

**THIOXANTHENE DERIVATIVES OF PHARMACOLOGICAL INTEREST:
1,2,4-TRICHLORO AND 2,4,5,6-TETRACHLORO DERIVATIVES
OF 9-(3-DIMETHYLAMINOPROPYLIDENE)THIOXANTHENE**

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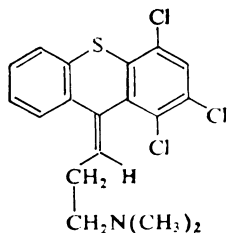
Reactions of 2,4,5-trichlorothiophenol (*II*) with 2-iodobenzoic acid and 2,3-dichlorothiophenol with 3,5-dichloro-2-iodobenzoic acid gave the acids *III* and *IX* which were cyclized to thioxanthones *VI* and *XV*. Reactions of these ketones with 3-dimethylaminopropylmagnesium chloride afforded the amino alcohols *VII* and *XVI* which were transformed by the acid catalyzed dehydration to the title compounds *I* and *VIII*. 2-Chloro-9-[1-(2-hydroxyethyl)-4-piperidylidene]thioxanthene (*XVII*) was obtained by a modified synthesis. Compound *I* is inactive in the line of the CNS effects but it has high inhibitory activity in the *in vitro* tests towards gram-positive microorganisms. Compound *XVII* has properties of a mild tranquilizer.

9-(3-Dimethylaminopropylidene)thioxanthene (prothixene)¹⁻¹⁰ is a compound with significant central depressant and antihistamine activities and as such it became a prototype for deriving further similar substances. Out of the structural modifications there were especially the substitution in position 2 of the skeleton and the introduction of a six-membered heterocycle (piperidine, piperazine) into side chain which led to the design of very potent neuroleptic agents. The whole group was the object of several reviews¹¹⁻¹³ and many laboratories participated in the experimental investigations¹⁴⁻²⁴. Our research team contributed by the synthesis of a number of new compounds and by studies of the structure-activity relationships^{9,10,25-34}. With the 2-substituted derivatives a decisive influence on the activity appertains to the stereochemical structure in the vicinity of the ethene fragment double bond (geometrical isomerism): only substances with (*Z*)-configuration are neuroleptically active. For the determination of configuration in this series X-ray crystallography³⁵⁻³⁷, IR spectra^{9,26} and ¹H NMR spectra³⁸ were used. The best survey of synthetic methods used in the prothixene group was given by the Italian authors²⁴.

The best known drug of the prothixene series is the neuroleptic agent chlorprothixene, *i.e.* (*Z*)-2-chloro-9-(3-dimethylaminopropylidene)thioxanthene⁷⁻¹⁰. Out of its halogeno derivatives the following ones have been described until now: 3-fluoro³²,

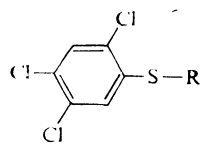
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6-fluoro³⁰, 6-chloro⁴, 7-fluoro³⁰, 7-chloro⁸, 7-bromo⁸, 3,6-difluoro³² and 6,7-difluoro³¹. The main purpose of the present paper is a description of syntheses of the title compounds *I* and *VIII*, i.e. the 1,4-dichloro and 4,5,6-trichloro derivatives of chlorprothixene.

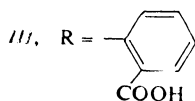
*I*

For preparing compound *I* we started from 2,4,5-trichlorothiophenol (*II*) whose preparation was described in the literature on the one hand by reduction of 2,4,5-trichlorobenzenesulfonyl chloride with zinc and sulfuric acid (without the isolation of the product) (ref.³⁹), and by treatment of 1,2,4-trichlorobenzene with sulfur monochloride and following reaction of the trisulfide formed with sodium hydroxide⁴⁰ on the other. We used a reduction of the mentioned sulfonyl chloride³⁹ by the Wagner method⁴¹, i.e. with red phosphorus and iodine in boiling acetic acid. In this way thiol *II* was obtained in a high yield. A reaction of the thiol *II* with 2-iodobenzoic acid in a boiling aqueous solution of potassium hydroxide in the presence of copper gave a mixture of the potassium salt of the acid *III* and of the disulfide *IV* which was extracted with boiling benzene. Decomposition of the undissolved product with hydrochloric acid afforded the acid *III* and evaporation of the benzene extract gave the disulfide *IV* which was formed by oxidation of a part of the thiol *II* with air oxygen. Both products were characterized by mass spectra; in the case of the disulfide *IV* the fragmentation proceeds analogously like described for diphenyl disulfide^{42,43}. The formation of disulfide *IV* by a different reaction was mentioned in the literature⁴⁰. By a reaction of the thiol *II* with (2-iodophenyl)acetic acid⁴⁴ in dimethylformamide at 150°C in the presence of potassium carbonate and copper there was prepared the homologous acid *V* as an intermediate for further work. The cyclization of the acid *III* with sulfuric acid at 95°C proceeds smoothly and affords 1,2,4-trichlorothioxanthone (*VI*) whose identity was corroborated by spectra. Reaction of this ketone with 3-dimethylaminopropylmagnesium chloride⁴⁵ in tetrahydrofuran resulted in the tertiary amino alcohol *VII* which was dehydrated by heating with dilute sulfuric acid. The amine *I* was obtained first in the form of the hydrochloride whose decomposition with sodium hydroxide released the base already in the crude state almost homogeneous. Crystallization gave a pure product which

