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Analogs of Phenothiazines. 5. Synthesis and Neuropharmacological Activity of Some Piperidylidene Derivatives of Thioxanthenes, Xanthenes, Dibenzoxepins, and Acridans

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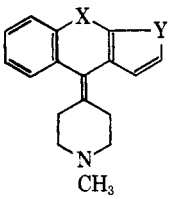
A series of piperidylidene derivatives of thioxanthenes, xanthenes, dibenzoxepins, and acridans was prepared and examined for neuropharmacological activity. Several of these compounds having an appropriate substituent, *e.g.*, CF_3, Cl, SMe, in the 2 position of the tricyclic nucleus were potent neuroleptic agents. For example, in a ptosis production test in rats 1-methyl-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine (11) and its 10-methylacridan congener 17 were seven to eight times more potent than chlorpromazine. In the same test the *N*-cyclobutylmethyl analog (26) of 11 was the most effective member of the series; it was about 18 times more potent than chlorpromazine. In the piperidylidene derivatives of tricyclic compounds, for which neuroleptic activity has not been reported previously, the spatial relationship between the basic nitrogen and the tricyclic nucleus is more restricted than in their antipsychotic aminopropyl- and aminopropylidene-substituted relatives. Some consequences of this observation on the conformational requirements for potent neuroleptic activity of tricyclic compounds are considered.

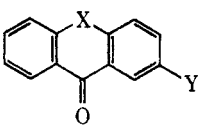
Cyproheptadine (**1a**), a clinically useful antipruritic drug, has potent antihistamine and antiserotonin properties, but it is without notable action on the central nervous system.[1] Antihistamine and antiserotonin activities also have been reported[2] for a series of piperidylidene-substituted tricyclic compounds, including the thioxanthene **1b**,[2] the xanthene **1c**,[2] and the dibenzo[*b,e*]thiepin, perithiadene **1d**.[3] Central depressant, as well as imipramine-like (antidepressive), actions were likewise noted for the latter compound,[3] whereas several benzothieno relatives, **1e**[4] and **1f**,[5,6] caused significant antidepressive effects. Sedative, narcosis-potentiating, adrenolytic, and antipyretic properties are claimed for **1b**,[7] and related piperidines, *i.e.*, side chain reduced congeners of **1**, are claimed as antispasmodics.[8] Although a more distantly related dibenzo[*b,f*]thiepin, bearing a 4-methylpiperidinyl substituent, produces neuroleptic actions in animals,[9] this kind of activity has not previously been recorded for piperidylidene derivatives of compounds with a typical psychotropic tricyclic nucleus.

In the course of an extensive study of structure–activity relationships in the phenothiazine series,[10] we prepared a piperidylidene-substituted trifluoromethylthioxanthene (**11**, Table II) and found it to be remarkably potent in several animal tests for neuroleptic activity. To examine the influence of chemical structure on neuroleptic activity a series of related piperidylidene, and a few piperidine, derivatives of thioxanthenes, xanthenes, dibenzoxepins, and acridans was prepared and tested pharmacologically. The results of this investigation are described in this paper.

Synthesis. Tricyclic carbinols (**3–10**, Table I, and **35**), prepared by addition of Grignard reagents derived from



1a, X = Y = CH=CH
b, X = S; Y = CH=CH
c, X = O; Y = CH=CH
d, X = CH_2S; Y = CH=CH
e, X = CH_2S; Y = S
f, X = $(CH_2)_2$; Y = S



2
X = S, O, CH_2O, NMe, NEt
Y = H, Cl, CF_3, SMe

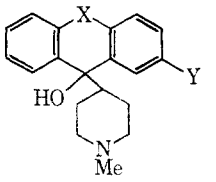
4-chloro-1-methylpiperidine or α-3-chlorotropane[11] (the β-isomer[12] failed to react with Mg under similar conditions) to ketones **2**, were dehydrated to olefins (**11–31**, Table II, and **36**) under acidic or thermal conditions. The requisite 9-acridanones (**2**, X = NH) were obtained by cyclization of appropriate 2-carboxydiphenylamines, produced by Ullman condensation of a halogen-substituted benzoic acid with an aniline or of an anthranilic acid with a halobenzene, as described in the Experimental Section. Cyclization with $POCl_3$ afforded 9-chloroacridines which were converted to acridines by alkaline decomposition of intermediate 9-(*p*-toluenesulfonylhydrazides).[13] 10-Substituted derivatives (**2**, X = NMe, NEt) were prepared by alkylation of 9-acridanones.

The secondary amine **23**, obtained by HCl hydrolysis of the cyanamide **22** derived from **11** by the von Braun reaction, was converted to N-substituted piperidylidenes **24–31** by conventional methods.

Reduction of the ylidenes **11** and **36** using P–HI gave the saturated piperidine (**32**) and tropane (**37**) derivatives, respectively. A piperidyl-substituted acridan **33** was ob-

†This article is dedicated with appreciation to Dr. Alfred Burger, my former postdoctoral professor, long-time friend, and consultant.

