Thioxanthene Psychopharmacological Agents. II. 9-(3-Aminopropylidene)-N,N-dimethylthioxanthene-2-sulfonamides

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Thiothixene (*cis*-**4**), an established major antipsychotic agent for the treatment of schizophrenia, was prepared to explore the hypothesis that replacement of the phenothiazine moiety by thioxanthene in clinically useful antipsychotic drugs will minimize extrapyramidal effects, while maintaining efficacy in schizophrenia. Three synthetic routes to the title compounds were developed, each of which affords a mixture of geometric isomers. In every case the *cis* isomer proved to be substantially more active pharmacologically than the *trans* isomer. Scheme I involved conversion of 9-acetyl-N,N-dimethylthioxanthene-2-sulfonamide (**1**) to a Mannich base followed by reduction and dehydration to afford a 1:1 isomer mixture. Synthesis of N,N-dimethyl-9-oxothioxanthene-2-sulfonamide (**9**) from *o*-bromobenzoic acid and benzenethiol provided the key intermediate for the two alternate routes. Grignard reaction of a 3-chloro-N,N-dialkylpropylamine with **9** with subsequent dehydration afforded a more direct and efficient route to the title compounds. Finally, a Wittig synthesis utilizing **9** and a 3-aminopropylidenetriphenylphosphorane represented a convenient alternate with certain technical advantages. Psychopharmacological testing results are discussed.

The preceding article describes the synthesis of several 9-(3-aminopropyl)thioxanthene-2-sulfonamides.[1] Certain of these new compounds possess a psychopharmacological profile similar to that of the phenothiazine neuroleptics. Maximum potency is achieved when the ring substituent at C-2 is dimethylsulfamoyl. The second phase of this program involved synthesis of 9-(3-aminopropylidene)-N,N-dimethylthioxanthene-2-sulfonamides designed (1) to further explore the hypothesis that replacement of the phenothiazine moiety by thioxanthene in clinically useful antipsychotic drugs will minimize effects upon the extrapyramidal system, while maintaining antischizophrenic potency, (2) to evaluate the biological results of the restriction conferred upon the side chain by the C-9 double bond in terms of drug–receptor requirements, and (3) to explore the structure–activity relationship associated with the side-chain amine.

Synthesis.—Each of the more attractive synthetic approaches to the title compounds requires a common intermediate, ketone **9**, upon which the aminopropylidene side chain can be constructed by known synthetic methods, *e.g.*, Grignard addition,[2] Wittig reaction,[3] or acetylide addition.[4] Thus preparation of ketone **9** was our primary goal, since it was deemed essential to the synthetic versatility vital to a meaningful structure–activity study; however, alternate routes were considered and explored.

Success in preparing the first member of the title series was achieved, not *via* **9**, but, curiously enough, by way of the route depicted in Scheme I. After several orienting runs, the key intermediate **1** could be obtained consistently in 30–39% yield by acetylation of 9-lithio-N,N-dimethylthioxanthene-2-sulfonamide;[1] the balance was largely recoverable as unchanged starting material. The isolation procedure[5] employing Girard reagent T allowed up to 45% recovery of starting material and provided **1** in excellent purity. Condensation of **1** with HCHO and $Me_2NH \cdot HCl$ under Mannich conditions yielded **2**, whose structural assignment is supported by uv, ir, nmr, and elemental analyses. Amine exchange[6] with 1-methylpiperazine afforded **3** in essentially quantitative yield.

Several methods for converting ketone **3** to olefin **4** were examined; the most satisfactory results were obtained upon $NaBH_4$ reduction followed by dehydration with $POCl_3$–pyridine. No attempt was made to separate the intermediate epimeric alcohols, since each should lead to a similar distribution of olefinic isomers. The exact isomer ratio in the crude reaction mixture was not determined, but was estimated to be *ca.* 1:1 by paper chromatographic assay.[7]

The mixture of *cis*- and *trans*-**4** bases could be crystallized from Et_2O, but repeated recrystallization did not provide a single component. Separation was accomplished by taking advantage of the great difference in solubility of the dioxalate salts in 50% aqueous EtOH. The precipitated salt provided *trans*-**4** and the mother liquor *cis*-**4**. Psychopharmacological testing results demonstrated that *cis*-**4** was substantially more active than *trans*-**4**.[8] By heating crude *trans*-**4** dioxalate in acid, an equilibrium mixture (63% *trans* and 37% *cis*) was obtained and a second crop of *cis*-**4** was isolated *via* the oxalate procedure. While *cis*-**4** is the minor isomer at equilibrium, it has been obtained in up to 70% yield by reequilibrating and recycling *trans*-**4** several times. Similar results have been obtained using H_3PO_4 instead of oxalic acid.

All spectroscopic data at hand confirmed that *cis*-**4** and *trans*-**4** were geometric isomers, but did not allow unambiguous stereochemical assignment. X-Ray crystallographic analysis on the biologically active isomer

(1) J. F. Muren and B. M. Bloom, *J. Med. Chem.*, **13**, 14 (1970).

(2) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941); G. E. Bonvicino, H. G. Arlt, Jr., K. M. Pearson, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 2383 (1961); R. D. Hoffsommer, D. Taub, and N. L. Wendler, *ibid.*, **27**, 4134 (1962); P. V. Petersen, N. O. Lassen, and T. O. Holm, U. S. Patent 3,116,291 (1963); R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Med. Chem.*, **8**, 555 (1965).

(3) J. R. Tretter, U. S. Patent 3,354,155 (1967).

(4) W. Ried and J. Schönherr, *Chem. Ber.*, **93**, 1879 (1960); L. R. Peters and G. F. Hennion, *J. Med. Chem.*, **7**, 390 (1964).

