *ca.* 110	
25	++	ED_{50} *ca.* 5.1	6.7 (4.6–9.5)	1.3 (0.9–1.8)	1.1 (0.5–2.7)	0.19 (0.07–0.41)
26	+	90.6 = 55%	22.7 = 13%	22.7 = 28%		13.6 = 65%
34		222 = 50%			DD_{50} *ca.* 78.2	22.2 = 4%
35	++					
36	–					
38	++	9.1 (6.0–13.6)	5.8 (4.1–7.0)	3.2 (2.2–4.5)		9.1 = 93%
39	–	22.8 = 0%		22.8 = 0%		22.8 = 18%
Chlorpromazine	++	11.9 (6.6–21.4)	10.3 (8.0–13.5)	10.8 (7.3–15.8)	5.8 (4.3–7.9)	2.2 (1.4–3.3)
Trifluoperazine		1.0 (0.7–2.2)	0.79 (0.39–1.6)	1.8 (0.9–3.8)	1.2 (0.9–1.6)	ED_{50} < 1.7
Perphenazine		1.0 (0.8–1.3)		2.5 (1.7–3.8)	DD_{50} *ca.* 0.9	
Promazine		28.2 (19.1–41.6)	91 (57.5–144.0)	18 (12.7–25.6)	DD_{50} *ca.* 15.6	

[a]See Exptl Section for description of pharmacol tests. Unless indicated otherwise, results are given as ED_{50}'s with 95% fiducial limits in parentheses or as response (%) at the indicated dose and are expressed as base (mg/kg, po). [b]See Exptl Section, characteristic hind limb spread and catalepsy at 5–50 mg/kg, ++; at 100–200 mg/kg, +; and at a dose greater than 200 mg/kg, –.

Table V. Pharmacological Activity of 9-(Aminopropyl)thioxanthenes and -xanthenes[a]

No.	Dose range,[b] rat	Conditioned avoidance, rat	Ptosis production, rat	Rage, mouse	Depression of spontaneous motor activity, mouse	Antiapomorphine, dog
53	–	310.1 = 30%			DD_{50} *ca.* 124.1	ED_{50} *ca.* 23.0
56	–		31.9 = 13%	19.9 = 29%		
57	+	50 = 44%		25 = 29%		
58	++	ED_{50} *ca.* 10.9	10.3 (7.4–14.7)	13.2 (7.5–23.1)	DD_{50} *ca.* 8.3	3.7 = 78%
59		5 = 67%	7.8 (5.1–12.0)	17.8 (10.1–31.2)		5 = 100%
		10 = 70%				
62		303.5 = 30%			DD_{50} *ca.* 86.7	21.7 (sc) = 76%
63	–	355.6 = 50%				22.2 = 0%
64	–	ED_{50} *ca.* 183.3			DD_{50} *ca.* 55.0	15.3 = 46%
65	++	ED_{50} *ca.* 8.1	10.7 (9.4–12.2)	11.5 (8.4–15.9)	12.0 (5.9–30.8)	ED_{50} *ca.* 3.5
66	++	ED_{50} *ca.* 24.4	21.1 = 25%	21.1 = 29%		
68		5.5 (4.6–6.6)	6.6 (4.8–9.2)	12.8 = 28%		
				17.0 = 72%		

[a]Footnote *a*, Table IV. [b]Footnote *b*, Table IV.

of a double bond between C-9 and the side chain, and a cis configuration† at the double bond. However, the data of these authors are difficult to interpret because the relative potencies of standard phenothiazine neuroleptics determined by their procedures do not correlate with the relative potencies of these agents in the clinic or in producing neuroleptic-like pharmacological effects in animals, *i.e.*, in tests such as blockade of conditioned avoidance response, ptosis, catalepsy, and amphetamine antagonism.[12,13] For example, these workers[9] report that promazine, chlorpromazine, and trifluoperazine are approximately equipotent in reducing spontaneous motor activity of mice, whereas it is well established in the clinic and in certain animal tests that trifluoperazine is at least 10 times more potent than chlorpromazine which in turn is more potent than promazine.

According to the data of Møller Nielsen, *et al.*,[9] the unsaturated thioxanthene derivative without a substituent in the 2 position (**20**) is about as potent as its phenothiazine analog, promazine, and more potent than the corresponding saturated thioxanthene (**53**), and its 2-chloro derivative (**56**), an analog of chlorpromazine. In dose-range studies and the conditioned avoidance test in rats we find the unsaturated derivative, **20**, and its two congeners, **21** and **22**, as well as the saturated derivative **53** (Table V), are much less potent than promazine.