Table I. 1-Methyl-4-piperidyl-Substituted Tricyclic Carbinols



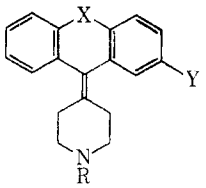
No.	X	Y	Mp, °C	Recrystn Solvent	Yield, %	Formula[a]	Dose range,[b] rat
3	S	CF_3	241–243	EtOAc–hexane	69	$C_{20}H_{20}F_3NOS$	–
4	O	CF_3	191–192	Et_2O–hexane	83	$C_{20}H_{20}F_3NO_2$	–
5	CH_2O	H	150–152	EtOAc–hexane	50	$C_{20}H_{23}NO_2$	
6[c]	CH_2O	Cl	229–231	EtOH	33		
7	NMe	H	184–188	*d*	92		
8	NMe	CF_3	201–203	MeCN	57	$C_{21}H_{23}F_3N_2O$	–
9	NMe	SMe	117–120	*d*	67		
10	NEt	Cl	104–107	*d*	81		

[a]All compounds for which the formula is given were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values. [b]See ref 10 for a description of this test; characteristic hind limb spread, ptosis, and decreased motor activity at an oral dose of 1–10 mg/kg, ++; at 10–100 mg/kg, +; and at >100 mg/kg, −. Chlorpromazine has a ++ ranking in this test. [c]2-Chloro-6,11-dihydro-11-(4-methylpiperidinyl)dibenz[*b*,*e*]oxepin-11-ol. [d]Crystalline product, obtained by trituration with Et_2O, was used for further reaction without purification.

tained by addition of 1-methyl-4-piperidylmagnesium chloride to 2-chloroacridine; **34** was derived by catalytic hydrogenation of the acridinium chloride resulting from treatment of **8** with HCl.

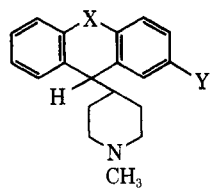
The piperidylidene **11**, which does not give benzylic or vinylic proton signals in its nmr, was isomerized (NaH–DMSO) to afford **38**. The nmr spectrum of **38** showed the expected vinylic and benzylic proton signals.

Table II. Piperidylidene Derivatives of Thioxanthenes, Xanthenes, Dibenzoxepins, and Acridans

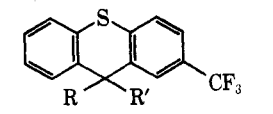


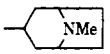
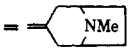
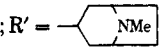
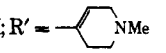
No.	X	Y	R	Salt	Mp, °C	Recrystn solvent	Method[a]	Yield %	Formula[b]	Dose range,[c] rat
11	S	CF_3	Me	Maleate	183–184	*n*-BuOH–Et_2O	C	95	$C_{24}H_{22}F_3NO_4S$	++
12	S	Cl	Me	Maleate	208–209[d]	EtOH–Et_2O	C[e]	88	$C_{23}H_{22}ClNO_4S$	++
13	O	CF_3	Me	Cyclohexyl-sulfamate[f]	192–194	EtOH–Et_2O	C	34	$C_{26}H_{31}F_3N_2O_4S$[g]	++
14	CH_2O	H	Me	HCl	286–288	EtOH–Et_2O	D	65	$C_{20}H_{22}ClNO$	–
15	CH_2O	Cl	Me	HCl	307–309	MeOH–Et_2O	D	45	$C_{20}H_{21}Cl_2NO$	+
16	NMe	H	Me	*h*	191–192	EtOH	E	38	$C_{20}H_{22}N_2$[i]	–
17	NMe	CF_3	Me	Maleate[j]	173–174	EtOAc–Et_2O	E	71	$C_{25}H_{25}F_3N_2O_4$	++
18	NMe	Cl	Me	Maleate	201–203	EtOH–Et_2O	B–E	46	$C_{24}H_{25}ClN_2O_4$[i]	++
19	NMe	SMe	Me	*h*	168–169	*n*-BuOH	E	75	$C_{21}H_{24}N_2S$	+
20	NEt	CF_3	Me	Citrate	190–191	MeOH–Et_2O	B–E	14	$C_{28}H_{31}F_3N_2O_7$	++
21	NEt	Cl	Me	Citrate	178–180	MeOH–Et_2O	E	84	$C_{27}H_{31}ClN_2O_7$	+
22	S	CF_3	CN	*h*	156–158	MeCN	*k*	87	$C_{20}H_{15}F_3N_2S$	
23	S	CF_3	H	HCl	302–304	MeOH–Et_2O	*k*	82	$C_{19}H_{17}ClF_3NS$	+
24	S	CF_3	$(CH_2)_2CH_3$	Dimaleate[l]	126–128	Me_2CO–Et_2O	*m*	35	$C_{30}H_{30}F_3NO_8S$	++
25	S	CF_3	CH_2-c-C_3H_5	HCl[n]	148–150	*i*-PrOH–Et_2O	*o*	74	$C_{23}H_{23}ClF_3NS$[p]	+
26	S	CF_3	CH_2-c-C_4H_7	HCl	277–279	EtOH–Et_2O	*o*	60	$C_{24}H_{25}ClF_3NS$	++
27	S	CF_3	$CH_2CH{=}CH_2$	HCl	238–240	EtOH–Et_2O	*k*	67	$C_{22}H_{21}ClF_3NS$[q]	+
28	S	CF_3	$(CH_2)_2OH$	Maleate	187–189	EtOH–Et_2O	*k*	59	$C_{25}H_{24}F_3NO_5S$	++
29	S	CF_3	$(CH_2)_2OAc$	HCl	206–207	Me_2CO	*r*	49	$C_{23}H_{23}ClF_3NO_2S$	+
30	S	CF_3	$(CH_2)_2Cl$	HCl	235–237	EtOH–Et_2O	*k*	89	$C_{21}H_{20}Cl_2F_3NS$[s]	–
31	S	CF_3	$(CH_2)_3$-COC_6H_4-4-F	Maleate	171–173	EtOH	*k*	37	$C_{33}H_{29}F_4NO_5S$	–