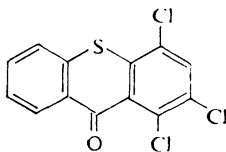
was characterized by means of the IR spectrum as (*E*)-*I*; the presence of a satellitic band at 792 cm^{-1} is typical for a sterically affected 1,2-disubstituted benzene ring of the thioxanthene skeleton (in the case of (*E*)-chlorprothixene⁴⁶ at *c.* 785 cm^{-1}). A rather selective formation of the (*E*)-isomer is apparently given by the steric situation in this case. For pharmacological testing the base was transformed to the excellently water-soluble methanesulfonate (monohydrate).



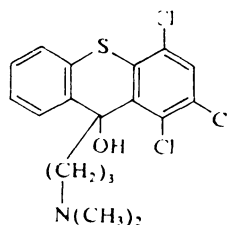
II, R = H



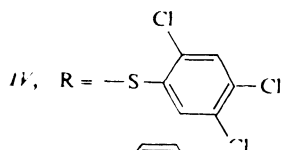
III, R =



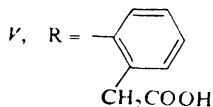
VI



VII



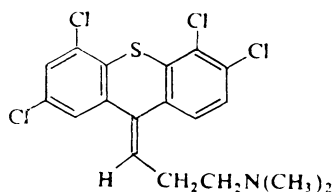
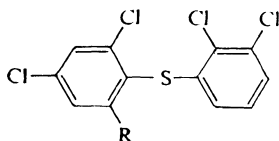
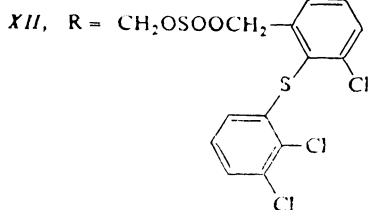
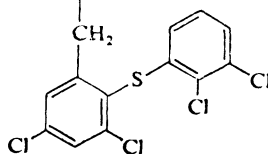
IV, R =



V, R =

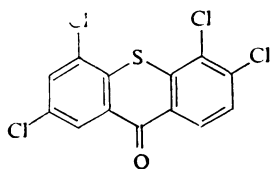
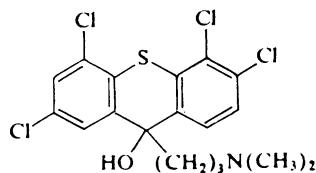
For preparing compound *VIII* we needed 3,5-dichloro-2-iodobenzoic acid⁴⁷ and 2,3-dichlorothiophenol⁴⁸ as starting materials. In an attempt at carrying out the reaction of both compounds in boiling aqueous solution of potassium hydroxide in the presence of copper, solvolysis took place and 3,5-dichlorosalicylic acid⁴⁹ was obtained. The acid *IX* was then prepared by reaction of the sodium salts of 2,3-dichlorothiophenol and 3,5-dichloro-2-iodobenzoic acid in boiling tert-butyl alcohol in the presence of copper. Its reduction with diborane, generated *in situ* by treatment of sodium borohydride with boron trifluoride etherate in tetrahydrofuran, gave the alcohol *X*, crystallizing as a 6 : 1 solvate with cyclohexane. In an attempt at transforming this alcohol to the chloro derivative *XI* by treatment with thionyl chloride in boiling benzene we isolated a crystalline product which was identified as the sulfurous ester *XII*. Sometimes we meet with such a course of reaction of substituted benzyl alcohols with thionyl chloride⁵⁰. Reaction of the crude product, which apparently consisted of the chloride *XI*, as well as of the sulfurous ester *XII*, with sodium cyanide in aqueous dimethyl sulfoxide at 60°C , had likewise an anomalous course. The crystalline product obtained corresponded by the content of most of the elements (C, H, Cl,

S) to the composition of the desired nitrile *XIII* but the nitrogen content is approximately only half of the theoretical value which indicates a doubled molecule *XIV* with one nitrogen atom only. We have already met a similar type of products in reactions of substituted benzyl chlorides with alkali cyanides⁴⁷. The mass spectra of compounds *XII* and *XIV* do not record the molecular ions but only fragmentation products.

*VIII**IX*, R = COOH*X*, R = CH₂OH*XI*, R = CH₂Cl*XIII*, R = CH₂CN*XIV*, R = CH(CN)-

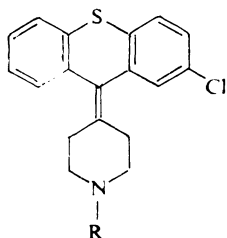
Cyclization of the acid *IX* with polyphosphoric acid at 150°C gave the desired 2,4,5,6-tetrachlorothioxanthone (*XV*). Its reaction with 3-dimethylaminopropylmagnesium chloride⁴⁵ in tetrahydrofuran gave the tertiary alcohol *XVI* which was dehydrated by boiling with dilute hydrochloric acid. The olefinic amine *VIII* was isolated in the form of the crystalline hydrogen oxalate which was purified by crystallization. The oily base, released from the pure salt, shows in the IR spectrum a band

at 877 cm^{-1} corresponding to a sterically unaffected C—H bond in position 1 of the skeleton; for compound *VIII*, therefore, the (*E*)-configuration (with regard to the atom of chlorine in position 2 and the side chain) is assigned.

