Thioxanthene Psychopharmacological Agents. I. 9-(3-Aminopropyl)thioxanthene-2-sulfonamides

JAMES F. MUREN AND BARRY M. BLOOM

Medical Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Connecticut 06340

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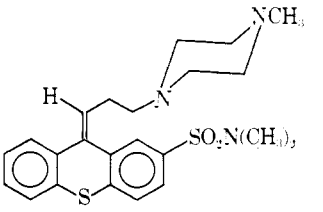
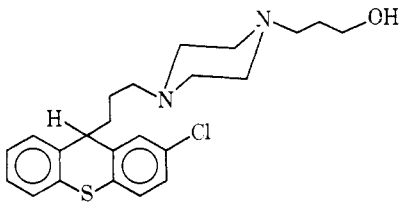
As part of a program to discover antipsychotic agents free of the tendency to induce extrapyramidal side effects, a series of 9-(3-aminopropyl)thioxanthene-2-sulfonamides was prepared. Two synthetic routes were employed, both involving sulfonation of thioxanthene at C-2 and alkylation of the C-9 carbanion as key steps. Several of the resultant compounds possess a behavioral and pharmacological profile in animals similar to that of the phenothiazine neuroleptics. Maximum potency is achieved with **5a** which at comparable dose levels exhibits significantly lower tremorigenic potential than thioproperazine, its phenothiazine structural counterpart.

Thiothixene, an established major antipsychotic agent for the treatment of schizophrenia,[1] is a product of our long-range research effort to provide more effective drug therapy in various forms of mental disease. The rationale for synthesis of thiothixene and its analogs was derived primarily from clinical observations with xanthiol, a related thioxanthene derivative.

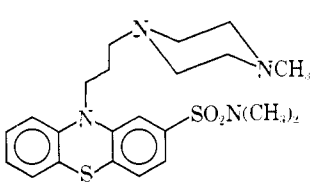
Chlorpromazine and several chemically related phenothiazine derivatives are generally accepted as effective in treatment of schizophrenia psychoses.[2,3] Although their use is attended by a variety of side effects, *e.g.*, extrapyramidal symptoms ranging from



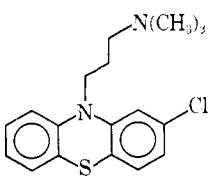
thiothixene



xanthiol



thioproperazine



chlorpromazine

mild restlessness to grotesque involuntary muscular activity, dramatic therapeutic efficacy has made them indispensable in the treatment of mental illness. Clinical experience with xanthiol[4] indicated that the phenothiazine nucleus may be replaced by thioxanthene without qualitative alteration of the effects upon psychotic symptomatology. Of particular interest to us, however, was the observation that extrapyramidal effects associated with xanthiol occur less frequently than with most phenothiazines. On the assumption that this reduced neurotoxicity is a function of the thioxanthene nucleus, we set out to construct a thioxanthene compound with maximum antipsychotic potency and a proportionate improvement in therapeutic ratio. Drug design was guided largely by the well-documented phenothiazine structure–activity relationships.[5] Our choice of the essential aromatic ring substituent was prompted by the unusual potency and efficacy of thioproperazine, a phenothiazine-2-sulfonamide,[6] claimed to be capable of reaching the most drug-resistant patients.

Our chemical program logically divided into two units. We shall discuss the 9-(3-aminopropyl)thioxanthene-2-sulfonamides here and deal with their C-9 unsaturated counterparts in the following article.[7]

Synthesis.—Two routes, which differed only in reaction sequence, satisfactorily provided the 9-(3-aminopropyl)thioxanthene-2-sulfonamide derivatives required (1) to discover that the potent central depressant activity of thioproperazine is retained by its thioxanthene analog and (2) to evaluate the effect of variation of structure at the side-chain N and the sulfonamide N.