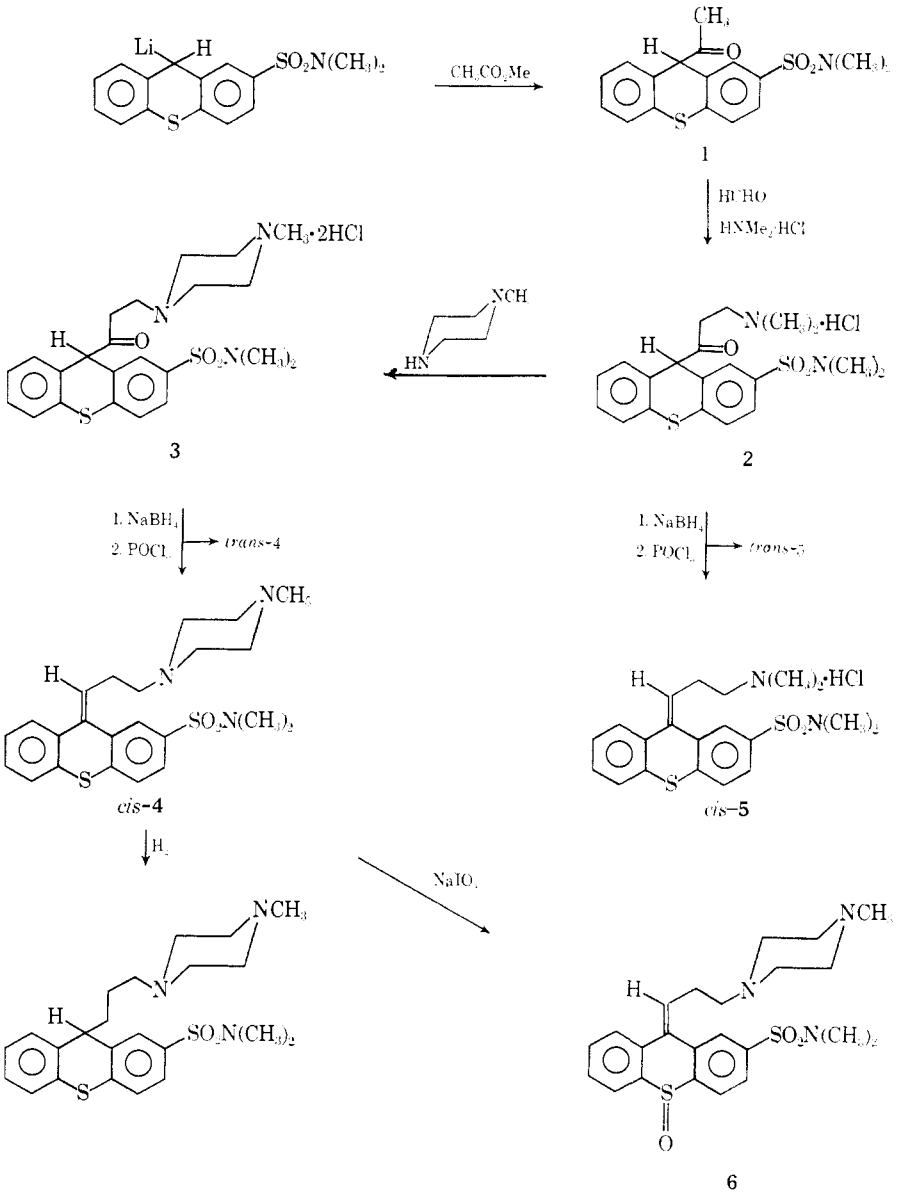
(5) C. L. Teitelbaum, *J. Org. Chem.*, **23**, 646 (1958).

(6) H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, **70**, 4230 (1948).

(7) Isomers *cis*-**4** and *trans*-**4**, as well as *cis*/*trans*-**5** and *cis*/*trans*-**19**, separated and could be determined, one in the presence of the other, when a mixture was applied to Whatman No. 1 paper buffered at pH 2.1 with glycine-HCl, impregnated with *MeOH*–(CH_2OH)$_2$ (6:4), and developed with C_6H_6–$CHCl_3$ (1:1), saturated with (CH_2OH)$_2$, for 16 hr using a descending technique. Elution of the developed zones by 0.01 *N* methanolic HCl followed by uv assay at 305 mμ allowed quantitative evaluation of isomer ratio within ±1%.

(8) A. Weissman, *Psychopharmacologia*, **12**, 142 (1967).

SCHEME I



substantiated our *cis*-**4** assignment.[9] In this case, and in each subsequent example throughout this work, the minor equilibrium isomer was much more active biologically and absorbed higher wavelength uv radiation (260, 310 mμ *vs.* 252, 301 mμ). These properties provided the basis for all succeeding stereochemical assignments.

Hydrogenation of *cis*-**4** over Pd–C afforded the expected dihydro derivative[1] in low yield. Oxidation of *cis*-**4** by $NaIO_4$, when both basic nitrogens were protonated, provided sulfoxide **6**.

Application of the reduction–elimination sequence to amino ketone **2** led to isolation of *cis*-**5** and *trans*-**5** by fractional crystallization of the HCl salts.

Sulfonation of thioxanthen-9-one under a variety of experimental conditions led only to unsatisfactory yields of key intermediate **9**. The major product of chlorosulfonation followed by treatment with excess Me_2NH was disulfonamide **11**. Ketone **9** was eventually obtained by total synthesis from *o*-bromobenzoic acid *via* sulfonamide **7**. Displacement of bromide ion from **7** by thiophenolate ion provided carboxylic acid **8**. Attempted cyclization of **8** by HF failed, but use of P_2O_5 or $(CF_3CO)_2O$ led to an anhydride (ir absorption at 5.60, 5.87 μ) which was slowly converted to **9** upon prolonged heating. H_2SO_4 was an effective cyclizing agent, but polyphosphoric acid provided consistently better yields of **9**.

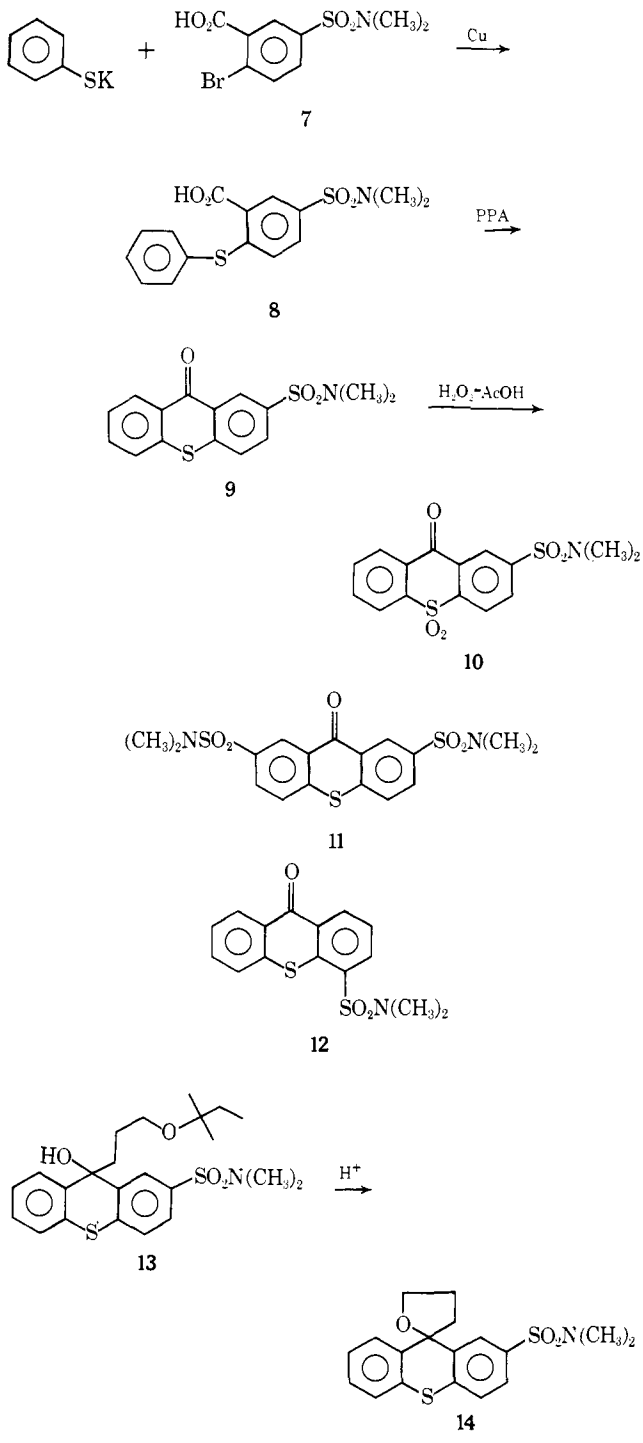
The structure assigned to ketone **9** was supported by microanalysis, as well as ir, uv, and nmr spectral data. Furthermore, at pH 3–4 *cis*-**4** was quantitatively converted to **9** by treatment with aqueous $KMnO_4$. Oxidation of ketone **9** by H_2O_2 or *m*-chloroperbenzoic acid led to the corresponding sulfone (**10**).