*XV**XVI*

In connection with the work described we were interested in 2-chloro-9-[1-(2-hydroxyethyl)-4-piperidylidene]thioxanthene (*XVII*), for which the properties of a low-cataleptic tranquillizer or neuroleptic could be expected. Its preparation was described in patent²¹ from the analogous 1-methyl derivative *XVIII* (ref.⁵¹) by demethylation with cyanogen bromide, a following alkaline hydrolysis and the final reaction of the noncharacterized secondary amine *XIX* with oxirane in methanol. We carried out a synthesis of compound *XVII* using a preparatively more favourable route and modified also the synthesis of the starting 1-methyl derivative *XVIII* (ref.⁵¹). A reaction of 2-chlorothioxanthone⁹ with 1-methyl-4-piperidylmagnesium chloride⁵² afforded the tertiary alcohol *XXI* (its preparation was described⁵¹ similarly by making use of 1-methyl-4-piperidylmagnesium bromide). The dehydration of the alcohol *XXI* by treatment with boiling formic acid, which is described in the patent⁵¹, did not proceed in our hands under the conditions described; the reaction was then carried out by treatment with hydrogen chloride in boiling acetic acid. The olefinic amine *XVIII* was isolated as the hydrogen maleate (we found a higher melting point in comparison with the literature⁵¹ value). The demethylation was effected with ethyl chloroformate in boiling benzene. The neutral product isolated, *i.e.* the carbamate *XX*, was subjected without characterization to hydrolysis with a concentrated potassium hydroxide solution in ethanol. The secondary amine *XIX* was obtained and characterized as methanesulfonate. The introduction of the hydroxyethyl group was carried out by alkylation of compound *XIX* with 2-bromoethanol in boiling acetone in the presence of potassium hydroxide. The base *XVII* obtained has a melting point differing completely from the value, given by the literature²¹; the identity of our product was corroborated by spectra. For pharmacological testing, the hydrogen oxalate of compound *XVII* was prepared.

Compound *I* was tested in the form of the methanesulfonate monohydrate by methods of the general pharmacological screening. Acute toxicity in mice, $\text{LD}_{50} = 75\text{ mg/kg i.v.}$; the basic dose used in the screening, $\text{D} = 15\text{ mg/kg i.v.}$ In the dose *D* on *i.v.* administration the compound proved inactive in the rotarod test in mice

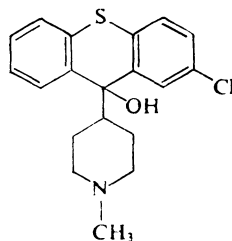


XVII, R = CH₂CH₂OH

XVIII, R = CH₃

XX, R = H

XX, R = COOC₂H₅



XXI

(no discoordinating action), in the test of potentiation of the thiopental sleeping in mice and in the test of antiamphetamine action in mice. In the test following the influence on the spontaneous motility of mice the dose D showed a mild exciting effect. The same dose brought about deep drops of the blood pressure of short duration in normotensive rats and it decreased the pressor response to a standard dose of adrenaline. In the form of a 1% solution it is inactive in the usual tests for local anaesthetic activity (application to the rabbits eye is strongly irritant). In a concentration of 10 µg/ml it has no spasmolytic effects on the isolated rat duodenum. Compound I is free of the CNS effects and with the exception of a slight adrenolytic effect it has neither neurovegetative nor peripheral neurotropic effects.

Compound XVII was evaluated on oral administration in the form of the hydrogen oxalate (the doses given calculated per base) with specific concentration to the effects expected. Acute toxicity in mice, LD₅₀ = 347 mg/kg. Discoordinating effect in the rotarod test in mice, ED₅₀ = 32 mg/kg (a dose of 100 mg/kg brings about ataxia in 100% mice even in 24 h after the administration); in rats, ED₅₀ = 34 mg/kg. Inhibition of the locomotor activity in mice followed by the photo-cell method of Dews (in the interval of 1 h after administration), D₅₀ = 10 mg/kg (after 24 h the doses of 10–50 mg/kg already without effect). Cataleptic action in rats: a dose of 50 mg/kg brings about catalepsy in 30% animals. Compound XVII fulfilled in principle the expectation and proved to be a low-cataleptic tranquillizer. The results obtained, however, do not warrant any more detailed investigations.

The acid V in an oral dose of 100 mg/kg revealed antiinflammatory action in the test of kaolin edema in rats. The same dose is approximately the ED₅₀ in the test for analgesic activity in mice using chemical stimulation (intraperitoneal administration of acetic acid).

Compounds I and V were further tested for antimicrobial activity *in vitro* (micro-organisms and the minimum inhibitory concentrations [MIC] in µg/ml – unless

they exceed 100 µg/ml — are given): *Streptococcus* β-haemolyticus, *I* 3·1, *V* 100; *Streptococcus faecalis*, *I* 6·2; *Staphylococcus pyogenes aureus*, *I* 3·1; *Escherichia coli*, *I* 12·5; *Proteus vulgaris*, *I* 50; *Saccharomyces pasterianus*, *I* 50, *V* 50; *Trichophyton mentagrophytes*, *I* 50, *V* 50. Because of the relatively high antimicrobial activity of compound *I*, its testing was continued using 20 strains of *Staphylococcus pyogenes aureus* and 20 strains of *Escherichia coli*. While the activity against *Staphylococcus pyogenes aureus* could be confirmed (MIC between 3·1 and 6·2 µg/ml), the activity towards *Escherichia coli* was not reliable (MIC > 100 µg/ml). Further testing, therefore, was discontinued.