The most useful synthetic approach to the N,N-dialkylsulfonamides involves alkylation of an appropriate thioxanthene-2-sulfonamide (**3**) carbanion. When thioxanthene in $CHCl_3$ is treated carefully with *ca.* 1 equiv of chlorosulfonic acid, monosulfonation occurs almost exclusively at C-2 to afford **1**, which can be smoothly and quantitatively converted to the corresponding sulfonyl halide (**2**) with $SOCl_2$ in DMF[8] (Scheme I). The sulfonamide derivatives (**3**) were obtained in high yield from **2** and an appropriate secondary amine. Assignment of the substituent at C-2 was confirmed by spectral and chemical evidence: the nmr spectrum of **3a** exhibits a finely split one-proton signal at 7.75 ppm, and **2** was converted to 2-chlorothioxanthene by PCl_5.

Alkylation of **3a** was most conveniently performed by addition of 3-(dimethylamino)propyl chloride to the Li derivative prepared at 10° to minimize dimerization. $NaNH_2$ in toluene and NaH in DMF were also effective

(1) 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).

(2) J. O. Cole, *Arch. Gen. Psychiat.*, **10**, 246 (1964).

(3) J. Kinross-Wright, *J. Amer. Med. Ass.*, **200**, 461 (1967).

(4) C. Z. K. Mitis, *Diseases Nervous System*, **21**, 584 (1960).

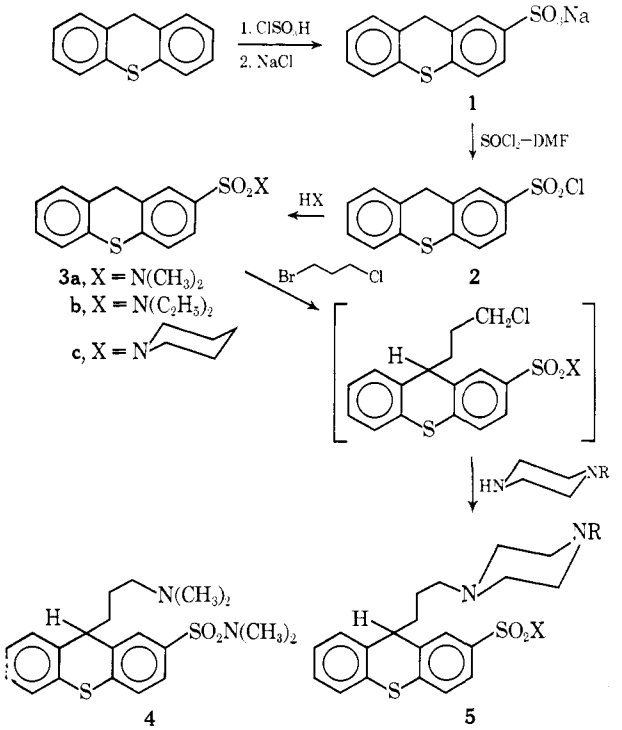
(5) M. Gordon in "Psychopharmacological Agents," Vol. II, M. Gordon, Ed., Academic Press, Inc., New York, N. Y., 1967, Chapter 1.

(6) J. Denham and D. J. E. L. Carrick, *J. Metal Sci.*, **107**, 326 (1961).

(7) J. F. Muren and B. M. Bloom, *J. Med. Chem.*, **13**, 17 (1970).

(8) W. A. Gregory, U. S. Patent 2,888,486 (1959).