A by-product encountered in the synthesis of **9** was suspected to be 4-sulfonamide isomer **12**. Confirmation was obtained by synthesis of **12** from *o*-chlorobenzenesulfonyl chloride,[10] by amination, then treatment with *o*-mercaptobenzoic acid followed by polyphosphoric acid cyclization.

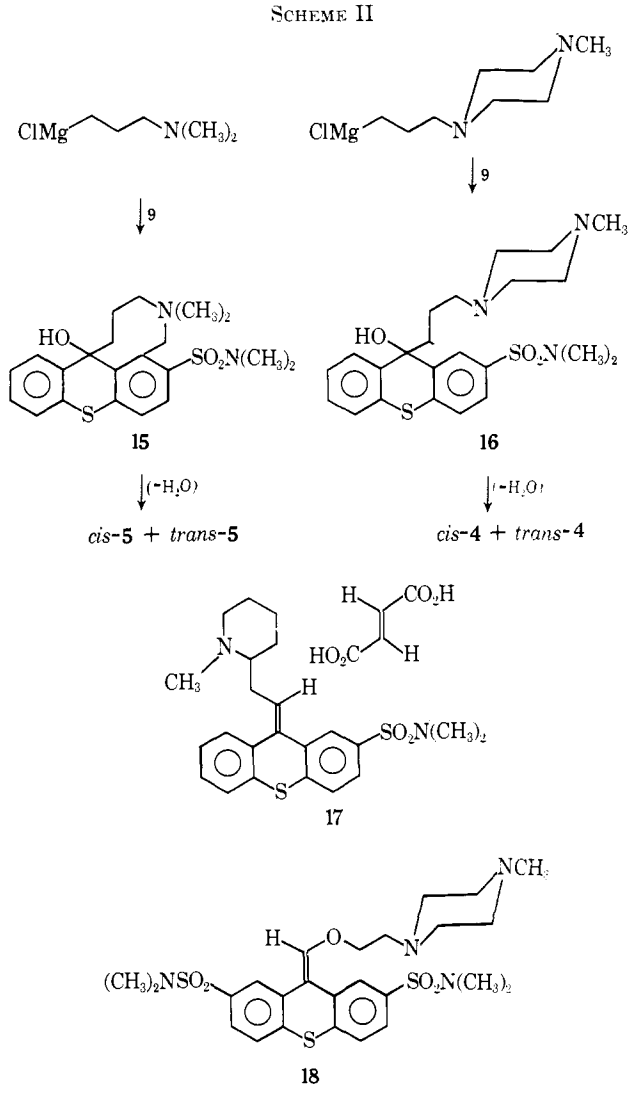
In an attempt to prepare 9-(3-bromopropylidene)-

(9) J. P. Schaefer, *Chem. Commun.*, 743 (1967).

(10) H. Meerwein, G. Dittmar, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).



SCHEME II

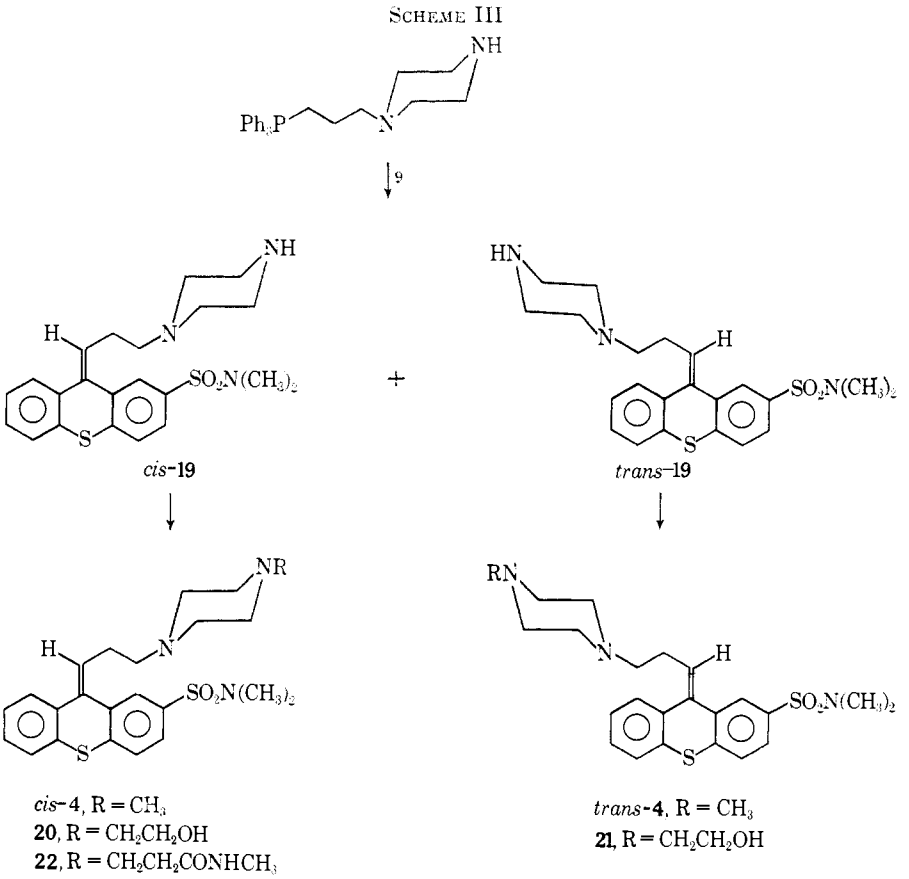


N,N-dimethylthioxanthene-2-sulfonamide, an intermediate which would permit us to undertake a structure–activity study of side-chain amine analogs, we prepared carbinol **13**. Treatment with HBr under a variety of conditions led only to spiro ether **14** or gross decomposition. Ether **14** could be prepared in excellent yield by simply dissolving **13** in concentrated HCl, but we were not able to effect transformation into the desired olefin.

With ketone **9** available a more direct and efficient synthetic route to *cis*-**4** and *cis*-**5** was developed (Scheme II). Treatment of **9** with 3-(dimethylamino)propylmagnesium chloride afforded carbinol **15** in high yield. Reaction was essentially complete upon addition of the ketone at room temperature. After heating a solution of **15** in dilute HCl for 1 hr, the familiar 3:2 mixture of *trans*-**5** and *cis*-**5** was obtained. A similar sequence provided *cis*-**4**, *trans*-**4**, and **17**. The *cis* isomer of **17** was detected, but could not be isolated in pure form for proper characterization. Ketone **11** yielded disulfonamide **18**, a single product since the thioxanthene ring system is symmetrically substituted. This fact supported by nmr evidence confirmed the structures assigned to both **11** and **18**.