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P₂O₅ at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ¹H NMR spectra (C²HCl₃ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with Varian MAT 311 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2,4,5-Trichlorothiophenol (*II*)

A stirred and refluxing mixture of 380 ml acetic acid, 12 g iodine and 74 g red P was treated over 70 min with a solution of 210 g crude 2,4,5-trichlorobenzenesulfonyl chloride³⁹ (m.p. 66–68°C) in 270 ml acetic acid. The reaction was exothermic and the stirring and refluxing was continued for 5 h. After standing overnight, 110 ml water were added and the mixture was stirred and refluxed for 1 h. After cooling to 45°C, 150 ml water and 300 ml benzene were added. The mixture was stirred for 10 min, filtered and the solid was washed with 100 ml benzene. The aqueous layer of the filtrate was extracted with benzene, the benzene layers were combined, washed with water, dried and evaporated; 144 g (90%), m.p. 110–113°C. Lit.^{39,40} gave the melting point of 112–113°C (ref.⁴⁰).

2-(2,4,5-Trichlorophenylthio)benzoic Acid (*III*)

A stirred solution of 31 g KOH in 300 ml water was successively treated with 25·0 g *II*, 29·1 g 2-iodobenzoic acid and 1·0 g Cu and the mixture was refluxed for 14 h. After standing overnight the solid was filtered and dried (product A). The filtrate was acidified and the precipitated solid was filtered (4·0 g product B). The product A was extracted with 150 ml boiling benzene and the undissolved potassium salt of *III* was filtered off. The filtrate was evaporated and gave 1·7 g bis(2,4,5-trichlorophenyl) disulfide (*IV*), m.p. 149–150°C (benzene). Mass spectrum, *m/z* (%): 422 (M⁺ corresponding to C₁₂H₄Cl₆S₂, 40%), 428 (32), 424 (90), 358 (M–2 S, 20), 211 (C₆H₂.Cl₃S, 71), 176 (100). IR spectrum: 875, 880 (solitary Ar–H), 3 030, 3 055 cm⁻¹ (Ar). For C₁₂H₄Cl₆S₂ (425·0) calculated: 33·91% C, 0·95% H, 50·05% Cl, 15·09% S; found: 34·11% C, 0·86% H, 50·27% Cl, 14·94% S. Lit.⁴⁰, m.p. 142–143°C.

The potassium salt of *III* was decomposed by heating with 80 ml hydrochloric acid to 80°C, the mixture was diluted with water and allowed to stand overnight at room temperature. Product B was added, the crude acid *III* was filtered, washed with water and crystallized from acetone with

filtration of the warm solution (removal of Cu); 32.0 g (82%), m.p. 248–252°C. Analytical sample, m.p. 253–254°C (acetone). Mass spectrum, m/z : 332 (M^+ corresponding to $C_{13}H_7Cl_3O_2S$), 252, 137 (base peak). UV spectrum: λ_{max} 311.5 nm ($\log \epsilon$ 3.83), infl. at 252 nm (4.09). IR spectrum: 747, 895 (4 adjacent and solitary Ar—H), 913, 1 340, **1 683**, 2 500, 2 550, 2 635, 2 670, infl. 3 070 (COOH), 1 471, 1 569, 1 590, 3 030, 3 050, 3 090 cm^{-1} (Ar). For $C_{13}H_7Cl_3O_2S$ (333.6) calculated: 46.80% C, 2.12% H, 31.88% Cl, 9.61% S; found: 47.11% C, 2.00% H, 31.74% Cl, 9.89% S.

3,5-Dichloro-2-(2,3-dichlorophenylthio)benzoic Acid (IX)

A) Na (10.2 g) was dissolved in 220 ml tert-butyl alcohol and the solution was successively treated with 40.8 g 2,3-dichlorothiophenol⁴⁸, 73 g 3,5-dichloro-2-iodobenzoic acid⁴⁷ and 3.4 g Cu. The mixture was stirred and refluxed for 8 h, then partly evaporated under reduced pressure and filtered with charcoal. The filtrate was diluted with water and acidified with hydrochloric acid. The precipitated product was filtered after standing overnight and crystallized from aqueous ethanol; 49.0 g (62%), m.p. 177–180°C. Analytical sample, m.p. 183–185°C (benzene). UV spectrum: λ_{max} 290 nm ($\log \epsilon$ 3.72), infl. at 245 nm (4.15). IR spectrum: 700, 766, 870 (3 adjacent and solitary Ar—H), 926, 1 298, **1 705**, 2 540, 2 628, 2 690, 2 778, infl. 3 140 cm^{-1} (Ar). (COOH), 1 548, 1 562, 3 034 cm^{-1} (Ar). For $C_{13}H_6Cl_4O_2S$ (367.7) calculated: 42.47% C, 1.64% H, 38.46% Cl, 8.72% S; found: 42.56% C, 1.60% H, 38.11% Cl, 9.00% S.