SCHEME I



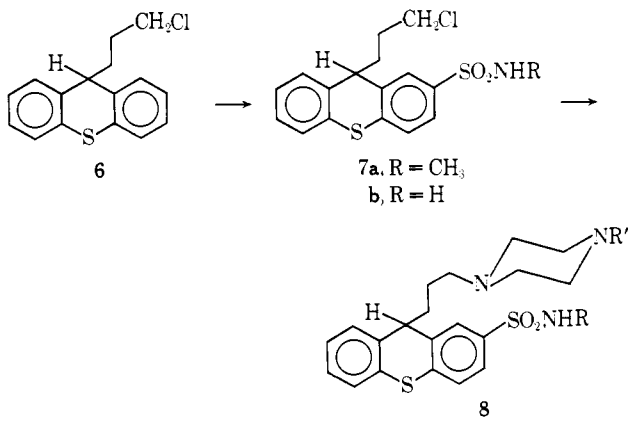
in promoting carbanion formation at C-9; however, higher temperatures were necessary and the yields of **4** were consistently low. In the case of the 3-(1-piperazinyl)propyl derivatives (**5a–g**, Table I) the carbanion solution was added slowly to 1-bromo-3-chloropropane. Purification of the intermediate 9-(3-chloropropyl)thioxanthene-2-sulfonamide was cumbersome, so it was merely freed from the excess halide before treatment with the appropriate substituted piperazine. The products were purified as the crystalline dimaleate salts (**5a**, **b**, **c**, **f**, and **g**) or by chromatography on basic alumina (**5d** and **e**).

Synthesis of **8a–c** was accomplished by sulfonation of 9-(3-chloropropyl)thioxanthene (**6**), conversion to the sulfonyl chloride, and treatment with NH_3 or $MeNH_2$. The resulting 9-(3-chloropropyl)thioxanthene-2-sulfonamide (**7**) was used to alkylate an appropriately substituted piperazine to provide 8 purified as the crystalline dimaleate salt (Scheme II).

Pharmacology.—Representative compounds were tested for ability to depress nondiscriminated avoidance behavior in rats,[9] antagonize apomorphine-induced emesis in dogs,[10] and produced tremors and catalepsy in monkeys.[10] Several of these compounds possess a behavioral and pharmacological profile similar to that of chlorpromazine and thioproperazine. Maximum activity is achieved when the C-2 ring substituent is dimethylsulfamoyl, and the side-chain amine is incorporated into an N,N-dialkylpiperazine ring. The most potent compound in this series is **5a**, which clearly disrupts avoidance behavior at a dose of 1.0 mg/kg ip and blocks emesis a 0.05 mg/kg iv. No evidence of tremors or catalepsy was detected in monkeys receiving a daily oral dose of 25 mg/kg of **5a** over a 6-day period.

(9) (a) A. Weissman and K. F. Finger, *Biochem. Pharmacol.*, **11**, 871 (1962); (b) A. Weissman, *J. Exp. Anal. Behavior*, **2**, 271 (1959).
(10) A. Weissman, *Psychopharmacologia*, **12**, 142 (1967).

SCHEME II



At the same dose thioproperazine produces pronounced cataleptic and tremorigenic effects.

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 spectrometer, uv spectra with a Cary Model 11 recording spectrometer, and nmr spectra with a Varian A-60 spectrometer (Me_4Si as internal standard).

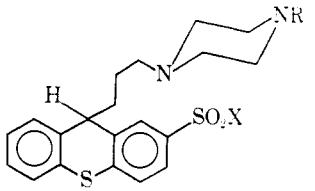
Thioxanthene-2-sulfonic Acid Sodium Salt (1).—A solution of thioxanthene (32.2 g, 0.160 mole) in 160 ml of $CHCl_3$ was cooled to 0° and $ClSO_3H$ (12.4 ml, 0.190 mole) was added as rapidly as possible while maintaining the internal temperature below 10°. After the addition was complete, the reaction mixture was allowed to approach room temperature during 30 min, then refluxed for an additional 20 min. The deep red solution was poured onto 100 g of crushed ice and 20 g of NaCl was added to convert the sulfonic acid to its crystalline sodium salt. After filtering the slurry through a sintered-glass funnel, the filter cake was washed with $CHCl_3$ and 20% NaCl solution. The crude sodium sulfonate was digested in 1500 ml of boiling H_2O, treated with a little Darco G-60, and filtered at the boiling point. Crystallization was allowed to proceed overnight at 4° and, after filtration and drying for 12 hr at 100° (0.1 mm), 33.3 g (69%) of **1** (colorless plates) was obtained: mp >295°; ir (KBr) 8.3, 9.5 (SO_2), 15.1 μ (SO); uv max (MeOH) 253, 274 mμ (log ε 3.8, 4.1). *Anal.* ($C_{13}H_9NaO_3S_2$) C, H; Na: calcd, 7.65; found, 8.33.