Ring substitution of unsaturated (type I) compounds leads to geometrical isomerism. As noted previously[9] and from data in Table IV, in all instances one of the isomers, presumably cis[6,9,†] (chlorprothixene *vs.* **24**, **25** *vs.* **26**, **35** *vs.* **36**, and **38** *vs.* **39**), is considerably more potent than the other. Introduction of Cl in the 2 position leads, in the case of the cis isomer of the unsaturated thioxanthene (chlorprothixene), to marked enhancement of potency but appears to have little effect on activity of the saturated derivative (**56**). In the saturated thioxanthene series, a 2-MeS derivative (**57**) is somewhat more effective than its Cl counterpart (**56**). Introduction of the 2-CF_3 group greatly enhances potency of not only the unsaturated thioxanthene (**25**) but of the saturated congener (**58**) as well. Similar chlorpromazine-like potency is evidenced by **59**, an analog of **58** in which the NMe_2 group is replaced by *N*-methylpiperazino moiety. The unsaturated trifluoromethylthioxanthene with an *N*-methylpiperazino group (**29**) was ineffective in the mouse rage test at 25 mg/kg, and at 100 mg/kg it produced only a 20% response in the rat ptosis test; however, the isomer composition was not established. The isomeric purity of the corresponding hydroxyethylpiperazino derivative (**33**) also was not determined; however, it produced significant neuroleptic-like activity at 10 mg/kg. A recent report suggests that in the 2-Me_2NSO_2 thioxanthenes with a piperazino group in the side-chain-unsaturated derivatives (Ib) and the corresponding saturated compounds are about equipotent.[6] Thus, whether an unsaturated thioxanthene will be much more potent than its corresponding saturated analog appears to depend on other structural features in the molecule.

Evidently the 9-H in saturated thioxanthenes cannot be replaced with a larger group without loss of neuroleptic-like properties. The 9-Me derivatives (**55** and **61**, Table III) did not produce neuroleptic-like effects in rats at 182 mg/kg.

In our tests the 2-unsubstituted xanthene derivatives (**34**, **62**, **63**), like the corresponding thioxanthene analogs, show very weak, if any, neuroleptic-like activity. Also in analogy with the thioxanthenes, substitution with Cl in the 2 position of the xanthenes does not result in potent activity in the saturated (**64**) series; however, in the unsaturated series, one of the isomers (**35**), but not the other (**36**), produces chlorpromazine-like effects in the rat dose-range test. Similarly, substitution with CF_3 in the xanthene series produces potent activity in both unsaturated (**38**) and saturated (**65**) derivatives.

It is noteworthy that in the saturated 2-trifluoromethylxanthene series replacement of Me_2N (**65**)[29] with *N*-methylpiperazino (**66**) decreases neuroleptic-like activity whereas this structural change in the phenothiazine, and perhaps also in thioxanthene, derivatives appears to consistently increase potency. Replacement of the *N*-Me group of the piperazine moiety with the $HO(CH_2)_2$ group enhances potency, but the resulting compound (**68**) is not significantly more potent than the Me_2N derivative (**65**). Whether similar structural effects are observed in unsaturated xanthenes has not been determined. Initial attempts to isolate the more active geometric isomer of the CF_3-substituted *N*-methylpiperazine derivative (**42**), which was ineffective in the rat ptosis and mouse rage tests at 20.7 mg/kg, were not successful due to the facile isomerization that occurs in compounds of this type.[14] A 2-Cl derivative (**37**) produced no significant neuroleptic-like activity and only 30% blockage of the conditioned avoidance response at 80 mg/kg in rats; however, again the stereochemistry of this compound was not established.

Secondary N-methylated amines of types I and II in all instances were less potent than their Me_2N parents. In mice the unsaturated thioxanthene **23**, at 44 mg/kg, caused only decreased motor activity. The 2-CF_3-substituted analog **27** (presumably cis), derived from **25**, produced only 57% response in the mouse rage test at 4.3 mg/kg and twice this dose was required to produce chlorpromazine-like activity in the same species. Isomeric (presumably trans) **28** did not produce neuroleptic-like activity in mice at 90 mg/kg. The saturated thioxanthene **54** produced only decreased motor activity and distended testes at 88 mg/kg in mice. The 2-CF_3 analog **60** was about 0.1 as potent as **58**, its tertiary amine precursor, in the test for depression of motor activity in mice (DD_{50} *ca.* 79 mg/kg). Similarly, the CF_3-substituted saturated xanthene **69** was less potent than the parent tertiary amine **65**; it produced no response in the mouse rage test at 25 mg/kg and only 57% response at 50 mg/kg in the rat ptosis test.