B) An attempt to carry out the reaction by refluxing the mixture of 5.0 g KOH in 50 ml water, 6.0 g 2,3-dichlorothiophenol⁴⁸, 10.0 g 3,5-dichloro-2-iodobenzoic acid⁴⁷ and 0.5 g Cu led to a dark oily product which was dissolved in benzene. The solution was kept for several days at 0°C. There crystallized 0.5 g 3,5-dichlorosalicylic acid, m.p. 225–228°C (benzene).

3,5-Dichloro-2-(2,3-dichlorophenylthio)benzyl Alcohol (X)

A stirred mixture of 10.0 g IX and 20 ml tetrahydrofuran was treated at a maximum temperature of 5°C over 1 h with 1.1 g $NaBH_4$, then at 13–15°C over 1 h with 4.25 g $BF_3 \cdot O(C_2H_5)_2$ under nitrogen, stirred for 3 h at room temperature and allowed to stand overnight. The solid was filtered off, the filtrate was evaporated *in vacuo* and the residue was distributed between benzene and 50 ml 5% NaOH. The organic layer was dried with K_2CO_3 and evaporated *in vacuo*; 7.9 g (82%), m.p. 87–94°C. Analytical sample, m.p. 92–94°C (cyclohexane). The analysis indicated a 1 : 6 solvate with cyclohexane. Mass spectrum, m/z : 352 (M^+ corresponding to $C_{13}H_8Cl_4OS$), 299 ($M - H_2O - Cl$, base peak). IR spectrum: 698, 770, 860 (3 adjacent and solitary Ar—H), 1 070 (CH_2OH), 1 550, 1 563, 1 570 (Ar), 3 190 cm^{-1} (OH). 1H NMR spectrum: δ 7.58 and 7.49 (2 d, $J = 1.3$ Hz, 1 + 1 H, 4,6- H_2), 7.20 (q, $J = 8.0$; 1.5 Hz, 1 H, 4-H in dichlorophenylthio), 6.94 (t, $J = 8.0$ Hz, 1 H, 5-H in dichlorophenylthio), 6.30 (q, $J = 8.0$; 1.5 Hz, 6-H in dichlorophenylthio), 4.74 (s, 2 H, $ArCH_2O$), 2.20 (s, 1 H, OH), 1.41 (s, CH_2 of cyclohexane). For $C_{13}H_8Cl_4OS + 1/6 C_6H_{12}$ (368.1) calculated: 45.68% C, 2.74% H, 38.52% Cl, 8.71% S; found: 45.63% C, 2.57% H, 38.00% Cl, 8.48% S.

Bis[3,5-dichloro-2-(2,3-dichlorophenylthio)benzyl] Sulfite (XII)

A stirred solution of 7.13 g X in 15 ml benzene was treated at 75°C with a solution of 2 ml $SOCl_2$ in 5 ml benzene and the mixture was refluxed for 1 h. The volatile components were distilled off *in vacuo* and the residue crystallized from light petroleum; 5.6 g (74%), m.p. 94–96°C. Repeated crystallization from a mixture of benzene and light petroleum led finally to XII, m.p. 141–143°C. Mass spectrum, m/z : 351 ($C_{13}H_7Cl_4OS$), 335, 333, 300, 299, 265, 205, 177, 142.

IR spectrum: 695, 770, 865, 885 (3 adjacent and solitary Ar—H), 730, 818 (S—O), 1 547, 1 560, 1 570, 3 030 cm^{-1} (Ar). For $\text{C}_{26}\text{H}_{14}\text{Cl}_8\text{O}_3\text{S}_3$ (754.2) calculated: 41.41% C, 1.87% H, 37.61% Cl, 12.75% S; found: 41.41% C, 1.94% H, 36.90% Cl, 12.53% S. A similar reaction of 37.5 g *X* and 16 g SOCl_2 in 75 ml benzene gave 40 g inhomogeneous product (containing evidently *XII* as well as *XI*) which was used for further reaction without separation.

2,3-Bis[3,5-dichloro-2-(2,3-dichlorophenylthio)phenyl]propionitrile (*XIV*)

The preceding crude product (40 g mixture of *XI* and *XII*) was dissolved in 150 ml warm dimethyl sulfoxide and the solution was added dropwise at 60°C over 15 min to a stirred solution of 6.0 g NaCN in a mixture of 75 ml dimethyl sulfoxide and 15 ml water. The mixture was stirred for 1 h at 60°C, cooled, diluted with 500 ml water and extracted with chloroform. The extract was washed with water, dried and evaporated. Repeated crystallization of the residue from benzene gave a product melting at 180–182°C which is considered to be *XIV*. Mass spectrum, m/z (%): 365 (35), 363 (63), 361 (50), 330 (8), 328 (18), 326 (18), 303 (35), 301 (90), 299 (90), 295 (15), 293 (70), 291 (100). For $\text{C}_{27}\text{H}_{13}\text{Cl}_8\text{NS}_2$ (699.2) calculated: 46.38% C, 1.87% H, 40.57% Cl, 2.01% N, 9.17% S; found: 46.35% C, 1.83% H, 39.36% Cl, 2.09% N, 8.74% S.