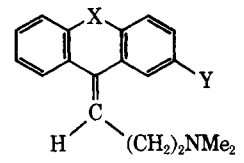
[a]See Experimental Section, General Procedures. [b]All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values unless noted otherwise. [c]See footnote *b*, Table I. [d]Reported mp 193.1–194.1° (ref 2). [e]Preparation of this compound by HCOOH dehydration of 2-chloro-9-(1-methyl-4-piperidyl)thioxanthen-9-ol (ref 2) gave a product, maleate, mp 193–195°. Glpc indicated this product to consist of 16% of unchanged carbinol plus 84% of **12**. [f]Base, bp 170–180° (0.3 mm), mp 81–83° (from EtOH). [g]C, N: calcd, 59.53; 5.34; found, 59.06, 4.84. [h]Base. [i]Analyzed for C and H. [j]HCl salt, mp 215–217° (from *n*-BuOH–Et_2O). *Anal.* ($C_{21}H_{22}ClF_3N_2 \cdot H_2O$) C, H, N, H_2O. [k]See Experimental Section. [l]Neutral equivalent: calcd, 155.4; found, 156.3. [m]Prepared by $LiAlH_4$ reduction of product of **23** and excess $(EtCO)_2O$ at 100° for 2 hr. [n]Dimaleate, mp 123–124.5° (from MeCN–Et_2O). Neutral equivalent: calcd, 633.6; found, 657.1. [o]Prepared by $LiAlH_4$ reduction of product of **23** (0.02 mol) and appropriate acyl chloride (0.01 mol) in PhH for 2 hr at 25°. [p]*Anal.* Calculated for 0.5 mol of *i*-PrOH; ir absorbtion at 2.9 μ. [q]C: calcd, 62.33; found, 61.00. Analyzed for Cl. [r]Prepared from **28** and AcCl in PhH, 0.5 hr of reflux. [s]*Anal.* Calculated for 0.5 mol of H_2O. Analyzed for H_2O.



32, X = S; Y = CF_3
33, X = NH; Y = Cl
34, X = NMe; Y = CF_3



35, R = OH; R′ = 
36, R, R′ = 
37, R = H; R′ = 
38, R = H; R′ = 



39a, X = S; Y = Cl
b, X = CH_2O; Y = 2-Cl
c, X = S; Y = CF_3
d, X = O; Y = CF_3

Pharmacology. Results and Discussion. The results of examination of some piperidine- and piperidylidene-substituted tricyclic compounds for their ability to induce overt effects characteristic of the neuroleptic agents, *e.g.*, ptosis, catalepsy, and decreased motor activity, in rats are presented in Tables I and II. Further studies of selected compounds in rat ptosis production and mouse rage tests are tabulated in Table III.

Tricyclic carbinols **3**, **4**, and **8**, as well as the meso-substituted tricyclic piperidines **32–34** and the related tropanes **35–37**, were ineffective in eliciting neuroleptic-like symptoms in rats at doses below 100 mg/kg. In contrast, many of the piperidylidene congeners (Table II) caused pronounced neuroleptic-like responses in the rat dose range test.

The influence of substitution of the 2 position of the tricyclic nucleus of the piperidylidene derivatives more or less approximated that noted for related tricyclic antipsychotic agents;[14] *i.e.*, the order of increasing potency was roughly H < Cl ≈ SMe < CF_3. Thus, in the thioxanthene series as noted in the rat ptosis production test (Table III), a 2-CF_3-substituted analog **11** was about seven times more potent than its 2-Cl counterpart **12**. In the acridan series both the 2-CF_3- (**17**) and 2-Cl- (**18**) substituted relatives caused marked effects in the rat dose range study; a 2-SMe congener (**19**) was somewhat less effective and the corresponding unsubstituted acridan **16** was without notable neuroleptic-like activity at doses below 100 mg/kg.