Scheme III depicts a third preparative sequence which allowed investigation of piperazine analogs and obviated the isomer separation problem at the final stage. The ylide derived from 3-(1-piperazinyl)propyltriphenylphosphonium bromide[3] reacted smoothly with ketone **9** to provide a 1:1 mixture of *trans*-**19**, which was isolated *via* the less soluble dioxalate salt, and *cis*-**19** was recovered as the ditosylate salt. Both isomers were obtained in preparative quantities and were treated with various alkylating agents to provide N-4-substituted derivatives **20**, **21** and **22**. Independent methylation of *cis*-**19** and *trans*-**19** afforded products identical in all respects with *cis*-**4** and *trans*-**4** obtained by Schemes I and II. In fact, recent development work has demonstrated that reaction of ketone **9** with the ylide derived from 3-(4-methyl-1-piperazinyl)propyltriphenylphosphonium bromide represents the most

SCHEME III



cis-4, R = CH_3
20, R = CH_2CH_2OH
22, R = $CH_2CH_2CONHCH_3$

trans-**4**, R = CH_3
21, R = CH_2CH_2OH

convenient and economical route to *cis*-**4** (thiothixene), the most important product of this work.

Pharmacology.—The potential antipsychotic activity of the test compounds was assessed by their ability to antagonize amphetamine-induced lethality in aggregated mice and disrupt conditioned avoidance behavior in rats at doses no greater than $0.33LD_{50}$. Test methods have been described in a prior publication.[8]

The data in Table I indicate that compounds *cis*-**4**, *cis*-**5**, **20**, and **22** exhibit activity equal to or greater than that of chlorpromazine. In each case where data comparing *cis*–*trans* pairs were available, the *cis* isomer was by far the more potent. Variation of the side-chain amine did not significantly reduce potency, except in the case of secondary amine **19**.

TABLE I
PHARMACOLOGICAL ACTIVITIES

Compd	LD_{50}, mg/kg (mice) ip	Median effective dose, mg/kg ip: Antiamphetamine (mice)	Median effective dose, mg/kg ip: Antiavoidance (rats)
cis-**4** (thiothixene)	100	0.30	1.0–3.2
trans-**4**	235	10–32	>32
cis-**5**	100–178	3.2–10	5.7
trans-**5**	100–320	>100	NT[a]
6 (*cis*-**4**, oxide)	320–1000	>100	>32
cis-**19**	32–100	10–32	>32
trans-**19**	100–320	>100	>32
20 (*cis*)	100–320	0.32–1.0	3.2–10
21 (*trans*)	100–320	>32	>32
22 (*cis*)	100–320	1.0–3.2	3.2–10
Chlorpromazine HCl	165	1.6	3.2–10

[a] Not tested.

A detailed psychopharmacological analysis of *cis*-**4** (thiothixene) and *trans*-**4** has been reported by Weissman.[8] Thiothixene exerts many effects characteristic of antipsychotic drugs, but exhibits unusual selectivity in its over-all pharmacological profile. In double blind trials thiothixene has been established as a major antipsychotic agent for the treatment of schizophrenia.[11]

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points (Thomas–Hoover capillary melting-point apparatus) are uncorrected. Ir spectra were measured with a Perkin–Elmer Model 21 spectrophotometer, uv spectra with a Cary Model 11 or 13 recording spectrophotometer, and nmr spectra with a Varian A-60 spectrometer (Me_4Si as internal standard).

9-Acetyl-N,N-dimethylthioxanthene-2-sulfonamide (1).—A well-stirred suspension of N,N-dimethylthioxanthene-2-sulfonamide[1] (122 g, 0.40 mole) in 400 ml of anhydrous 1,2-dimethoxyethane under N_2 was cooled in ice and treated with 3 *M* *n*-BuLi in purified heptane (133 ml, 0.40 mole) at such a rate that the reaction temperature did not rise above 10°. After the addition was complete, the ice bath was removed and MeOAc (29.6 g, 0.40 mole) was added during 1 hr. The mixture was stirred at 25° for 3 hr and the crude product was isolated by neutralization with 3 *N* aqueous NH_4Cl, extraction with EtOAc, and evaporation of the solvent. The residue, which contained primarily ketone **1** and starting material, was dissolved in 200 ml of EtOH and stirred at reflux for 1 hr with Girard reagent T (50 g) and Amberlite IRC-50(H) cation-exchange resin (1 g). Upon cooling the

(11) D. M. Gallant, M. P. Bishop, E. Timmons, and A. R. Gould, *Current Ther. Res.*, **8**, 153 (1966); M. P. Bishop, T. E. Fulmer, and D. M. Gallant, *ibid.*, **8**, 509 (1966); J. Simeon, A. Keskiner, D. Ponce, T. Itil, and M. Fink, *ibid.*, **9**, 10 (1967); A. A. Kurland, A. Pinto, B. H. Dim, and C. A. Johnson, *ibid.*, **9**, 298 (1967).

mixture was diluted with 800 ml of H_2O and filtered, and the filtrate was stirred overnight with 200 ml of 37% formalin solution. The white, crystalline precipitate, when filtered and dried (0.10 mm), provided 54.1 g (39%) of **1**: mp 127–129°; ir (KBr) 5.88 (C=O), 7.47, 8.64 μ (SO_2); uv max (MeOH) 253, 289 mμ (log ϵ 3.8, 4.1); nmr ($CDCl_3$) δ 2.01 (s, 3 H), 2.67 (s, 6 H), 4.97 (s, 1 H), 7.1–7.7 (m, 6 H), 7.75 (m, 1 H, H-1). *Anal.* ($C_{17}H_{17}NO_3S_2$) C, H, N.

The deep orange 2,4-dinitrophenylhydrazone prepared from **1** melted at 228–229.5° ($CHCl_3$). *Anal.* ($C_{23}H_{21}N_5O_6S_2$) C, H, N.

N,N-Dimethyl-9-[3-(dimethylamino)propionyl]thioxanthene-2-sulfonamide Hydrochloride (2).—Ketone **1** (54.1 g, 0.155 mole), paraformaldehyde (10.6 g), and $Me_2NH \cdot HCl$ (16.4 g, 0.20 mole) were dissolved in 100 ml of *i*-PrOH at reflux under N_2, 1 ml of concentrated HCl was added, and the solution was maintained at reflux for 24 hr. The cooled reaction mixture was concentrated to *ca.* 60 ml, diluted with 60 ml of EtOAc, and stored at 4° overnight to afford 39.1 g (57%) of **2**, mp 185–187°, after recrystallization from *i*-PrOH. A second recrystallization from *i*-PrOH provided pure **2**: mp 187–189°; ir (KBr) 3.7–4.1 (NH^+), 5.79 (C=O), 7.47, 8.64 μ (SO_2); nmr ($CDCl_3$) δ 2.2 (m, 2 H, CH_2CO), 2.66 (s, 6 H, SO_2NMe_2), 2.71 (s, 6 H, NMe_2^+), 3.1 (m, 2 H, CH_2N^+), 5.41 (s, 1 H, CHCO), 7.1–7.8 (m, 6 H), 7.89 (m, 1 H, H-1). *Anal.* ($C_{20}H_{24}N_2O_3S_2 \cdot HCl$) C, H, N.

N,N-Dimethyl-9-[3-(4-methyl-1-piperazinyl)propionyl]thioxanthene-2-sulfonamide Dihydrochloride (3).—A solution of **2** (17.6 g, 0.040 mole) and 10 g of 1-methylpiperazine in 40 ml of *i*-PrOH was heated at reflux for 3 hr using a stream of N_2 to facilitate removal of the by-product, Me_2NH. The cooled reaction mixture was dissolved in EtOAc, washed twice with H_2O, and concentrated *in vacuo* to remove excess 1-methylpiperazine. An Et_2O solution of the residue was treated with excess ethereal HCl. The precipitated dihydrochloride was collected and crystallized from EtOH to yield 18.3 g (86%) of **3**, mp 206–209°. One recrystallization from EtOH yielded pure **3**, which decomposed at 210° and analyzed correctly only after vacuum drying (100° at 0.1 mm for 20 hr). *Anal.* ($C_{23}H_{29}N_3O_3S_2 \cdot 2HCl$) C, H, N.