[2-(2,4,5-Trichlorophenylthio)phenyl]acetic Acid (*V*)

A stirred mixture of 30 ml dimethylformamide, 10.6 g *II*, 8.0 g K_2CO_3 and 0.3 g Cu was heated to 50°C and treated with 13.1 g (2-iodophenyl)acetic acid⁴⁴, then heated for 7 h to 150°C, after standing overnight diluted with 250 ml water and strongly acidified with hydrochloric acid. The precipitated product was filtered, washed with water and dried; 16.3 g (94%), m.p. 150 to 158°C. Analytical sample, m.p. 160–163°C (aqueous ethanol). IR spectrum: 755, 765, 890 (4 adjacent and solitary Ar—H), 1 243, 1 708, 2 545, 2 645, 2 720, 3 160 (COOH), 1 478, 1 570, 1 598, 3 000, 3 050, 3 065 cm^{-1} (Ar). ^1H NMR spectrum ($\text{C}^2\text{H}_5\text{SOC}^2\text{H}_3$): δ 12.50 (bs, 1 H, COOH), 7.80 (s, 1 H, 3-H in trichlorophenylthio), 7.48 (bs, 4 H, 3,4,5,6- H_4), 6.65 (s, 1 H, 6-H of trichlorophenylthio), 3.75 (s, 2 H, ArCH_2CO). For $\text{C}_{14}\text{H}_9\text{Cl}_3\text{O}_2\text{S}$ (347.6) calculated: 48.36% C, 2.61% H, 30.60% Cl, 9.22% S; found: 48.35% C, 2.70% H, 30.36% Cl, 9.18% S.

1,2,4-Trichlorothioxanthone (*VI*)

III (30 g) was added under stirring to 300 g H_2SO_4 at 95°C. The mixture was stirred and heated to 95°C for 30 min, after cooling poured into 2.5 l ice-cold water and allowed to stand overnight. The precipitated product was filtered, washed with water and dried; 27.0 g (95%), m.p. 190–195°C. Analytical sample, m.p. 203–206°C (acetic acid). Mass spectrum, m/z (%): 314 (M^+ corresponding to $\text{C}_{13}\text{H}_5\text{Cl}_3\text{OS}$, 22%), 216 (25), 298 (23), 296 ($\text{M}-\text{CO}$, 25), 255 (22), 218 (11), 216(16), 202 (15), 181 (15), 165 (10), 149 (48), 58 (100). UV spectrum: λ_{max} 262 nm ($\log \epsilon$ 4.56), 309 nm (3.80), 374 nm (3.73). IR spectrum: 750, 875 (4 adjacent and solitary ArH), 1 465, 1 595 (Ar), 1 655 cm^{-1} (ArCOAr'). For $\text{C}_{13}\text{H}_5\text{Cl}_3\text{OS}$ (315.6) calculated: 49.47% C, 1.60% H, 33.70% Cl, 10.16% S; found: 48.74% C, 1.90% H, 32.65% Cl, 10.22% S.

2,4,5,6-Tetrachlorothioxanthone (*XV*)

A mixture of 10.0 g *IX* and 100 g polyphosphoric acid was vigorously stirred and heated to 150°C for 1 h. After cooling it was diluted with ice and water, the precipitated product was filtered, washed with water and dried; 9.6 g (96%), m.p. 254–259°C. A sample (1.0 g) was crystallized from 500 ml acetic acid; 0.6 g, m.p. 277–278°C. For $\text{C}_{13}\text{H}_4\text{Cl}_4\text{OS}$ (350.1) calculated: 44.61% C, 1.15% H, 40.51% Cl, 9.16% S; found: 44.87% C, 1.13% H, 40.24% Cl, 9.37% S.

1,2,4-Trichloro-9-(3-dimethylaminopropyl)thioxanthene-9-ol (VII)

Grignard reagent, prepared from 3.2 g Mg and 16.0 g 3-dimethylaminopropyl chloride in 80 ml tetrahydrofuran (small quantities of iodine and ethyl iodide were used for starting the reaction) (ref.⁴⁵), was treated under stirring at room temperature over 1 h with a suspension of 20.8 g *I* in 120 ml tetrahydrofuran and refluxed for 12 h. The solvent was evaporated, the residue was decomposed with 400 ml 10% NH_4Cl and extracted with benzene. The extract was washed with water, dried with MgSO_4 , filtered with charcoal and evaporated. The residue was dissolved in 50 ml warm benzene, the solid precipitated by cooling (3.5 g *VI*, m.p. 199–201°C) was filtered off, the filtrate was evaporated and the residue crystallized from a small volume of benzene: 15.0 g (68%), m.p. 102–106°C. Analytical sample, m.p. 123–125°C (benzene). IR spectrum: 750, 760, 772, 869 (4 adjacent and solitary ArH), 1096, 1119 (tert. C—OH), 1572 (Ar), 2680, 2758, infl. 3080 cm^{-1} (O—H...N). ^1H NMR spectrum: δ 7.98 (m, 1 H, 8-H), 7.49 (s, 1 H, 3-H), c. 7.80 (m, 3 H, 5,6,7- H_3), 2.35 (s, 6 H, CH_3NCH_3), 1.00–2.50 (m, 3 CH_2 and OH). For $\text{C}_{18}\text{H}_{18}\text{Cl}_3\text{NOS}$ (402.8) calculated: 53.67% C, 4.51% H, 26.41% Cl, 3.48% N, 7.96% S; found: 53.86% C, 4.52% H, 26.00% Cl, 3.36% N, 8.03% S.