Similarly, the influence of the tricyclic nucleus on the neuroleptic potency of meso-substituted *N*-methylpiperidylidene derivatives generally varied in a manner similar to that of other tricyclic antipsychotics. Thus, the 2-CF_3-substituted thioxanthene **11**, xanthene **13**, 10-methylacridan **17**, and 10-ethylacridan **20** caused neuroleptic-like symptoms in the rat dose range test at doses less than 10 mg/kg. In the rat ptosis production test (Table III) both the thioxanthene **11** and 10-methylacridan **17** were about seven to eight times more potent than chlorpromazine. Among 2-Cl-substituted tricyclic piperidylidenes the thioxanthene **12** and 10-methylacridan **18** showed a high degree of activity in the rat dose range test, whereas the 10-ethylacridan **21** and the 6,11-dihydrodibenz[*b*,*e*]oxepin **15** were somewhat less effective.

Substitution of the piperidylidene N was examined only in the 2-trifluoromethylthioxanthene series. In general, rat dose range observations indicated the N-substituted piperidylidenes, *e.g.*, **11**, **24**, **26**, and **28**, were more potent than the corresponding unsubstituted amine **23**; however, in some instances, *e.g.*, **27** and **29**, no striking differences were noted and two of the tertiary amines, **30** and **31**, were less effective than **23**. Quantitative data provided by examination in the rat ptosis production test (Table III) suggest that the *N*-cyclobutylmethyl-substituted piperidylidene **26** is the most potent member of the series. Its potency in this assay was nearly 18 times that of chlorpromazine and only slightly less than that of trifluoperazine.

Table III. Pharmacological Activity of Piperidylidene Derivatives

No.	Ptosis production, rat[a]	Rage, mouse[a]
11	1.4 (0.9–2.2)	4.5, 86%
12	10.4 (7.3–14.9)	
17	1.2 (0.82–1.8)	2.3 (1.0–4.9)
26	0.58 (0.34–1.0)	3.7, 86%
Chlorprothixene (**39a**)	~25.5	~4.3
39c[b]	6.7 (4.5–9.5)	1.3 (0.9–1.8)
39d[b]	5.8 (4.1–7.0)	3.2 (2.2–4.5)
Chlorpromazine	10.3 (8.0–13.5)	10.8 (7.3–15.8)
Trifluoperazine	0.79 (0.39–1.6)	1.8 (0.9–3.8)

[a] See Experimental Section for description of pharmacological tests (ref 10). 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] Reference 10. The cis orientation has been established (ref 26) for this compound.

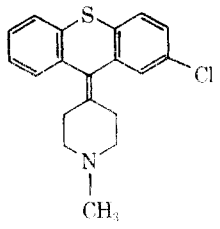
Although the piperidine ring in the tricyclic piperidylidene derivatives can assume various conformations, the spatial orientation of the basic N relative to each of the benzene rings of the tricyclic system is essentially the same in all conformers and is considerably more restricted than in related aminopropyl- and aminopropylidene-substituted tricyclics. Thus, the observation that in the rat some of the piperidylidene derivatives are as potent as, or more potent than, the corresponding congeners with more flexible side chains may have implications regarding the conformational requirements for binding of the antipsychotics at CNS receptor sites. Of course, it must be emphasized that the pharmacological results reported herein were derived following oral administration to animals and do not take into account variables, such as absorption, tissue distribution, metabolism, etc., which might significantly influence the activity of the test compounds.

In the solid-state structure of chlorpromazine[15] the amino group of the side chain is oriented toward the Cl-substituted aromatic ring. Horn and Snyder[16] have noted that the solid-state structures of dopamine[17] and norepinephrine[18] are superimposable upon a portion of this structure of chlorpromazine. On the basis of this observation and biochemical and pharmacological evidence that the neuroleptics postsynaptically interfere with dopaminergic transmission in the CNS,[19-21] they[16] have proposed that antipsychotic activity may be related to selective interaction of the tricyclic neuroleptics with central catecholamine receptors. The conformation assumed by the drugs during the interaction would presumably resemble the solid-state conformation of chlorpromazine.

Among aminopropylidene-substituted tricyclic neuroleptics, the cis isomers **39**, in which the side chain is oriented toward the substituted aromatic ring, are considerably more potent than the trans isomers.[14] For example, the *cis*-thioxanthene **39a**[22] and the related *cis*-dibenzoxepin **39b**[23] are approximately equipotent with their phenothiazine analog, chlorpromazine.[23,24] The cis geometry has also been established for a related clinically useful an-

tipsychotic thioxanthene, thiothixene.[25] Recently, the neuroleptically more potent geometrical isomers of the thioxanthene **39c** and xanthene **39d**[10] have been shown[26] to have cis geometry by nmr techniques as described for related compounds.[27]

Horn and Snyder[16] suggest that the cis isomers are more potent than the trans forms because only the cis isomers can assume a conformation resembling that of chlorpromazine in the solid state. However, the finding that the piperidylidene derivatives show potent neuroleptic-like activity seems to argue against these speculations. These compounds cannot assume a conformation which is superimposable upon that of the solid-state chlorpromazine structure. In contrast, aminopropyl- and aminopropylidene-substituted tricyclics can assume conformations similar to some of the conformers of the piperidylidene derivatives. However, the difference in potency of cis and trans isomers of aminopropylidene tricyclics remains to be explained because both isomers can readily assume conformations which are superimposable upon the piperidylidene derivatives (compare formulas **40**–**42**).