The 10,10-dimethyldihydroanthracene **74** is a side-chain-reduced analog of the antidepressant melitracene.[30] It produced slight imipramine-like activity in the test for prevention of reserpine-induced ptosis in rats,[21] 44.5 mg/kg gave a 50% response. A derivative (**75**) of dibenzocycloheptane, a ring system associated with imipramine-like activity, did not produce overt effects in rats at 89 mg/kg and it was inactive in the mouse rage test at 44.5 mg/kg. As in the case of the thioxanthenes **55** and **61**, the relative inactivity of **75** may be associated with Me substitution of the bridgehead C.

Diphenylmethanes III (Table II, **44–52**) and IV (Table III, **70–73**) generally were devoid of significant activity in the pharmacological tests in which most neuroleptic agents are effective.

Aminoalkyl derivatives (V) of diphenylcarbinol, xanthen-9-ol, and thioxanthen-9-ol (Table I) are structurally related to the potent antiemetic diphenidol (VI). For this reason most of these compounds were studied for antiemetic activity in the dog antiapomorphine test.[22] In this test both di-

†The pharmacologically active isomers were originally assigned the trans configuration (ref 9); however, X-ray crystallographic analysis has subsequently established that chlorprothixene is the cis isomer.[28]

phenidol and chlorpromazine are effective. Substitution of one of the phenyl groups of diphenidol had a variable influence on apomorphine-blocking activity. Introduction of a *p*-Cl (**14**) or *p*-CF_3 (**19**) substituent increased potency somewhat; however, a *m*-Cl derivative (**13**) was only about 0.5 as potent as the parent and both meta (**18**) and ortho (**17**) CF_3 congeners were still less effective. A branched-chain analog **9** was significantly less potent than Vl in the dog antiapomorphine test. Replacement of the piperidyl substituent of Vl with an *N*-methylpiperazino group also resulted in a marked decrease in potency; 7 had significantly weaker antiemetic activity than the parent. Several benzene-ring-substituted derivatives (**11**, **12**, **16**) of **7** likewise were only weakly effective in this test. The xanthen-9-ol **4** was also less active than Vl.

Like diphenidol,[22] most of the carbinols (Table I) had only limited activity in other tests in which most neuroleptic agents are effective. The thioxanthenol **1** and the xanthenol **6** were only weakly effective in the mouse rage test, and **5** was inactive at 25 mg/kg. Diphenylcarbinols **11**, **12**, **15**, and **16** (300 mg/kg of dimaleate salts) produced no observable response and **19** (230 mg/kg) produced only slightly decreased motor activity, ptosis, and low body posture in rats.

Experimental Section‡

Pharmacology. Materials and Methods. Compds studied are listed in Tables I, II, and III. Unless otherwise indicated, compds were administered orally in the form (salt or base) indicated in Tables I–III. All doses of compds are expressed as the base, unless otherwise indicated. Adult male albino rats of the Sprague–Dawley and Wistar strains and male albino mice from Carworth Farms (CF_1) were employed in the expts. Adult mongrel dogs of both sexes were used in the antiapomorphine test.

In all tests, observations and values are reported at the time of peak drug effect. The log-probit method[31] was used for analysis of quantal dose–response data. Analysis of quantitative dose–response data and calcns of fiducial limits (Feiller's limits) were performed by the method of Finney.[32]

Dose Range. Various doses of the compd were administered orally to rats or mice and overt effects were recorded over an extended period of time until the animals appeared normal. Animals were observed for at least 6 hr on the day of treatment and at least once daily for 7–10 days after compd administration. In this test moderate doses of neuroleptic agents, such as chlorpromazine produce decreased motor activity, decreased curiosity, ptosis, low body posture, hypotonia, and a characteristic hind limb spread. At higher doses, catalepsy (*i.e.*, the animal maintains the set position in which feet are placed on 4 appropriately spaced No. 7 rubber stoppers for 30 sec) and loss of myotactic reflex were observed. Compds in Tables IV and V were examined for their ability to produce these symptoms.

Conditioned avoidance response test[33,34] and statistical analysis of the data were performed as described previously.[35] The ED_{50} in the conditioned response test is the dose which prevents 50% of the rats from responding to a conditioned stimulus (buzzer) by jumping onto a pole.