Thioxanthene-2-sulfonyl Chloride (2).—A slurry of dry **1** (30.0 g, 0.10 mole) in 50 ml of DMF was treated with $SOCl_2$ (8.0 ml), gently warmed until homogenous, then immediately poured onto crushed ice. After a short period of stirring, the precipitated colorless oil crystallized, was filtered, washed with H_2O, and air-dried yielding 28.7 g (97%) of crude **2**, mp 78–79.5°. A small sample dissolved in hot hexane and treated with Darco g-60 provided pure **2** as colorless rosettes: mp 82–83°; ir (KBr) 7.32, 8.55 μ (SO_2); uv max (MeOH) 240, 252, 317 mμ (log ε 4.1, shoulder, 4.0). *Anal.* ($C_{13}H_9ClO_2S_2$) C, H, Cl.

A mixture of **2** (3.0 g) and PCl_5 (10 g) was heated at 160–170° (oil bath) for 6 hr, treated with ice, and extracted with C_6H_6. The extract was washed (5% $NaHCO_3$, H_2O), dried ($MgSO_4$), and evaporated yielding a yellow solid (1.76 g), which was chromatographed on basic Al_2O_3 (Woelm, activity III). Elution with hexane afforded 375 mg of white crystalline 2-chlorothioxanthene (mp 101–103°), which was identified by ir spectra comparison and mixture melting point with an authentic sample, followed by 240 mg of yellow 2-chlorothioxanthen-9-one (mp 151–153°).

N,N-Dimethylthioxanthene-2-sulfonamide (**3a**).—Crude **2** prepared from 30.0 g of **1** was stirred with 50 ml of liquid Me_2NH at the boiling point. After allowing excess amine to evaporate, H_2O was added, and the precipitate was filtered, washed with H_2O, and dried to afford **3a** (23.8 g, 78%), mp 163–165°. One recrystallization from EtOH–$CHCl_3$ yielded pure **3a**: mp 164–165.5°; ir (KBr) 7.46, 8.67 μ (SO_2); uv max (MeOH) 228, 253, 291 mμ (log ε 4.2, 3.8, 4.0); nmr ($CDCl_3$) δ 2.69 (6 H), 3.92 (2 H),

TABLE I
9-[3-(1-PIPERAZINYL)PROPYL]THIOXANTHENE-2-SULFONAMIDES



No.	R	X	Method	Yield, %	Mp, °C	Formula[a]
5a	CH_3	$N(CH_3)_2$	A	60	174–176	$C_{23}H_{31}N_3O_2S_2 \cdot 2C_4H_4O_4$[b]
5b	CH_2CH_2OH	$N(CH_3)_2$	A	60	131.5–133	$C_{24}H_{33}N_3O_3S_2 \cdot 2C_4H_4O_4$
5c	$CH_2CH_2CH_2OH$	$N(CH_3)_2$	A	35	163–165	$C_{25}H_{35}N_3O_3S_2 \cdot 2C_4H_4O_4$
5d	SO_2CH_3	$N(CH_3)_2$	A	42	140–155	$C_{23}H_{31}N_3O_4S_3 \cdot HCl$
5e	$SO_2N(CH_3)_2$	$N(CH_3)_2$	A	32	165–170	$C_{24}H_{34}N_4O_4S_3 \cdot HCl$
5f	CH_3	$N(CH_2CH_3)_2$	A	50	170.5–172	$C_{25}H_{35}N_3O_2S_2 \cdot 2C_4H_4O_4$
5g	CH_3		A	40	178–179.5	$C_{26}H_{35}N_3O_2S_2 \cdot 2C_4H_4O_4$
8a	CH_3	NH_2	B	44	152–155	$C_{21}H_{27}N_3O_2S_2 \cdot 2C_4H_4O_4$
8b	CH_3	$NHCH_3$	B	43	151–152	$C_{22}H_{29}N_3O_2S_2 \cdot 2C_4H_4O_4$
8c	CH_2CH_2OH	$NHCH_3$	B	30	160–210	$C_{23}H_{31}N_3O_3S_2 \cdot 2C_4H_4O_4$