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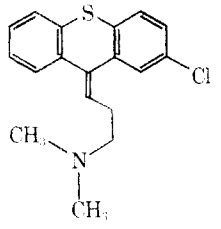
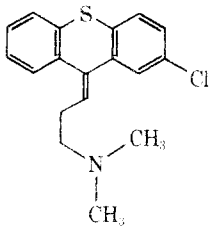


41 (cis)



42 (trans)

It is possible that the piperidylidene derivatives do not interact with CNS receptors in the fashion that the aminopropyl and aminopropylidene tricyclics do. However, structure-activity correlations between the three classes of tricyclic derivatives are consistent with the view that they do interact in the same way. Much more information is needed before the detailed conformational requirements for antipsychotic activity can be defined.

Experimental Section[‡]

Pharmacology. Materials and Methods. Unless otherwise indicated, compounds were administered orally as the salt or base described in Tables I and II and all doses are expressed as the base. Adult male albino rats of the Sprague-Dawley and Wistar strains and male albino mice from Carworth Farms (CF_1) were employed in the experiments.

Observations and values in all tests are reported at the time of peak drug effect. Dose range and ptosis production tests in rats and the rage test in mice were performed as described previously.[10]

Chemistry. General Procedures. A. Alkylation of 9-Acridanones. To a stirred suspension of 4.7 g (0.11 mol) of a 56.1% dispersion of NaH in mineral oil in 250 ml of DMSO at 35° was added, in portions, 0.1 mol of the appropriate substituted (2-Cl,[28] 2-SCH_3,[29] or 2-CF_3) 9-acridanone. The mixture was stirred at 25–35° for 30 min, and then 0.25 mol of alkyl iodide (MeI or EtI) was added dropwise. After being heated at 65° for 1 hr, the mixture was poured into 1.5 l. of H_2O. Precipitated solid was extracted ($CHCl_3$). The extracts were dried and concentrated, and the residue was recrystallized to give 2,10-disubstituted 9-acridanones (Table IV).

Table IV. 2,10-Disubstituted 9-Acridanones (**2**)

2 X	2 Y	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
NMe	Cl	175–176	Hexane	73	$C_{14}H_{10}ClNO$[b,c]
NEt	Cl	162–163	EtOH	84	$C_{15}H_{12}ClNO$[d]
NMe[e]	SMe	132–134	Me_2CO	66	$C_{15}H_{13}NOS$
NMe	CF_3	178–180	EtOH–H_2O	94	$C_{15}H_{10}F_3NO$
NEt	CF_3	195–197	EtOAc	85	$C_{16}H_{12}F_3NO$

[a] Footnote *a*, Table I. [b] Analyzed for C and H. [c] C: calcd, 69.00; found, 69.77. [d] C: calcd, 69.90; found, 69.29. [e] Prepared by stirring and refluxing a mixture of 2-methylthio-9-acridanone (0.2 mol), KOH (0.8 mol), MeI (0.3 mol), and 1 l. of Me_2CO for 1.5 hr.

B. Preparation of Tricyclic Carbinols 3–10 (Table I). 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 under N_2. After reaction had begun, 13.4 g (0.1 mol) of 4-chloro-1-methylpiperidine in 50 ml of THF was added at a rate causing reflux. After the addition was completed the mixture was stirred and refluxed for 1 hr, and then it was brought to 0° and 0.075 mol of the tricyclic ketone (2-chlorothioxanthen-9-one, 2-trifluoromethylthioxanthen-9-one,[30,31] 2-trifluoromethylxanthen-9-one,[30,31] 10-methyl-9-acridanone,[32] the 2,10-disubstituted 9-acridanones listed in Table III, 6,11-dihydrodibenz[*b*,*e*]oxepin-11-one,[33] or 2-chloro-6,11-dihydrodibenz[*b*,*e*]oxepin-11-one[34]) was added in portions. The mixture was stirred and refluxed for 2 hr (in the case of 9-acridanones, the mixture was stirred at 0–10° for 1 hr) and then it was poured into a solution of of 26.5 g (0.5 mol) of NH_4Cl in 500 ml of ice–H_2O. The mixture was extracted (CH_2Cl_2 or Et_2O). In some instances the extracts were dried and concentrated to give crude tricyclic carbinols which were dehydrated to piperidylidene derivatives without purification. Carbinols 3–6 (Table I) were obtained by recrystallization of the residual solid. In the case of acridan-9-ols, the extract was extracted with 1 *N* HCl. The acidic solution was made alkaline (NaOH) and the mixture was extracted with CH_2Cl_2. The extract was dried and concentrated and the residue was triturated with Et_2O to give 7–10 (Table I).

C. HCl Dehydration of Tricyclic Carbinols 11–13. A mixture of 0.1 mol of tricyclic carbinol (3, 4, or 2-chloro-9-(1-methyl-4-piperidyl)thioxanthen-9-ol[2]) and 200 ml of 12 *N* HCl was stirred and refluxed for 1.5 hr. The mixture was concentrated *in vacuo*. A solution of the resulting residue in H_2O was washed with Et_2O, then it was made alkaline (NaOH), and the precipitated oil was extracted with Et_2O. The Et_2O solution was dried and concentrated and the residue liquid was converted to a salt (11–13, Table II).