Ptosis production[36] was studied using preselected nonptotic rats. The ED_{50} in this test is the dose of compd causing 50% of the rats to exhibit ptosis of both eyes at any time following administration.

In this test, ptosis is defined as 15 sec or more of uninterrupted closure (70% or greater) of the palpebral fissure during a 90-sec observation period.

Rage Test.[37] Compds were examined for their ability to suppress foot-shock-induced fighting episodes in pairs of mice as described previously.[37] The ED_{50} in the rage test is the dose of compd which suppresses fighting episodes in 50% of fighting pairs.

Depression of Spontaneous Motor Activity. Spontaneous motor activity of mice was measured by a modification[38] of the photoelectric cell counter method of Winter and Flataker.[39] The depressant dose 50 (DD_{50}) is that which reduces the average counts of the treated mice to half that of control animals tested concomitantly.

Antiapomorphine Test. Antiemetic activity was assessed from the ability of compds to diminish frequency of apomorphine-induced emesis in dogs by a modification[22] of the method of Chen and Ensor.[40] The ED_{50} is defined as the dose of compd which reduces the frequency of emesis of treated dogs to a value 50% below that of controls tested at the same time.

Prevention of reserpine-induced ptosis was measured in rats as described previously.[21] The ED_{50} is the dose of compd which prevents significant ptosis (*i.e.*, 70% or greater closure of the palpebral fissure lasting for 15 or more sec) in rats treated with 1 mg/kg (iv) of reserpine.

Chemistry. General Procedures. A. Prepn of Diphenylcarbinol Derivs. Several drops of EtBr were added to a stirred suspension of 2.43 g (0.1 g-atom) of Mg turnings in 5 ml of THF. After reaction was initiated 0.1 mole of the appropriate chloroalkylamine [3-chloro-*N*,*N*-dimethylpropylamine,[23] 3-chloro-*N*,*N*,2-trimethylpropylamine,[41] 1-(3-chloropropyl)-4-methylpiperazine,[42] 1-(3-chloropropyl)pyrrolidine,[43] 1-(3-chloropropyl)piperidine,[23] 1-(3-chloro-2-methylpropyl)piperidine,[44] or 1-(2-benzyloxyethyl)-4-(3-chloropropyl)piperazine[45,46]] in 50 ml of THF was added at a rate to maintain reflux. After addn was completed the mixt was stirred and refluxed for 2 hr, then a soln of 0.065 mole of ketone (2-chloroxanthone,[46] 2-trifluoromethylxanthone,[47,48] 2-trifluoromethylthioxanthone,[47,48] 10,10-dimethyl-9-anthrone, 3- or 4-chlorobenzophenone or 2-,[49] 3-,[49] or 4-trifluoromethylbenzophenone[19]) in 75 ml of THF was added during 1 hr. The mixt was refluxed an addnl hr, then about two-thirds of the solvent was removed *in vacuo*. The mixt was poured into an aqueous soln of 16.4 g (0.3 mole) of NH_4Cl. Cryst products were filtered. Noncryst compds were extd (Et_2O) and the exts were dried, concd, and converted to salts as indicated in Table I.

B. HCl Dehydration of Diphenylcarbinol Derivs. The prepn of **29** is an example of this procedure. A mixt of 21.1 g (0.05 mole) of **2** and 150 ml of 12 *N* HCl was stirred and refluxed for 3 hr. The soln was concd *in vacuo*, the residue was dissolved in H_2O, and the aqueous soln was made alk (NaOH). The mixt was extd with Et_2O. The exts were dried and concd, and the residual amine was converted into a dihydrochloride (**29**), Table II.

C. Ac_2O Dehydration of Diphenylcarbinol Derivs. A soln of 0.1 mole of the appropriate aminoalkyldiphenylcarbinol and 200 ml of Ac_2O was refluxed for 2 hr, and then concd *in vacuo*. The residue was suspended in H_2O, the mixt was made strongly alk (NaOH) and was extd (Et_2O). The ether soln was dried and concd. Residual olefinic amines were distd and/or converted to salts, Table II.