N,N-Dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]thioxanthene-2-sulfonamide (4).—$NaBH_4$ (3.0 g) and crude free base **3** (obtained as above) in 100 ml of EtOH were heated at reflux for 3 hr. After dilution with H_2O, the mixture was thoroughly extracted with EtOAc, and the extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to yield a white, semisolid mixture of epimeric carbinols. The ir spectrum (CCl_4) exhibited broad bonded OH at 3.1–3.2 μ with only a vestige of the 5.87-μ CO absorption. This mixture was dehydrated by dissolving in 20 ml of anhydrous C_6H_5N, adding dropwise a solution of 18.4 ml of $POCl_3$ in 60 ml of C_6H_5N at 5°, allowing the mixture to warm to 25° during 0.5 hr, then heating at 80° for 0.5 hr. The amber solution was immediately poured into ice water, solid K_2CO_3 was added to saturate the aqueous phase, the products were extracted into EtOAc, and the volatiles were removed by evaporation at 0.1 mm. The tan residue (14.6 g) crysallized upon trituration with boiling Et_2O to yield 11.7 g (66%) of pure crystalline **4** (1 3:2 mixture of *trans*-**4** and *cis*-**4** as determined by paper chromatography,[7] mp 114–118°. Isolation of the isomer components was effected by dissolving 4.44 g (0.010 mole) of the base in 50 ml of hot 50% EtOH and adding a solution of oxalic acid dihydrate (2.52 g, 0.020 mole) in 50 ml of the same solvent. Crystallization was allowed to proceed at room temperature Filtration afforded a crystalline dioxalate salt which was highly enriched in *trans*-**4** while the mother liquor contained a high proportion of the more soluble *cis*-**4** dioxalate. Crude *trans*-**4** dioxalate was recrystallized from 50% aqueous EtOH to yield pure *trans*-**4** dioxalate which decomposes at 229°. *Anal.* ($C_{23}H_{29}N_3O_2S_2 \cdot 2C_2H_2O_4$) C, H, N.

Treatment of *trans*-**4** dioxalate, with aqueous K_2CO_3, extraction by CH_2Cl_2, and crystallization from Et_2O provided 2.36 g (53%) of pure *trans*-**4**: mp 123–124.5°; ir (KBr) 6.04 (C=C), 7.35, 8.65 (SO_2), 12.5 μ (vinyl CH); uv max (MeOH) 229, 252, 301 mμ (log ϵ 4.5, 4.2, 3.9); nmr ($CDCl_3$) δ 2.27 (s, 3 H, N-Me), 2.4–2.7 (m, 12 H), 2.72 (s, 6 H, SO_2NMe_2), 5.99 (m, 1 H, vinyl CH), 7.2–7.6 (m, 6 H, aromatic CH), 7.89 (m, 1 H, H-1). *Anal.* ($C_{23}H_{29}N_3O_2S_2$) C, H, N.

The mother liquor containing crude *cis*-**4** dioxalate was concentrated *in vacuo* to near dryness, treated with aqueous K_2CO_3, and extracted with CH_2Cl_2. Three recrystallizations from Et_2O afforded 0.90 g (21%) of pure *cis*-**4**: mp 147.5–149°; ir (KBr) 6.12 (C=C). 7.47, 8.70 (SO_2), 12.4 μ (vinyl CH); uv max (MeOH) 228, 260, 310 mμ (log ϵ 4.6, 4.2, 3.9); nmr ($CDCl_3$) δ 2.28 (s, 3 H, N-Me), 2.4–2.7 (m, 12 H), 2.72 (s, 6 H, SO_2NMe_2), 6.03 (m, 1 H, vinyl CH), 7.2–7.7 (m, 6 H, aromatic CH), 7.86 (m, 1 H, H-1). *Anal.* ($C_{23}H_{29}N_3O_2S_2$) C, H, N.

Either isomer, when dissolved in 2 *N* aqueous HCl and heated for 4 hr on a steam bath, leads to the same equilibrium mixture, *i.e.*, 63% *trans*-**4** and 37% *cis*-**4** (as determined by paper chromatography assay).

***cis*-N,N-Dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]thioxanthene-2-sulfonamide 10-Oxide Dimaleate (6).**—A solution of *cis*-**4** (4.44 g, 0.010 mole) in aqueous trifluoroacetic acid (2.28 g, 0.020 mole, in 40 ml of H_2O) was treated with 0.5 *M* aqueous $NaIO_4$ (60 ml, 0.030 mole) at such a rate so as to maintain a 24° reaction temperature. When the addition was complete (*ca.* 40 min), the deep yellow solution was poured into 100 ml of 1 *N* aqueous $KHCO_3$, stirred vigorously for 0.5 hr, and extracted with CH_2Cl_2. The extract was washed with aqueous $KHCO_3$, dried ($MgSO_4$), and evaporated to yield a yellow oil, which was treated with 0.20 mole of maleic acid in Me_2CO. The crystalline precipitate (4.98 g, 72%) decomposed at 181.5°. A small sample was recrystallized from MeOH to provide pure **6**: mp 185.5 dec; ir (KBr) 7.39, 8.65 (SO_2), 9.70 μ (SO). *Anal.* ($C_{23}H_{29}N_3O_3S_2 \cdot 2C_4H_4O_4$) C, H, N.

N,N-Dimethyl-9-[3-(dimethylamino)propylidene]thioxanthene-2-sulfonamide (5).—Following the procedure for preparing **4**, amino ketone **2** (17.6 g, 0.040 mole) was reduced with $NaBH_4$, then treated with $POCl_3$–C_6H_5N to yield a pair of geometric isomers which were separated by treating a solution of the amorphous free base mixture in EtOH with anhydrous HCl. The less soluble hydrochloride fraction was recrystallized twice from EtOH to yield 5.8 g (34%) of *trans*-**5**: mp 226–228°; uv max (EtOH) 230, 252, 304 mμ (log ϵ 4.5, 4.2, 3.9). *Anal.* ($C_{20}H_{24}N_2O_2S_2 \cdot HCl$) C, H, N.

The more soluble hydrochloride fraction was recrystallized three times from MeCN to yield 2.4 g (14%) of *cis*-**5**: mp 210–212°; uv max (EtOH) 228, 260, 310 mμ (log ϵ 4.6, 4.2, 3.9). *Anal.* ($C_{20}H_{24}N_2O_2S_2 \cdot HCl$) C, H, N.