D. Ac_2O Dehydration of Tricyclic Carbinols 14 and 15. A stirred mixture of 0.012 mol of tricyclic carbinol 5 or 6 and 60 ml of Ac_2O was stirred and refluxed for 4 hr. After distillation of excess Ac_2O, the residual liquid was dissolved in EtOH, an excess of HCl gas was added, and the solution was refluxed for 10 min. Concentration of the solution afforded crystalline piperidylidenes (14 and 15, Table II).

E. Thermal Dehydration of Acridan-9-ols 16–21. A mixture of 0.03 mol of the appropriate acridan-9-ol and 150 ml of xylene (tetralin was employed for the preparation of 16) was refluxed azeotropically for 4 hr (22 hr was required for the preparation of 19). Concentration of the resulting solution afforded 16, 18, 19, and 21 (Table II). Piperidylidene derivatives 17 and 20 were prepared by distillation of requisite acridanols at 0.1–0.5 mm.

***N*-Phenyl-5-trifluoromethylanthranilic Acid.** A stirred mixture of 10 g (0.045 mol) of 2-chloro-5-trifluoromethylbenzoic acid,[35] 10 g (0.073 mol) of K_2CO_3, 1.0 g of powdered Cu, 1 g of $CuCO_3$, and 100 ml of $PhNH_2$ was heated at 90° for 16 hr. The mixture was diluted with Et_2O and filtered. The filtrate was extracted with 1 *N* HCl; then the Et_2O solution was dried and concentrated to give 9.6 g (76%) of yellow crystals, mp 162–164° (hexane). *Anal.* ($C_{14}H_{10}F_3NO_2$) C, H.

[‡] All melting points were determined by the capillary method and are uncorrected. Microanalyses were obtained by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by the symbols of elements, results were within ±0.4% of calculated values. The nmr spectra were obtained with a Varian T-60 spectrometer using Me_4Si as an internal reference and $CDCl_3$ as the solvent at ambient temperature.

9-Chloro-2-trifluoromethylacridine. A stirred mixture of 26.0 g (0.093 mol) of *N*-phenyl-5-trifluoromethylanthranilic acid and 122 g (0.8 mol) of $POCl_3$ was gradually heated to 95°. After cooling the mixture briefly to control the exotherm, it was refluxed for 6 hr. Excess $POCl_3$ was removed *in vacuo* and the residue was dissolved with 600 ml of warm PhH. The solution was poured into a stirred mixture of 1 l. of ice-H_2O and 100 ml of 28% aqueous NH_3. The PhH layer was separated, dried, and concentrated to give 23.4 g (90%) of crystalline product, mp 131–133°, after washing with cyclohexane. *Anal.* ($C_{14}H_7ClF_3$) C, H, N.

2-Trifluoromethyl-9-acridanone. A stirred mixture of 11.1 g (0.04 mol) of 9-chloro-2-trifluoromethylacridine and 250 ml of 1.2 *N* HCl was heated at 100° for 4 hr. After being cooled, the mixture was filtered to give 10.7 g (97%) of yellow crystals, mp 335° dec, after recrystallization from aqueous pyridine. *Anal.* ($C_{18}H_8F_3NO$) C, H, F, N.

***N*-(*p*-Methylthiophenyl)anthranilic Acid.** A stirred mixture of 450 g (3.3 mol) of K_2CO_3, 375 g (1.5 mol) of 2-iodobenzoic acid, 210 g (1.5 mol) of 4-methylthioaniline[36] [bp 88–91.5° (0.1 mm)], 15 g of copper bronze powder, and 1 l. of H_2O was stirred and refluxed for 20 hr; then it was filtered. The filtrate was acidified with 12 *N* HCl. The precipitated solid was filtered, dried, and extracted with 12 l. of Me_2CO. Dilution of the Me_2CO extract with an equal volume of H_2O gave 306 g (29%) of yellow needles, mp 193–194° (lit.[29] mp 195–196°), from EtOH. *Anal.* ($C_{14}H_{13}NO_2S$) C, H, N.

2-Methylthio-9-acridanone. To a mixture of 432 g of P_2O_5 and 270 ml of 85% H_3PO_4 at 110°, 51 g (0.2 mol) of *N*-(*p*-methylthiophenyl)anthranilic acid was added in one portion. The mixture was heated at 110° for 45 min and then it was poured into 3 l. of ice-H_2O. The crystalline solid was washed with 2 *N* Na_2CO_3 and H_2O, dried, and recrystallized (EtOH) to give 86 g (90%) of yellow crystals, mp 267–268° (lit.[29] mp 260–261°). *Anal.* ($C_{14}H_{11}NOS$) C, H, N.