[a] All compounds analyzed correctly for C, H, and N. [b] Maleate salt.

7.1–7.7 (m, 6 H), 7.75 (m, 1 H, H-1). *Anal.* ($C_{15}H_{13}NO_2S_2$) C, H, N.

N,N-Diethylthioxanthene-2-sulfonamide (3b) was prepared in the same manner from Et_2NH in 78% yield, mp 93–94.5° (EtOH). *Anal.* ($C_{19}H_{21}NO_2S_2$) C, H, N.

1-(Thioxanthene-2-sulfonyl)piperidine (3c) was prepared in the same manner from piperidine in 89% yield, mp 155–157.5° (EtOH). *Anal.* ($C_{18}H_{19}NO_2S_2$) C, H, N.

N,N-Dimethyl-9-[3-(dimethylamino)propyl]thioxanthene-2-sulfonamide (4).—A well-stirred suspension of **3a** (6.11 g, 0.020 mole) in 40 ml of 1,2-dimethoxyethane under N_2 was cooled in ice and treated with 3 *M* *n*-BuLi in purified heptane (8.0 ml, 0.024 mole) at such a rate that the reaction temperature did not rise above 10°. 3-(Dimethylamino)propyl chloride (2.92 g, 0.024 mole) was added immediately to the deep reddish brown solution. After stirring for 1 hr at room temperature, the solution was heated at reflux for 2 hr. The pale yellow suspension was concentrated *in vacuo*, treated with 30 ml of 1 *N* HCl, and filtered through a bed of Supercel, and the filtrate was washed with EtOAc. The crude free base (6.21 g) was obtained by making the filtrate strongly alkaline with 10 *N* aqueous NaOH and extracting with $CHCl_3$. Conversion to the maleate salt was effected by combining a solution of free base in hot EtCOMe with a solution of maleic acid (1.86 g, 0.016 mole) in hot EtCOMe and cooling slowly to room temperature. After drying at 100° (0.05 mm), pure **4** maleate (6.37 g, 63%) melted at 162–164°; ir (KBr) 7.46, 8.66 μ (SO_2); uv max (MeOH) 230, 255, 296 mμ (log ϵ 4.1, 3.8, 4.1). *Anal.* ($C_{20}H_{26}N_2O_2S_2 \cdot C_4H_4O_4$) C, H, N.

9-[3-(1-Piperazinyl)propyl]thioxanthene-2-sulfonamides are listed in Table I, and their preparation is illustrated by the following methods.