D. Addn of Amines to 9-(2-Propenylidene)-2-trifluoromethylthioxanthene (VIII). A soln of 8.0 g (0.026 mole) of VIII§ and 50 ml of amine [piperidine, pyrrolidine, 1-methylpiperazine, or 1-(2-hydroxyethyl)piperazine] was heated at 100° for 20 hr. It was concd and the residue was suspended in 1 *N* H_3PO_4. After the mixt was extd with Et_2O the acidic soln was made alk (KOH) and the pptd material was extd (Et_2O). The ext was dried and concd to give mixts of isomeric amines. Hydrochlorides (**29**, **30**, **32**, and **33**) were prepd and recrystd from solvents indicated in Table II to give single isomers (A). The filtrate from isolation of **30** was concd, the residue was suspended in 2 *N* NaOH, and the mixt was extd (Et_2O). After it was dried, the Et_2O soln was concd and the residual amine was converted to a cyclohexylsulfamate (**31**). A second isomer was not isolated from prepn of **29**, **32**, and **33**.

E. Catalytic Hydrogenation of Olefins. This method is exemplified by the hydrogenation and hydrogenolysis of **43**. A mixt of 14.5 g (0.025 mole) of **43**, 4 g of 10% Pd/C, and 150 ml of EtOH was hydrogenated at 25° at an initial H_2 pressure of 3.5 kg/cm². After H_2 uptake was completed (12 hr) the mixt was filtered, the filtrate was concd and the residue was dissolved in H_2O. The aqueous soln was made alk (NaOH) and the mixt was extd (Et_2O). The exts were dried and residual 4-[3-(2-trifluoromethyl-9-xanthenyl)-propyl]-1-piperazineethanol was converted to a dihydrochloride (**68**).

F. P-HI Reduction of Olefins. Prepn of **58** illustrates this procedure. A mixt of 15.0 g (0.043 mole) of *N*,*N*-dimethyl-2-trifluoro-

‡Mp and bp are not corrected. Microanalyses were performed by Miss Margaret Carroll and coworkers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories. Where analyses are reported by the symbols of the elements, anal results were within ±0.4% of the calcd values. Nmr spectra were obtained on a Varian A-60 Spectrometer (Me_4Si).

§In several expts, *N*,*N*-dimethyl-2-trifluoromethylthioxanthen-$\Delta^{9,\gamma}$-propylamine methiodide was employed instead of VIII. 1-Methylpiperazine and piperidine gave approx equal yields of the resp piperazine or piperidine from either starting material.

methylthioxanthen-$\Delta^{9,\gamma}$-propylamine,# 43 ml of 57% HI, 43 ml of AcOH, and 10.3 g (0.33 g-atom) of red P was stirred and refluxed for 2 hr. The mixt was filtered, the filtrate was dild with ice H_2O, made alk with NaOH, and extd (Et_2O). The exts were dried and concd. The residual liquid was distd and then it was converted into a maleate (58).

G. Alkylation of Diphenylmethane Derivs in PhMe. Prepn of 59 is an example of this procedure. A mixt of 2-trifluoromethylthioxanthene (13.4 g, 0.05 mole), 2.9 g (0.075 mole) of $NaNH_2$, and 200 ml of PhMe was stirred and refluxed for 2 hr. After the mixt was cooled to 25°, 17.6 g (0.1 mole) of 1-(3-chloropropyl)-4-methylpiperazine[42] in 50 ml of PhMe was added slowly. The mixt was stirred and refluxed for 20 hr, then 100 ml of H_2O was added slowly. The PhMe soln was sepd and extd with 1 *N* HCl. Acid exts were made alk with NaOH and the mixt was extd (Et_2O). The Et_2O soln was dried, concd, and converted into a dihydrochloride (59).

H. Alkylation of Diphenylmethane Derivs in DMSO. To a stirred suspension of 0.1 mole of a 52% dispersion of NaH in mineral oil in 50 ml of DMSO at 25° was added slowly a soln of the diphenylmethane deriv in 50 ml of DMSO, and the mixt was heated at 60–70° until H_2 evolution was completed. The mixt was cooled to 25° and a soln of 0.13 mole of 3-chloro-*N,N*-dimethylpropylamine[23] in 25 ml of DMSO was added slowly, then it was heated gradually to 100°. After 2 hr at 100° the stirred mixt was dild with H_2O and extd (Et_2O). The exts were extd with 1 *N* HCl. Acid exts were made alk with 2 *N* NaOH, the mixt was extd with Et_2O, and the Et_2O exts were dried and concd. Residual amines were distd and converted into the indicated salts (Table III).

1. Monodemethylation of Dimethylaminoalkyl Derivs. A mixt of 0.025 mole of the appropriate dimethylaminoalkyl deriv (bases from 25, 26, 58, 65, or *N,N*-dimethylthioxanthene-$\Delta^{9,\gamma}$-propylamine[14]) and 2.9 g (0.028 mole) of BrCN in 75 ml of C_6H_6 was stirred at 50° for 6 hr. The C_6H_6 soln was extd with 1 *N* HCl, dried, and evapd to give crude cyanamide derivs.