2-Bromo-5-(dimethylsulfamoyl)benzoic Acid (7).—To 160 ml of $ClSO_3H$ at 5° *o*-bromobenzoic acid (100 g, 0.50 mole) was added carefully and the greenish yellow solution was heated at 95–100° for 3 hr. Upon pouring the cooled mixture into a vigorously stirring ice–water slurry the intermediate sulfonyl chloride separated as a pale yellow crystalline solid, mp 151.5–154°, which was filtered and dissolved in 200 ml of liquid Me_2NH. The excess Me_2NH was allowed to evaporate overnight, the residue was dissolved in H_2O, and the solution was acidified to pH to with concentrated HCl. Crystallization of the precipitated product from H_2O afforded 90 g (58%) of **7**, mp 174–177°. Two recrystallizations from H_2O followed by vacuum drying provided pure **7**: mp 176–177.5°; ir (KBr) 5.90, 5.96 (C=O), 7.47, 8.58 μ (SO_2); uv max (MeOH) 240, 281 mμ (log ϵ 4.1, 3.1). *Anal.* ($C_9H_{10}BrNO_4S$) C, H, N.

5-Dimethylsulfamoyl-2-(phenylthio)benzoic Acid (8).—A well-stirred mixture of carboxylic acid **7** (61.6 g, 0.20 mole), 85% KOH pellets (28.4 g, 0.43 mole), benzenethiol (24.0 g, 0.22 mole), and Cu powder (1.0 g) in 500 ml of DMF under N_2 was heated at 120–130° for 20 hr. Upon cooling the mixture was filtered through a bed of Supercel. The filtrate was concentrated *in vacuo* to remove most of the DMF, diluted with 500 ml of H_2O, and carefully acidified to pH 2 with concentrated HCl. The precipitated product was filtered, washed (H_2O), and recrystallized from MeCN to yield 54.5 g (81%) of **8**, mp 214–217°. One recrystallization from C_6H_6 provided pure **8**: mp 215–217°; ir (KBr) 5.98 (C=O), 7.46, 8.60 μ (SO_2); uv max (MeOH) 281 mμ (log ϵ 4.2). *Anal.* ($C_{15}H_{15}NO_4S_2$) C, H, N.

N,N-Dimethyl-9-oxothioxanthene-2-sulfonamide (9).—A mixture of **8** (9.45 g, 0.028 mole) and 50 g of polyphosphoric acid (Matheson Coleman and Bell, 82–84% P_2O_5) was stirred at 90–100° for 16 hr, poured onto crushed ice, and extracted into $CHCl_3$. The extract was thoroughly washed with 1 *N* aqueous KOH and H_2O, dried ($MgSO_4$), and evaporated to yield 6.74 g (75%) of **9**, mp 174–176°. One crystallization from MeCN provided pure **9**: mp 176–177.5°; ir (KBr) 6.10 (C=O), 7.45, 8.61 μ (SO_2); uv max (MeOH) 224, 256, 281, 309, 376 mμ (log ϵ 4.3, 4.6, shoulder, 4.1, 3.7); nmr ($CDCl_3$) δ 2.75 (s, 6 H), 7.3–8.1 (m, 5 H), 8.59 (m, 1 H, H-8), 8.95 (d, 1 H, H-1). *Anal.* ($C_{15}H_{13}NO_3S_2$) C, H, N.

N,N-Dimethyl-9-oxothioxanthene-2-sulfonamide 10,10-Dioxide (10).—A mixture of **9** (3.19 g, 0.010 mole) and 5.0 ml of 30% H_2O_2 in 40 ml of glacial AcOH was stirred at reflux for 3 hr. Upon cooling ketosulfone **10** (2.89 g, 82%) crystallized as bright

yellow needles: mp 182–183.5°; ir (KBr) 5.95 (C=O), 7.42, 8.53 (SO_2, sulfonamide), 7.65, 7.75, 8.74 μ (SO_2, sulfone); uv max (EtOH) 236, 280 mμ (log ε 4.45, shoulders). *Anal.* ($C_{15}H_{13}NO_5S_2$) C, H, N.

N,N,N′,N′-Tetramethyl-9-oxothioxanthene-2,7-disulfonamide (11).—Thioxanthen-9-one (21.2 g, 0.10 mole) and 65 ml of $ClSO_3H$ were heated at 90–100° fo 15 hr. After pouring the mixture onto ice, the solid precipitate was filtered, vacuum dried over P_2O_5, triturated to a fine powder, and dissolved in 100 ml of liquid Me_2NH. When the excess amine had evaporated, the residual solid was digested in H_2O, filtered, and chromatographed on 250 g of basic Al_2O_3 (Woelm, activity III). Elution with Et_2O–CH_2Cl_2 (4:1) yielded a mixture of monosulfonamide **9** and disulfonamide 11. Subsequent elution with CH_2Cl_2 and dilution of the eluate with Et_2O afforded 12.2 g (29%) of pure crystalline 11: mp 277–279°; uv max (MeOH) 226, 259, 287, 315, 374 mμ (log ε 4.3, 4.5, 4.1, 4.2, 3.5). *Anal.* ($C_{17}H_{18}N_2O_5S_4$) C, H, N.

N,N-Dimethyl-*o*-chlorobenzenesulfonamide.—Slow addition of 42 g (0.20 mole) of *o*-chlorobenzenesulfonyl chloride[10] to 600 ml of 25% aqueous Me_2NH at 5° produced a heavy, white precipitate, which was filtered, washed (H_2O), and dried to provide 38.0 g (87%) of the sulfonamide, mp 38.5–39.5°. One recrystallization from Et_2O–hexane raised the melting point to 39–40° *Anal.* ($C_8H_{10}ClNO_2S$) C, H, N.

N,N-Dimethyl-9-oxothioxanthene-4-sulfonamide (12).—To a solution of *o*-mercaptobenzoic acid (18.5 g, 0.120 mole) and N,N-dimethyl-*o*-chlorobenzenesulfonamide (22.0 g, 0.100 mole) in 100 ml of anhydrous DMSO under N_2 at 150° was added 11.9 g (0.220 mole) of MeONa and 1.0 g of Cu powder with stirring. After stirring at 150° for 18 hr, the copper was filtered and washed with H_2O and Et_2O. The filtrate was diluted with 3 vol of H_2O and washed thoroughly with Et_2O to remove the unchanged aryl halide. Acidification of the aqueous layer to pH 2 precipitated a dark solid, which was filtered and dried. The solid (31 g) was pulverized and stirred for 4 hr at 100° with 150 g of polyphosphoric acid (Matheson Coleman and Bell, 82–84% P_2O_5). A procedure similar to that used to isolate ketone **9** provided 13.2 g (41%) of crude **12**, mp 172–175°. One recrystallization from Me_2CO and one recrystallization from MeCN afforded pure **12**: mp 177–179°; ir (KBr) 6.07 (C=O), 7.50, 8.61 μ (SO_2); uv max (MeOH) 224, 257, 290, 380 mμ (log ε 4.1, 4.6, shoulder, 3.8). *Anal.* ($C_{15}H_{13}NO_3S_2$) C, H, N.