2-Chloroacridine. A solution of 74 g (0.3 mol) of 2,9-dichloroacridine[37] and 56 g (0.3 mol) of *p*-toluenesulfonylhydrazide in 1.5 l. of $CHCl_3$ was allowed to stand at 25° for 3 days; then dry HCl was introduced to precipitate a yellow-green solid. After being washed with $CHCl_3$, the solid was added to a stirred solution of 240 g (6 mol) of NaOH in 900 ml of H_2O and 2.1 l. of ethylene glycol at 70–80°. The mixture was heated at 100° for 2 hr; then it was cooled, diluted with 6 l. of H_2O, and filtered to give 29 g (45%) of white needles, mp 169–170° (lit.[38] mp 170°).

1-Cyano-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine (22). To a stirred solution of 9.3 g (0.09 mol) of BrCN in 200 ml of PhH at 50–55° a solution of 26.2 g (0.07 mol) of base liberated from **11** in 150 ml of PhH was added dropwise during 1.5 hr. After being heated at 50–55° for 5 hr the mixture was filtered and the filtrate was extracted with 300 ml of 1 *N* H_3PO_4. The PhH solution was dried and concentrated to give **22**.

4-(2-Trifluoromethylthioxanthen-9-ylidene)piperidine Hydrochloride (23). A mixture of 26 g (0.07 mol) of **22**, 500 ml of AcOH, 50 ml of 12 *N* HCl, and 330 ml of H_2O was stirred and refluxed for 20 hr. The resulting solution was concentrated *in vacuo* to leave a solid residue of **23**. Base liberated from **23** had mp 128–130° (from Et_2O).

1-Allyl-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine Hydrochloride (27). A mixture of 8.0 g (0.024 mol) of **23** base, 2.8 g (0.012 mol) of allyl bromide, and 20 ml of PhH was stirred at 25° for 2 hr. The mixture was diluted with Et_2O and filtered to remove precipitated **23** · HBr. The filtrate was concentrated and the residue was treated with HCl to give **27**.

1-(2-Hydroxyethyl)-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine Maleate (28). A mixture of 5.0 g (0.014 mol) of **23** base, 3.0 g (0.07 mol) of ethylene oxide, and 40 ml of MeOH was stirred at 25° for 16 hr. The residue obtained by concentration *in vacuo* of the resulting solution was converted to a maleate **28**.

1-(2-Chloroethyl)-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine Hydrochloride (30). A stirred solution of 12.8 g (0.03 mol) of **28** base in 100 ml of $CHCl_3$ at 0° was saturated with HCl gas; then 15 ml of $SOCl_2$ was added and the solution was refluxed for 2 hr. After being cooled, the solution was diluted with Et_2O to give **30**.

1-[4-(4-Fluorophenyl)-4-oxobutyl]-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine Maleate (31). A mixture of 9.8 g (0.03 mol) of **23** base, 10.1 g (0.05 mol) of γ-chloro-*p*-fluorobutyrophenone, 2.9 g (0.035 mol) of $NaHCO_3$, and 0.2 g of KI was stirred and refluxed for 64 hr. The mixture was filtered and the filtrate concentrated *in vacuo*. A solution of the residue in Et_2O was stirred with 100 ml of 1 *N* HCl to give an insoluble HCl salt. The salt was filtered and suspended in H_2O and the mixture was made alkaline (NaOH). The precipitated oil was extracted with Et_2O. The Et_2O solution was treated with decolorizing carbon, dried, and concentrated. Treatment of the residual oil with maleic acid gave **31**.

9-(1-Methyl-4-piperidyl)-2-trifluoromethylthioxanthene Maleate (32). A mixture of 10 g (0.28 mol) of **11** base, 40 ml of AcOH, 40 ml of 57% HI, and 6.2 g (0.2 g-atom) of red P was stirred and refluxed for 4 hr. The mixture was poured into 250 ml of ice-H_2O, made alkaline (NaOH), and extracted with CH_2Cl_2. After being washed with H_2O, the CH_2Cl_2 solution was dried and concentrated. Treatment of the residual liquid with maleic acid in EtOAc gave 8.0 g (60%) of colorless crystals, mp 186–188° (from Me_2CO-Et_2O). *Anal.* ($C_{24}H_{24}F_3NO_4S$) C, H, N.

2-Chloro-9-(1-methyl-4-piperidyl)acridan (33) was prepared in 41% yield from 1-methyl-4-piperidylmagnesium chloride and 2-chloroacridine by general procedure B. Recrystallization from Me_2CO gave colorless crystals, mp 184–185°. *Anal.* ($C_{19}H_{21}ClN_2$) C, H, N.

10-Methyl-9-(1-methyl-4-piperidyl)-2-trifluoromethylacridan Maleate (34). A solution of 3.76 g (0.01 mol) of **8** in 75 ml of EtOH was acidified with dry HCl and diluted with Et_2O. A mixture of the precipitated yellow acridinium salt, 0.5 g of PtO_2, and 100 ml of EtOH was hydrogenated at 25° at an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (20 min), the mixture was filtered and the filtrate was concentrated. An aqueous solution of the residue was made alkaline (NaOH). The mixture was extracted with Et_2O; the extract was dried and concentrated to give an oil. A solution of the oil in EtOAc was treated with maleic acid to give 4.5 g (94%) of colorless crystals, mp 168–170° (from Me_2CO-Et_2O). *Anal.* ($C_{25}H_{27}F_3N_2O_4$) C, H, N.