To cyanamide derivs from 25 and 26 in 100 ml of Et_2O was added 33 ml of 3 *M* MeMgBr in Et_2O. The mixt was stirred and refluxed for 20 hr, then it was slowly poured into ice H_2O and excess NaOH. The Et_2O layer was sepd and the aqueous mixt was extd with Et_2O. The combined Et_2O solns were extd with 1 *N* HCl, the acid exts were made alk (NaOH), and the mixt was extd with Et_2O. After the Et_2O exts were dried, they were distd to give pale yellow liquids, bp 153–156° (0.15 mm), which were converted to hydrochlorides, 27 and 28.

For prepn of 23 and 69, crude cyanamides from 65 and *N,N*-dimethylthioxanthen-$\Delta^{9,\gamma}$-propylamine[11] (0.025 mole) were refluxed with 0.15 mole of NaOH in EtOH–H_2O for 24 hr and were isolated in the usual way.

For prepn of 60, crude cyanamide (0.3 mole) from 58 was stirred and refluxed for 17 hr with a soln of 300 ml of AcOH, 200 ml of H_2O, and 30 ml of 12 *N* HCl. The reaction mixt was concd, made alk, and processed in the usual manner.

Separation of Isomeric 3-Aminopropylidene Derivs. A. *N,N*-Dimethyl-2-trifluoromethylthioxanthene-$\Delta^{9,\gamma}$-propylamine Hydrochlorides[9] (25 and 26). A mixt of isomers was obtained in 71% yield from 1 by procedure C, bp 155–160° (0.25 mm). The olefinic mixt (24.9 g, 0.071 mole) was dissolved in 120 ml of EtOH and a soln of 34.8 g (0.142 mole) of styphnic acid in 185 ml of EtOH was added slowly. The mixt was heated to reflux and the resulting soln was allowed to cool to 25° to give 17.6 g (44%) of a bright yellow styphnate, mp 201–202°, after washing thoroughly with EtOH. *Anal.* ($C_{25}H_{21}F_5N_4O_8S$) C, H, N.

Free amine was liberated by passing a soln of the styphnate in Me_2CO through a column of basic alumina. The Me_2CO eluates were concd and converted to a hydrochloride of isomer B (26).

The combined filtrates and washings from prepn of the above styphnate were concd to 60 ml and cooled to 0° to give 25.6 g (45%) of orange cryst distyphnate, mp 143–145°. *Anal.* ($C_{31}H_{24}F_3N_7O_{16}S$) H, N; C, calcd 44.34; found 44.83.

An Me_2CO soln of the distyphnate was passed through a column of basic alumina, and the Me_2CO eluates were concd to give isomer A which was converted to a hydrochloride (25).

B. 2-Trifluoromethyl-*N,N,β*-trimethylxanthene-$\Delta^{9,\gamma}$-propylamine Hydrochlorides (40 and 41). A mixt of isomeric olefins was obtained from 3 in 85% yield by procedure C, bp 140–143° (0.3 mm). It was crystd from a min vol of petr ether (bp 30–60°) to give 12.0 g of cryst solid, mp 77–80°, which was recrystd from EtOH–H_2O to give 7.5 g, 82.5–83°. *Anal.* ($C_{20}H_{20}F_3NO$) C, H.

This base (isomer A) was converted to a hydrochloride (40). It was also converted to a picrate, mp 157.5–158.5° after recrystn (EtOH). *Anal.* ($C_{26}H_{23}F_3N_4O_8$) C; H, calcd 4.02; found 4.51.

The mother liquors from isolation of isomer A were concd and the residual liquid was treated with excess picric acid in EtOH to give 11.0 g of a picrate, mp 198–199°. *Anal.* ($C_{26}H_{23}F_3N_4O_8$) C, H.

A soln of this picrate in Me_2CO was passed through an alumina column and the eluates were concd to give isomer B which was converted to a hydrochloride (41).

C. *N,N*-Dimethyl-2-trifluoromethylxanthene-$\Delta^{9,\gamma}$-propylamine Hydrochlorides (38 and 39). A mixt of isomeric olefins was obtained in 82% yield from 4 by procedure C, bp 144–146° (0.12 mm). The mixt (6.5 g, 0.02 mole) was treated with 1 equiv of picric acid in EtOH to give 4.4 g of a picrate, mp 194–195° from Me_2CO–Et_2O. *Anal.* ($C_{25}H_{21}F_3N_4O_8$) C, H.