2,4,5,6-Tetrachloro-9-(3-dimethylaminopropyl)thioxanthene-9-ol (XVI)

Grignard reagent, prepared from 0.88 g Mg and 3.9 g 3-dimethylaminopropyl chloride in 20 ml tetrahydrofuran⁴⁵, was treated under stirring with 5.6 g *XV*, the mixture was refluxed for 2 h, allowed to stand overnight, decomposed with a solution of 8.0 g NH_4Cl in 30 ml water and extracted with benzene. The extract was washed with water, dried with MgSO_4 and evaporated. The residue gave by standing 5.4 g (77%) *XVI*, m.p. 205–211°C. Analytical sample, m.p. 212 to 214°C (benzene–light petroleum). IR spectrum (KBr): 812, 828, 860, 892 (2 adjacent and solitary Ar—H), 1575, 1600 (Ar), 2700, 2825 cm^{-1} (OH...N, N— CH_3). For $\text{C}_{18}\text{H}_{17}\text{Cl}_4\text{NOS}$ (437.2) calculated: 49.45% C, 3.92% H, 32.44% Cl, 3.20% N, 7.33% S; found: 49.62% C, 3.93% H, 32.37% Cl, 3.18% N, 7.32% S.

2-Chloro-9-(1-methyl-4-piperidyl)thioxanthene-9-ol (XXI)

Grignard reagent, prepared from 6.5 g Mg and 33.4 g 4-chloro-1-methylpiperidine in 150 ml tetrahydrofuran (iodine and 1,2-dibromoethane used for starting the reaction, cf.⁵²), was treated with a suspension of 30.8 g 2-chlorothioxanthone⁹ in 100 ml tetrahydrofuran under stirring. The mixture was refluxed for 4 h, after cooling decomposed with ice and a solution of NH_4Cl and the product was isolated by extraction with ether. Processing of the extract gave 27 g (63%) *XXI*, m.p. 220–222°C. Lit.⁵¹, m.p. 221.8–222.8°C. Yield of 85% was obtained when the reaction was carried out by refluxing for 12 h, tetrahydrofuran was evaporated, substituted with benzene and the mixture decomposed with the NH_4Cl solution.

1,2,4-Trichloro-9-(3-dimethylaminopropylidene)thioxanthene (*I*)

VII (8.5 g) was refluxed with a solution of 12.0 g H_2SO_4 in 60 ml water for 1.5 h. After cooling it was made alkaline with 10% NaOH and the base was extracted with benzene. The extract was washed with water, dried with MgSO_4 , filtered with charcoal and evaporated *in vacuo*. The residue was treated with 25 ml ethanol, the precipitated solid was filtered off and the filtrate was evaporated *in vacuo*; 6.6 g (81%) oily mixture of (*E*)- and (*Z*)-*I*. It was dissolved in 11 ml ethanol, the solution was treated with 2.1 ml 34% hydrochloric acid and then with 20 ml ether. The precipitated hydrochloride was filtered and crystallized from a mixture of ethanol and ether;

4.1 g (46%), m.p. 254–256°C. For $C_{18}H_{17}Cl_4NS$ (421.2) calculated: 51.32% C, 4.07% H, 33.67% Cl, 3.33% N, 7.61% S; found: 51.61% C, 4.06% H, 33.20% Cl, 3.39% N, 7.88% S.

Treatment of the pure hydrochloride with 10% warm NaOH gave the base which was isolated by extraction with benzene. Processing of the extract gave the crystalline base, to which (*E*)-configuration was assigned, m.p. 113–114°C (benzene–light petroleum). UV spectrum (heptane): λ_{max} 212 nm ($\log \epsilon$ 4.46), 230 nm (4.46), 323 nm (3.52), inflexes at 262 nm (4.15) and 285 nm (3.96). IR spectrum (CS_2): 712, 743, 761, **792**, 862 cm^{-1} (Ar—H). For $C_{18}H_{16}Cl_3NS$ (384.8) calculated: 56.19% C, 4.19% H, 27.65% Cl, 3.64% N, 8.33% S; found: 56.44% C, 4.40% H, 27.39% Cl, 3.64% N, 8.70% S.

Methanesulfonate monohydrate, m.p. 88–90°C (ethanol–ether). For $C_{19}H_{20}Cl_3NO_3S_2 + H_2O$ (498.9) calculated: 45.74% C, 4.44% H, 21.32% Cl, 2.81% N, 12.86% S; found: 45.88% C, 4.68% H, 21.45% Cl, 2.76% N, 12.53% S.