9-Hydroxy-9-[3-(1,1-dimethylpropoxy)propyl]-N,N-dimethylthioxanthene-2-sulfonamide (13).—A solution of 3-bromo-1-(1,1-dimethylpropoxy)propane[12] (20.9 g, 0.100 mole) in 200 ml of anhydrous Et_2O was added to 2.4 g of Mg (50 mesh, Nelco Metals, Inc.), 0.1 ml of 1,2-dibromoethane, and 10 ml of Et_2O under N_2 at such a rate so as to maintain gentle reflux. When the halide addition was complete (*ca.* 40 min), the mixture was stirred at reflux for an additional 60 min. Finely pulverized ketone **9** (12.8 g, 0.040 mole) was added in portions during 30 min. Sufficient Et_2O was introduced during this period to maintain efficient stirring. After an additional 60 min at reflux, the reddish brown complex was decomposed with 3 *N* aqueous NH_4Cl, the layers were separated, and the aqueous phase was extracted with C_6H_6. The combined extracts were dried ($MgSO_4$), the solvents were evaporated, ad the residue was crystallized from EtOAc–hexane to yield 15.7 g (87%) of carbinol **13**, mp 139–141.5°. One recrystallization from the same solvent pair afforded pure **13**: mp 140–142°; ir (KBr) 3.07 μ (OH); uv max (MeOH) 230, 254, 296 mμ (log ε 4.2, 3.8, 4.1). *Anal.* ($C_{23}H_{31}NO_4S_2$) C, H, N.

4,5-Dihydro-N,N-dimethylspiro[furan-2(3H),9′-thioxanthene]-2′-sulfonamide (14).—Hydroxy ether **13** (7.5 g, 0.017 mole) was dissolved in 100 ml of concentrated HCl. After 1.25 hr, the solution was diluted with H_2O and the resulting gum was chromatographed on basic Al_2O_3 (Woelm, activity III). The column was eluted with hexane–C_6H_6 (1:1) until a yellow band migrated to the base of the column. Upon crystallization from EtOAc–hexane the eluate yielded 4.7 g (77%) of **14**, mp 139–141°. One recrystallization from the same solvent pair afforded pure **14**: mp 141–142.5°, ir (KBr) 9.55 μ (C–O). *Anal.* ($C_{18}H_{19}NO_3S_2$) C, H, N.

Method A. 9-Hydroxy-N,N-dimethyl-9-[3-(dimethylamino)propyl]thioxanthene-2-sulfonamide (15).—3-Chloro-N,N-dimethylpropylamine (12.2 g, 0.100 mole) and 200 ml of anhydrous THF were added simultaneously from different dropping funnels to 2.43 g (0.100 g-atom) of Mg (50 mesh, Nelco Metals, Inc.), 0.1 ml of 1,2-dibromoethane, and 2 ml of THF under N_2 in such a manner so as to maintain gentle and continual reflux. When the addition was complete, the mixture was stirred at reflux until most of the metal had reacted (0.5–2 hr), pulverized ketone **9** (16.0 g, 0.050 mole) was added, and the mixture was stirred at 25° for 16 hr. The mixture was cooled to 10°, 60 ml of 3 *N* aqueous NH_4Cl was added dropwise, and the product was extracted with $CHCl_3$. After the extract was dried ($MgSO_4$) and the solvent was removed, the residue yielded 17.2 g (85%) of crystalline **15**, mp 88.5–91°, upon trituration with anhydrous Et_2O. Two recrystallizations from EtOAc–Et_2O failed to alter the melting point. The ir spectrum (KBr) exhibits a weak OH band at 2.93 μ and a very broad bonded OH absorption centered at *ca.* 3.6 μ. *Anal.* ($C_{20}H_{26}N_2O_3S_2$) C, H; N: calcd, 6.89; found, 6.06.

Method B. Conversion of 15 to *cis*-5 and *trans*-5.—A solution of **15** (15.5 g, 0.038 mole) in 380 ml of 2 *N* aqueous HCl was refluxed for 2 hr under N_2. The reartion mixture was cooled to 5° and adjusted to pH 12 with 10 *N* aqueous NaOH and the product was isolated by extraction into CH_2Cl_2. Both geometric isomers were isolated as above to yield 6.1 g (38%) of *trans*-**5**, mp 226–228°, and 2.3 g (14%) of *cis*-**5**, mp 209.5–212°.

1-(3-Chloropropyl)-4-methylpiperazine.—A solution of 1-methylpiperazine (20 g, 0.20 mole) and 1-bromo-3-chloropropane (15.8 g, 0.10 mole) in 40 ml of anhydrous Et_2O was stirred for 40 hr at 25°. The precipitated 1-methylpiperazine hydrobromide was filtered and the residue from the filtrate was distilled at reduced pressure to yield 66.3 g (75%) of colorless product: bp 54° (0.8 mm) [lit.[13] 94–96° (11 mm)]; $n^{25}D$ 1.4762. *Anal.* ($C_8H_{17}ClN_2$) Cl: calcd, 20.07; found, 20.22.

9-Hydroxy-N,N-dimethyl-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthene-2-sulfonamide (16) was prepared (method A) in 79% yield from 1-(3-chloropropyl)-4-methylpiperazine: mp 166–168° (MeCN). *Anal.* ($C_{23}H_{31}N_3O_3S_2$) C, H, N.

Conversion of 16 to *cis*-4.—Employing method B, **16** provided a mixture of *cis*-**4** and *trans*-**4** (2:3 ratio) in essentially quantitative yield. Treatment with 2 equiv of oxalic acid in 50% aqueous EtOH precipitated most of the *trans*-**4** dioxalate, and *cis*-**4** was recovered from the mother liquor by conversion to the free base and crystallization from Et_2O. The residue from the Et_2O mother liquors and the *trans*-**4** dioxalate were combined, dissolved in 2 *N* aqueous HCl, and heated at reflux until the mixture had been converted to the 2:3 equilibrium isomer ratio (*ca.* 1 hr). An additional crop of *cis*-**4** was isolated as above. Upon recycling the *trans* isomer four times *cis*-**4** (mp 147–149°) was recovered in 72% yield (based on **16**).

***trans*-N,N-Dimethyl-9-[2-(methyl-2-piperidyl)ethylidene]-thioxanthene-2-sulfonamide Fumarate** (17).—2-(2-Chloroethyl)-1-methylpiperidine, bp 90° (16 mm) [lit.[14] bp 86–87° (12 mm)], when subjected to the conditions of method A, yielded a yellow gum which was stirred with boiling 2 *N* aqueous HCl (not soluble) for 5 hr. The cooled reaction mixture was diluted with 5 vol of H_2O, and filtered to remove unchanged ketone **9**. Treatment of the filtrate with 10 *N* aqueous KOH liberated a 75% yield of the *cis*–*trans* isomer mixture. Fractional crystallization of the fumarate salt from EtOH provided the pure *trans* isomer **17**: mp 187–189°; uv max (EtOH) 230, 250, 302 mμ (log ε 4.6, 4.3, 4.0). *Anal.* ($C_{23}H_{28}N_2O_2S_2 \cdot C_4H_4O_4$) C, H, N.

9-Hydroxy-N,N,N′,N′-tetramethyl-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthene-2,7-disulfonamide was prepared in 50% yield *via* method A from ketone 11: mp 229–231° (MeOH). *Anal.* ($C_{23}H_{36}N_4O_5S_3$) C, H, N.

N,N,N′,N′-Tetramethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]thioxanthene-2,7-disulfonamide (18) was prepared in 95% yield *via* method A and isolated as the dimaleate salt: mp 193–194.5°; uv max (EtOH) 232, 249, 283, 306 mμ (log ε 4.6, 4.4, 4.2, 4.0); nmr ($CDCl_3$) δ 6.13 (m, 1 H, vinyl CH), 7.3–7.7 (m, 4 H, H-3,4,5,6), 7.88 (m, 2 H, H-1,8). *Anal.* ($C_{35}H_{34}N_4O_5S_3 \cdot 2C_4H_4O_4$) C, H, N.