An Me_2CO soln of this picrate was passed through a column of basic alumina and the eluates were concd. The resulting isomer B was converted to a hydrochloride (39).

Filtrates from prepn and recrystn of the above picrate were passed through a column of basic alumina and eluted with Me_2CO. The eluates were concd. To the residual liquid was added 1 equiv of styphnic acid in EtOH to give 4.5 g of a styphnate, mp 176–176.5° after several recrystns from Me_2CO–EtOH. *Anal.* ($C_{25}H_{21}F_3N_4O_9$) C, H.

The base (isomer A) isolated from this styphnate in the usual way was converted to a hydrochloride (38).

D. 2-Chloro-*N,N*-dimethylxanthene-$\Delta^{9,\gamma}$-propylamine Maleates (35 and 36). A mixt of isomeric olefins, bp 175–183° (0.45 mm), was obtained in 69.5% yield from 2-chloro-9-(3-dimethylaminopropyl)xanthen-9-ol[14] by procedure C. To the mixt (11.4 g, 0.038 mole) in 225 ml of EtOH was added 5.2 g (0.041 mole) of oxalic acid·$2H_2O$ in 100 ml of EtOH. The cryst salt (10.5 g) was filtered and then it was stirred with 275 ml of boiling EtOH. The hot mixt was filtered to give 5.5 g of cryst oxalate, mp 215–217°. The oxalate was converted to base which was treated with an equiv of maleic acid in EtOH–Et_2O to give a cryst maleate which was recrystd twice from *i*-PrOH to afford 4.3 g of isomer A (35).

All EtOH solns from prepn and purification of the above oxalate were combined and concd, and the base was isolated. The base was converted to 4.5 g of an HCl salt, mp 189–191°,** after 3 recrystns from *i*-PrOH–Et_2O. Base, liberated from this HCl salt, was converted to a maleate which was recrystd 3 times from *i*-PrOH to give 3.5 g of isomer B (36).

E. Attempted Separation of *cis*- and *trans*-1-Methyl-4-[3-(2-trifluoromethylxanthen-9-ylidene)propyl]piperazine Dihydrochlorides (42). Dehydration of 5 according to procedure C gave 86% of a mixt of isomers, bp 172–175° (0.2 mm). Crystn of the mixt (25 g) from petr ether (bp 30–60°), followed by several recrystns from aqueous MeCN gave 7.5 g of isomer A, mp 83.5–85°. *Anal.* ($C_{22}H_{23}F_3N_2O$) C, H.

Isomer A was converted to a dihydrochloride (42). Filtrates from isolation of isomer A were concd to leave a residual liquid having an ir spectrum different from that of isomer A; however, this material gave a dihydrochloride (MeCN–EtOH), mp 231° dec. having an ir spectrum identical with that of 42.

2-Chloroxanthene. A mixt of 38 g (0.165 mole) of 2-chloroxanthone[46] and 25 g of $H_2NNH_2·H_2O$ was heated in a sealed system at 200° for 20 hr. The mixt was extd with EtOH; the exts were concd. The residue was distd, bp 130–135° (0.3 mm), and the distillate was recrystd twice from EtOH to give 13.5 g (38%) of colorless crystals, mp 114.5–115°. *Anal.* ($C_{13}H_9ClO$) C, H.

2-Trifluoromethylthioxanthene. A mixt of 50 g (0.18 mole) of 2-trifluoromethyl-9-thioxanthone,[47,48] 320 ml of 85% $H_2NNH_2·H_2O$, and 200 ml of EtOH was heated at 235° with shaking for 8 hr in a high-pressure vessel. The soln was concd *in vacuo*, the residue was suspended in H_2O, and the mixt was extd (Et_2O). The exts were dried and concd to give 33 g (70%) of yellow crystals, mp 94–95° (MeOH). *Anal.* ($C_{14}H_9F_3S$) C, H.

2-Methylthiothioxanthene was prepd from 2-methylthio-9-thioxanthone[50] in the same manner as described for 2-trifluoromethylthioxanthene. Pale yellow crystals, mp 103.5–104.5°, from hexane, were obtained in 88% yield. *Anal.* ($C_{14}H_{12}S_2$) C, H.