2,4,5,6-Tetrachloro-9-(3-dimethylaminopropylidene)thioxanthene (VIII)

Crude XVI, prepared from 3.6 g XV, in 25 ml tetrahydrofuran was treated with 60 ml 1 : 3 diluted hydrochloric acid and the mixture was refluxed for 1 h. After cooling it was made alkaline with 20% NaOH and extracted with chloroform. The extracted was dried with K_2CO_3 and evaporated. The residue (2.6 g) was dissolved in 5 ml ethanol and the solution was treated with 0.4 g oxalic acid dihydrate. The mixture was heated for a short time to the boiling point and allowed to crystallize; 1.2 g hydrogen oxalate, m.p. 180–182°C. For $C_{20}H_{17}Cl_4NO_4S$ (509.2) calculated: 47.17% C, 3.37% H, 27.85% Cl, 2.75% N, 6.30% S; found: 47.32% C, 3.37% H, 27.60% Cl, 2.56% N, 6.07% S.

A sample of the salt was treated with 5% NaOH and the oily base was isolated by extraction with ether. The (*E*)-configuration (with regard to the 2,4-disubstituted ring and the side chain) was assigned on the basis of the IR spectrum (CS_2): 769, 819, 837, **877** cm^{-1} (Ar—H).

2-Chloro-9-(1-methyl-4-piperidylidene)thioxanthene (XVIII)

A solution of 6.6 g XXI in 50 ml acetic acid was saturated with 3.5 g HCl at room temperature and the mixture obtained was refluxed for 1 h. After cooling it was diluted with water, made alkaline with 20% NaOH and extracted with benzene. Processing of the extract gave the oily base which was dissolved in 8 ml ethanol and neutralized with 2.2 g maleic acid in 5 ml ethanol. Addition of ether induced crystallization; 5.5 g (65%) hydrogen maleate, m.p. 204–206°C (ethanol). For $C_{23}H_{22}ClNO_4S$ (443.9) calculated: 62.22% C, 4.99% H, 7.99% Cl, 3.06% N, 7.22% S; found: 62.38% C, 5.07% H, 8.23% Cl, 2.93% N, 7.44% S. Lit.⁵¹, m.p. 193.1–194.1°C.

2-Chloro-9-(4-piperidylidene)thioxanthene (XIX)

XVIII (6.9 g base obtained by decomposition of 9.2 g hydrogen maleate) was dissolved in 25 ml benzene and the solution was treated with a solution of 2.7 g ethyl chloroformate in 10 ml benzene. The mixture was refluxed for 3 h, washed with water, 10% H_2SO_4 and water, dried with $MgSO_4$ and evaporated. The oily residue (6.4 g, 79%) is the crude carbamate XX. It was added to a hot solution of 5.0 g KOH in 10 ml ethanol and the mixture was heated for 2 h under reflux in a bath of 130°C. After cooling the mixture was diluted with water and extracted with benzene. From benzene the base was extracted into 10% hydrochloric acid, the separated aqueous solution was made alkaline with 10% NaOH and the base was extracted again with benzene. Processing of the extract gave 3.7 g (69%) pure oily base. Methanesulfonate, m.p. 148–150°C (ethanol–

-ether). For $C_{19}H_{20}ClNO_3S_2$ (410.0) calculated: 55.66% C, 4.92% H, 8.65% Cl, 3.42% N, 15.64% S; found: 55.38% C, 5.08% H, 8.22% Cl, 2.92% N, 15.24% S.

2-Chloro-9-[1-(2-hydroxyethyl)-4-piperidylidene]thioxanthene (XVII)

A mixture of 3.7 g XIX, 60 ml acetone, 2.25 g 2-bromoethanol and 3.0 g K_2CO_3 was refluxed for 4 h. After cooling the solid was filtered off, washed with acetone and the filtrate was evaporated. The residue was dissolved in ether, the undissolved by-product was filtered off and the filtrate was evaporated to give 3.35 g (79%) base crystallizing from aqueous methanol and melting at 132 to 134°C. UV spectrum: λ_{max} 273 nm ($\log \epsilon$ 4.10), infl. 257 nm (3.81). IR spectrum (KBr): 741, 750, 809, 875 (4 and 2 adjacent and solitary Ar—H), 1060, 1070 (CH_2OH), 1552, 1570, 1590, 3005, 3045 (Ar), 2740, 2800 (CH_2-N), 3240 cm^{-1} (OH). 1H NMR spectrum: 7.10—7.50 (m, 7 H, ArH), 4.98 and 4.68 (2 bm, 1 + 1 H, equatorial 3,5- H_2 of piperidine), 3.52 (t, $J = 6.0$ Hz, 2 H, CH_2O), 3.20 (s, 1 H, OH), 2.78 (bm, 2 H, axial 3,5- H_2 of piperidine), 2.50 (t, $J = 6.0$ Hz, 2 H, CH_2N in hydroxyethylamino), 2.50 (bm, 2 H, equatorial 2,6- H_2 of piperidine), 2.00 (bm, 2 H, axial 2,6- H_2 of piperidine). For $C_{20}H_{20}ClNOS$ (357.9) calculated: 67.12% C, 5.63% H, 9.91% Cl, 3.91% N, 8.96% S; found: 66.90% C, 5.59% H, 10.20% Cl, 3.97% N, 9.00% S. Lit.²¹, m.p. 178—180°C.

Hydrogen oxalate, m.p. 132—135°C (ethanol-ether). For $C_{22}H_{22}ClNO_5S$ (447.9) calculated: 58.98% C, 4.95% H, 7.92% Cl, 3.13% N, 7.16% S; found: 58.72% C, 5.12% H, 8.31% Cl, 3.09% N, 7.52% S.

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