2-Trifluoromethyl-9-(3-tropanyl)thioxanthen-9-ol (35) was prepared from 2-trifluoromethylthioxanthen-9-one[30,31] and a Grignard reagent derived by refluxing a THF solution of α-3-chlorotropane[11] with Mg turnings for 24 hr (general procedure B). The crude product was distilled, bp 240–260° (1.0 mm), and the distillate was crystallized (MeCN) to give colorless crystals (19.6% yield), mp 195–197°. *Anal.* ($C_{22}H_{22}F_3NOS$) C, H, N.

3-(2-Trifluoromethylthioxanthen-9-ylidene)tropane (36) was prepared by HCl dehydration (general procedure C); mp 162–165° (from MeCN). *Anal.* ($C_{22}H_{20}F_3NS$) C, H, N.

2-Trifluoromethyl-9-(3-tropanyl)thioxanthene (37) was prepared by P-HI reduction of **36** in the same manner as described for preparation of **32** to give 67% of colorless crystals, mp 183–185° (from MeCN). *Anal.* ($C_{22}H_{22}F_3NS$) C, H, N.

9-(1-Methyl-1,2,5,6-tetrahydro-4-pyridyl)-2-trifluoromethylthioxanthene (38). A stirred mixture of 9.0 g (0.025 mol) of **11** base, 1.8 g (0.04 mol) of a 56.1% dispersion of NaH in mineral oil, and 50 ml of DMSO was heated at 60°. After H_2 evolution subsided, the mixture was heated at 95° for 15 min. The mixture was poured cautiously into ice-H_2O and extracted with CH_2Cl_2. The extract was dried and concentrated and the residual solid was recrystallized (MeCN) to give 5.5 g (61%) of pale yellow crystals: mp 113.5–115°; nmr ($CDCl_3$) δ 4.66 (d, 1, benzylic H), 5.00 (m, 1, vinylic H). *Anal.* ($C_{20}H_{18}F_3NS$) C, H, N.

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Molecular Structure and Conformation of the Nucleoside Antibiotic Derivative 2-Methylformycin with a C-Glycosidic Bond

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The molecular and crystal structure of 2-methylformycin, a synthetic analog of the antibiotic formycin, has been solved using X-ray techniques. The space group is the monoclinic $P2_1$. Cell dimensions measured on the diffractometer are a = 9.208 Å, b = 14.367 Å, c = 4.791 Å, and β = 101.91°. The pertinent conformational values are as follows: the conformation about the C-glycosidic bond is syn, the torsion angle is −154.8°, the sugar pucker is C(3′) endo, a conformation usually observed only for nucleosides in the anti conformation, and the conformation about the C(4′)–C(5′) bond is gauche–gauche. Hydrogen bonding is observed between the base and ribose moieties. There is an intramolecular hydrogen bond between O(5′) and N(3) and no significant "base stacking" is observed in the molecular packing. Because of this preferred conformation in the solid state, it is speculated from biological testing data that 2-methylformycin is a poorer substrate of adenosine deaminase than formycin.

Structural elucidation studies established[1,2] that formycin, an antibiotic isolated[3] from *Norcardia interforma*, was a C-nucleoside isomeric with the naturally occurring purine nucleoside adenosine. Formycin has demonstrated[4] the ability to inhibit the growth of various experimental tumor cell lines, *Xanthomonas oryzae*, as well as exhibit some immunosuppressive activity.[5] Formycin has functioned[6,7] effectively in place of adenosine at the polymeric level and formycin has also functioned as a substrate for enzymes specific for adenosine kinase[8] and adenosine deaminase.[9] This close relationship to adenosine in substrate specificity and biological activity was of considerable interest since adenosine exists predominantly in the anti conformation while formycin hydrobromide was reported[2] to exist in the syn conformation. This conformation could have been attributed in part to protonation at N-8 (N-2) although the site of protonation was presumed[2] to be at N-1 (N-6)‡ (see Figure 1) on the basis of bond distance data. This is of interest in view of a recent study which has established[10] that adenosine derivatives in the syn conformation are not substrates for adenosine deaminase and would suggest that a significant population of formycin must exist in the anti conformation in solution and *in vivo*. In fact, it has now been established[11] that formycin (nonproponated) exists between the classical syn and anti conformations (amphi form[12]) in the solid state.

Structure analysis of 2-methylformycin by X-ray techniques was undertaken by us to obtain precise information on the structure and its conformation as a part of our current studies on the structures of nucleic acids, their components, and their cytotoxic analogs, as well as to gain some insight into the preferred conformations which might be related to the difference in biological testing and

†This paper is dedicated to my former professor, Alfred Burger.

‡We would like to point out that instead of following the numbering system normally used for this pyrazolopyrimidine system, we follow that used in purine systems (followed by the pyrazolopyrimidine numbering in parentheses). We elected to use this convention in order to facilitate a comparison of our observations with those of the native compound and other purine systems.