9-Methyl-2-trifluoromethylthioxanthen-9-ol. To 16.9 g of a 5.21% soln of MeLi (0.04 mole) in Et_2O under N_2 was added, in portions, 10 g (0.036 mole) of 2-trifluoromethyl-9-thioxanthone.[47,48] The mixt was stirred and refluxed for 2.5 hr, then it was poured

#Either isomer, 25 or 26, as well as mixts of the isomers gave comparable results.

**This HCl salt is probably the same isomer described previously, mp 193–195°,[14] as we were unable to obtain a cryst HCl salt from isomer A.

slowly into 100 ml of 2 *N* HCl. The mixt was extd (Et_2O) and the exts were dried and concd to give 10.5 g (98%) of colorless crystals, mp 90–93°, from hexane. *Anal.* ($C_{15}H_{11}F_3OS$) C, H.

9-Methyl-2-trifluoromethylthioxanthene. A mixt of 10 g (0.034 mole) of 9-methyl-2-trifluoromethylthioxanthen-9-ol, 10.6 g (0.34 g-atom) of red P, 35 ml of AcOH, and 35 ml of 57% HI was stirred and refluxed for 2 hr. The mixt was dild with H_2O and filtered. The filtrate and filter cake were extd (Et_2O). The exts were dried and distd to give 8.0 g of pale yellow liquid, bp 115–120° (0.3 mm), nmr peak ($CDCl_3$) at δ 1.48 (3 H, d, J = 7 Jz), at 4.06 (1 H, q, J = 7 Hz), and at *ca.* 7.3 (7 H, m). *Anal.* ($C_{15}H_{11}F_3S$) C, H.

9-Methylthioxanthene[51,52] **and 10,11-dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene**[53,54] were obtained from 9-thioxanthone and 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one in the same manner as described for synthesis of 9-methyl-2-trifluoromethylthioxanthene.

9-(2-Propenylidene)-2-trifluoromethylthioxanthene (VIII). To a soln of 35 g (0.1 mole) of base liberated from **25**†† in Me_2CO was added excess MeI to give 47 g of colorless cryst methiodide, mp 216–217°. The methiodide was suspended in 400 ml of MeOH, an excess of OH form anion-exchange resin‡‡ was added, and the mixt was stirred for 30 min. The mixt was filtered, the filtrate was concd, and the residue was heated at 100° at 25 mm until gas evolution was completed. An Et_2O soln of the residue was dried and concd. Recrystn of the resulting solid from hexane gave 23.0 g (76%) of pale yellow crystals, mp 86–88°. *Anal.* ($C_{17}H_{11}F_3S$) C, H.

1-(2-Acetoxyethyl)-4-[3-(2-trifluoromethyl-9-xanthenyl)propyl]-piperazine Dimaleate (67). A soln of 9.2 g (0.02 mole) of base liberated from **68**, 3.4 g (0.04 mole) of AcCl and 100 ml of C_6H_6 was stirred and refluxed for 30 min and then concd *in vacuo*. Residual solid was dissolved in H_2O and the soln was made alk with NH_4OH. After extg the mixt with Et_2O, the exts were dried and concd and the remaining liquid was converted to a dimaleate (**67**).

***N*,*N*-Dimethyl-2-trifluoromethylthioxanthene-Δ$^{9,\gamma}$-propylamine 5-Oxide Hydrochloride (76).** To a soln of 3.0 g (0.0086 mole) of **26** in 20 ml of MeOH was added 1.73 g (0.01 mole) of 3-chloroperbenzoic acid. The soln was allowed to stand for 20 hr and then it was dild with Et_2O to give 3.0 g (96%) of colorless crystals, mp 192–194°, after recrystn from EtOH–Et_2O. *Anal.* ($C_{19}H_{19}ClF_3NOS$) C, H.

***N*-[3-(2-Trifluoromethyl-9-thioxanthenyl)propyl]-*N*-methylsuccinamic Acid (77).** A mixt of 10.1 g (0.03 mole) of base liberated from **60**, 3.6 g (0.036 mole) of succinic anhydride, and 40 ml of PhMe was refluxed for 3 hr. The soln was concd *in vacuo* and the residue was crystd from EtOH–H_2O to give 12.0 g (92%) of colorless crystals, mp 106–108°. *Anal.* ($C_{22}H_{22}F_3NO_3S$) C, H, N.

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††Isomer B (**26**) was converted to a diene by the same synthesis; however, the isomer composition of the product was not detd.

‡‡A strongly basic polystyrene alkyl quaternary amine (OH form) of medium porosity was employed. Research grade Rexyn 201 (OH) was purchased from the Fisher Scientific Co.