N,N-Dimethyl-9-[3-(1-piperazinyl)propylidene]thioxanthene-2-sulfonamide (19).—*n*-BuLi (270 ml of a 1.6 *M* solution in hexane (Foote Mineral Co.)), was added to a stirred slurry of anhydrous 3-(1-piperazinyl)propyltriphenylphosphonium bromide hydrobromide[3] (116 g, 0.210 mole), in 400 ml of anhydrous THF under N_2 at such a rate so as to maintain gentle reflux. Ketone **9**

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(63.9 g, 0.200 mole) was added to the deep red ylide solution and the mixture was stirred at reflux for 2 hr. After cooling the reaction mixture to 5°, 100 ml of H_2O was carefully added, then the aqueous phase was adjusted to pH 3 with 3 *N* aqueous HCl. The layers were separate and the aqueous layer was extracted with two 250-ml portions of C_6H_6 to remove unreacted ketone and Ph_3PO. The aqueous phase was clarified with Darco G-60, neutralized with 3 *N* aqueous KOH, and extracted throughly with C_6H_6 to provide 46.3 g (54%) of **19**, a 1:1 mixture of geometric isomers.

The *trans* isomer was isolated by conversion to the dioxalate salt in 50% aqueous EtOH. One recrystallization from the same solvent pair afforded pure *trans*-**19** dioxalate: mp 181–181.5° dec. *Anal.* ($C_{22}H_{27}N_3O_2S_2 \cdot 2C_2H_2O_4 \cdot H_2O$) C, H, N.

The free base from *trans*-**19** dioxalate, when treated with maleic acid in MeCN, provided *trans*-**19** dimaleate: mp 150–153°; uv max (EtOH) 302 mμ (log ε 3.9). *Anal.* ($C_{22}H_{27}N_3O_2S_2 \cdot 2C_4H_4O_4$) C, H, N.

The *cis* isomer was isolated by neutralization of the oxalate mother liquor to pH 10 with 3 *N* aqueous KOH, extracting thoroughly with CH_2Cl_2, and treatment of the enriched free base mixture with *p*-toluenesulfonic acid in hot MeOH. A single recrystallization from MeOH provided pure *cis*-**19** ditosylate: mp 207–208°, uv max (EtOH) 261, 310 mμ (log ε 4.2, 3.9). *Anal.* ($C_{22}H_{27}N_3O_2S_2 \cdot 2C_7H_8O_3S$) C, H, N.

Methylation of *trans*-19.—A solution of the free base of *trans*-**19** (172 mg) in 4 ml of 97% HCO_2H and 4 ml of 37% formalin was heated at reflux for 30 min. The residue was dissolved in CH_2Cl_2, washed with 1 *N* aqueous KOH, dried ($MgSO_4$), then evaporated to an oil which crystallized from *i*-PrOH, mp 119–121°. One recrystallization afforded a product which was identical with *trans*-**4**.

Methylation of *cis*-19.—In the same manner *cis*-**19** (free base) was converted to *cis*-**4**, mp 145–147°.

3-(4-Methyl-1-piperazinyl)propyltriphenylphosphonium Bromide Hydrobromide.—1-Methylpiperazine (10.0 g, 0.100 mole) was added carefully to a stirred slurry of 3-bromopropyltriphenylphosphonium bromide[15] (46.4 g, 0.100 mole) in 100 ml of *i*-PrOH. When heated to reflux, a deep red solution was obtained. After 2 hr at reflux, the solution was chilled to 5°. The crystalline product was filtered, washed with cold *i*-PrOH, and dried (100°, 0.3 mm) to provide 38.7 g (69%) of material, mp 244° dec. *Anal.* ($C_{26}H_{23}BrN_2P \cdot HBr$) C, H, Br. Upon standing in air this salt quickly absorbs 1 equiv of H_2O, which readily dissociates on vacuum drying.

cis-**N,N-Dimethyl-9-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propylidene}thioxanthene-2-sulfonamide (20) Dimaleate.**—A solution of *cis*-**19** free base (4.30 g, 0.010 mole) in 10 ml of anhydrous MeOH at 0° was treated with 1.0 ml of ethylene oxide under N_2. After heating the solution at reflux for 4 hr, the solvent was removed and the residue was treated with 2 equiv of maleic acid in EtOH to afford the crystalline dimaleate salt. Two recrystallizations from MeCN and one recrystallization from EtOH provided 2.38 g (33%) of pure **20** dimaleate: mp 126–128°; ir (KBr) 2.95 μ (OH); uv max (EtOH) 308 mμ (log ε 3.9). *Anal.* ($C_{24}H_{31}N_3O_3S_2 \cdot 2C_4H_4O_4$) C, H, N.

trans-**N,N-Dimethyl-9-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propylidene}thioxanthene-2-sulfonamide (21) dimaleate** was prepared by the same procedure in 60% yield: mp 180–182° (EtOH), uv max (EtOH) 302 mμ (log ε 3.9). *Anal.* ($C_{24}H_{31}N_3O_3S_2 \cdot 2C_4H_4O_4$) C, H, N.

cis-**4-[3-(2-N,N-Dimethylsulfamoylthioxanthen-9-ylidene)propyl]-N-methyl-1-piperazinepropionamide (22) Dihydrochloride.**—A solution of *cis*-**19** ditosylate (1.55 g, 0.002 mole) and 3-chloro-N-methylpropionamide[16] (0.49 g, 0.002 mole) in 5.0 ml of DMF under N_2 was stirred at 80° for 48 hr with 1.7 g of K_2CO_3. Upon cooling the reaction mixture was filtered, the filtrate was diluted with 4 vol of H_2O, and the product was isolated with $CHCl_3$. The crude base was treated with dry HCl in *i*-PrOH and the precipitated solid was recrystallized from *i*-PrOH to afford 0.69 g (57%) of **22** dihydrochloride: mp 244.5–246° dec, ir (KBr) 5.92 μ (amide I), uv max (EtOH) 310 mμ (log ε 4.0). *Anal.* ($C_{26}H_{34}N_4O_3S_2 \cdot 2HCl$) C, H, N.

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4′-Fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-*b*]indol-3(2H)-yl)butyrophenones

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The preparation and pharmacology of a new series of 4′-fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-*b*]indol-3(2H)-yl)-butyrophenones is discussed. These compounds possess a high degree of interesting CNS depressant activity.

The discovery in 1959[1] that a series of butyrophenone derivatives had pronounced CNS depressant activity in several mammalian species resulted in the preparation of a large number of related compounds. Several of these, the most notable being haloperidol, have been found to have useful antipsychotic activity in man.[2]

Chemically the more active members of this series are derived from six-membered heterocyclic nuclei, usually piperidine or piperazine, with the 4-(4′-fluoro)butyrophenone substituent at N-1 and a variety of substituents at the 4 position.[3,4] In this communication we will present a major departure from this general theme: a series of 4-(4-fluoro)butyrophenones derived from the centrally active hexahydroazepino[4,5-*b*]indoles[5] in which the butyrophenone moiety is attached to N-3 of the seven-membered heterocyclic ring. The compounds were prepared by alkylating the appropriate base with 4-chloro-4′-fluorobutyrophenone and are listed in Table I.

Experimental Section

Pharmacology. Methods.—Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported

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