Method A. N,N-Dimethyl-9-[3-(4-methyl-1-piperazinyl)propyl]thioxanthene-2-sulfonamide (5a).—A solution of the Li derivative **3a** in 1,2-dimethoxyethane (prepared as described for **4**) was siphoned dropwise by means of N_2 pressure into a flask containing 1-bromo-3-chloropropane (9.6 ml, 0.100 mol). The mixture was stirred at 25° for 1 hr and at reflux for 30 min, whereupon the solvents were removed by distillation at 10 mm using two portions of DMF to ensure complete removal of unreacted 1-bromo-3-chloropropane. After the reaction mixture had been concentrated to a viscous yellow oil, it was dissolved in 30 ml of EtCOMe, 1-methylpiperazine (4.0 g, 0.040 mole) was added, and the mixture was stirred under reflux for 15 hr. Upon cooling the solvent was evaporated *in vacuo* and the residual oil dissolved in EtOAc. The solution was washed with H_2O and extracted with two 50-ml portions of 1 *N* aqueous AcOH and two 50-ml portions of H_2O. The combined aqueous extracts were washed with EtOAc and made alkaline, and the precipitated oil was extracted with CH_2Cl_2. The extract was washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated to give 7.58 g (85%) of free base, which was characterized as **5a** dimaleate: ir (KBr) 7.45, 8.65 μ (SO_2); uv max (MeOH) 255, 296 mμ (log ϵ 3.9, 4.1).

9-(3-Chloropropyl)thioxanthene (6).—A well-stirred solution of thioxanthene (39.7 g, 0.20 mole) in 200 ml of dry C_6H_6 and 200 ml of dry C_6H_6 and 200 ml of anhydrous Et_2O under N_2 was treated with 3 *M* *n*-BuLi in purified heptane (70 ml, 0.21 mole). When butane evolution had subsided, the deep red carbanion solution was siphoned dropwise by means of N_2 pressure into a flask containing 1-bromo-3-chloropropane (96 ml, 1.0 mole) in 100 ml of Et_2O. The mixture was stirred at 20° for 1 hr and at reflux for 1 hr. Upon cooling the suspension was filtered through a bed of Supercel and the solvents were evaporated under reduced pressure. The residual red oil was distilled at 0.10 mm and a fraction boiling at 158–166° was collected. Crystallization from hexane yielded large colorless prisms (36.0 g, 66%), **6**: mp 52–53°; uv max (MeOH) 253, 269 mμ (log ϵ 3.8, 4.1). *Anal.* ($C_{16}H_{15}ClS$) C, H, Cl.

Method B. 9-[3-(4-Methyl-1-piperazinyl)propyl]thioxanthene-2-sulfonamide (8a).—Chlorosulfonic acid (5.87 ml, 0.090 mole) was added to a solution of **6** (16.5 g, 0.060 mole) in 60 ml of $CHCl_3$ as rapidly as possible while maintaining the reaction temperature below 10°. After removing the cooling bath, the mixture was stirred for 1 hr, then ice and NaCl were added. The sodium sulfonate was filtered, washed ($CHCl_3$), and dried (80° for 24 hr), then suspended in 30 ml of DMF and treated with 4.5 ml of $SOCl_2$. After stirring for 20 min, the suspension was poured into ice water, and crude sulfonyl chloride was extracted with Et_2O as a viscous yellow oil (19.8 g). Treatment with 50 ml of liquid NH_3, digestion of the reaction mixture with H_2O, then recrystallization of the insoluble product from C_6H_6 afforded 16.2 g (76%) of **7a**, mp 156–157.5°. *Anal.* ($C_{16}H_{16}ClNO_2S_2$) C, H, N.

A solution of **7a** (7.50 g, 0.021 mole) and 1-methylpiperazine (6.0 g, 0.06 mole) in 30 ml of EtCOMe was refluxed under N_2 for 20 hr. The reaction mixture was concentrated *in vacuo*, $CHCl_3$ was added, and the solution was washed well (H_2O) and dried ($MgSO_4$). Evaporation of the solvent yielded free base which was converted in EtOH to the dimaleate salt, mp 150–155°. One recrystallization from EtOH yielded 8.0 g of **8a**: ir (KBr) 7.39, 8.64 μ (SO_2); uv max (MeOH) 255, 294 mμ (log ϵ 3.8, 4.1).

Acknowledgment.—We wish to express our appreciation for the valuable technical assistance contributed by Mr. Hans Wiedermann. We are also indebted to Drs. A. Weissman and G. L. Wagle for the pharmacological testing results.