

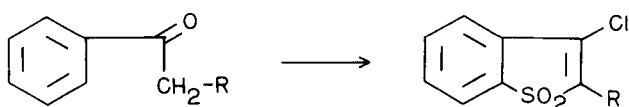
Parke, Davis and Company

Some Novel Cyclizations of Propiophenones with Chlorosulfonic Acid

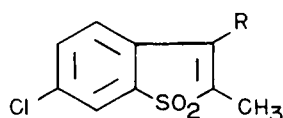
Robert F. Meyer



The reaction of chlorosulfonic acid with propiophenones was found to give the 3-chloro-2-methylbenzothiophene-1,1-dioxides (I) and (VIII); reaction of Mannich bases of acetophenone, with chlorosulfonic acid, gave the corresponding 3-chloro-2-substituted aminomethylbenzothiophene-1,1-dioxides (IX) and (X). The above structures were established by reaction with various nucleophiles and by hydrogenation. *o*-Hydroxypropiophenones, under the above conditions, are cyclized to the cyclic sulfones (XII) and (XIII). Ring opening with pyrrolidine gave the corresponding phenolic sulfonamides (XIV) and (XV).

The chlorosulfonation of acetophenone, depending on conditions, gives both α,o - and α,m -sulfonation products (1). On the other hand sulfonation of acetophenone or propiophenone is known to give the α -sulfonic acids exclusively (2). It was found that the chlorosulfonation of homologs of acetophenone gives 2-substituted 3-chlorobenzothiophene-1,1-dioxides in good yield:



Thus, the chlorosulfonation of *p*-chloropropiophenone at 100° gives 3,6-dichloro-2-methylbenzothiophene-1,1-dioxide (I) in over 60% yield. The halogen in the 3-position of I was subjected to the following nucleophilic displacements:

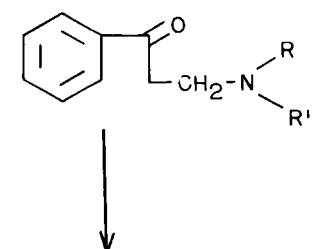



- I, R = -Cl
 II, R = -OCH₃
 III, R = -S--Cl
 IV, R = -S-CH₂-CH₂-NEt₂·HCl
 V, R = -NH-CH₂-CH₂-NEt₂
 VI, R = -N
 VII, R = -OH
 VIII, R = -Cl (*des*-6-Cl)

Sodium methoxide in methanol gave the 3-methoxy compound (II), *p*-chlorothiophenol or diethylaminoethanethiol gave the expected 3-thioethers (III) and (IV). Aminolysis with *N,N*-diethyl ethylenediamine or pyrrolidine gave the corresponding 3-amino compounds (V) and (VI). Compound VI on acid hydrolysis gave the expected "3-hydroxy compound," (VII), the infrared spectrum of which indicated its existence as 6-chloro-2-methylbenzothiophen-3(2*H*)-one-1,1-dioxide.

The chlorosulfonation of propiophenone itself to give 3-chloro-2-methylbenzothiophene-1,1-dioxide (VIII) is more difficult. At room temperature starting material is recovered unchanged. At 100° the benzene nucleus is chlorosulfonated probably in the 6-position. Compound VIII is obtained in poor yield when the chlorosulfonation is carried out at 65-75°.

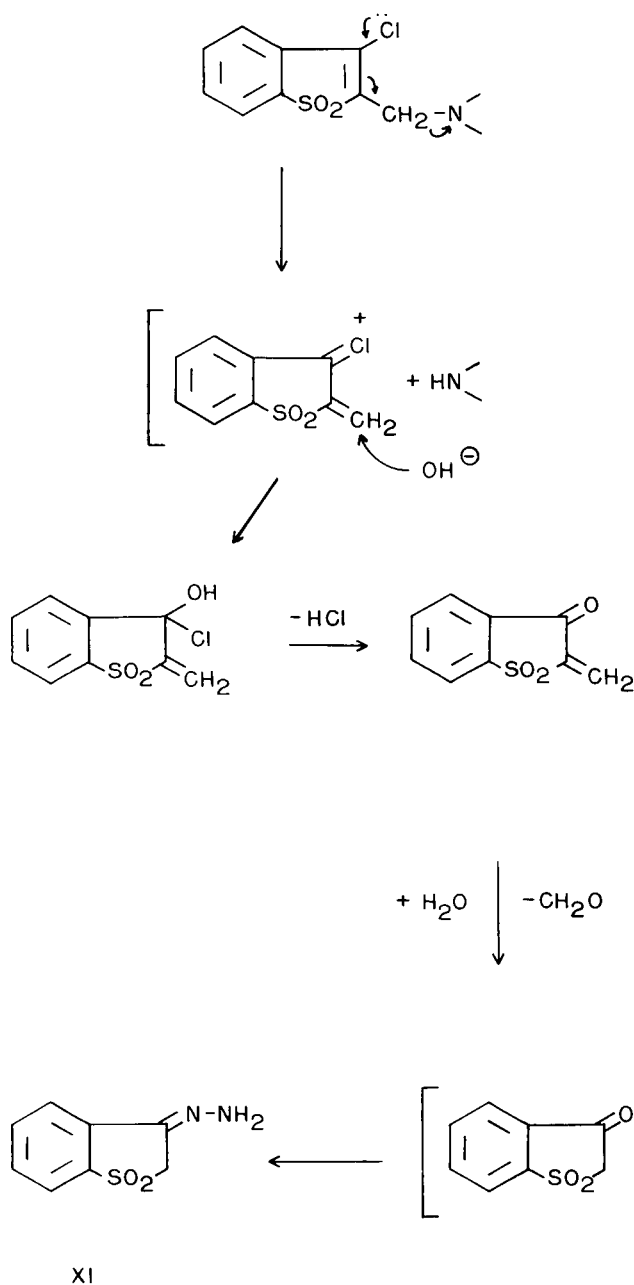
The cyclization of Mannich bases of acetophenone with chlorosulfonic acid proceeds smoothly at 100° to give the benzothiophene-1,1-dioxides IX and X:

IX, R, R' = CH₃X, R=R' = 

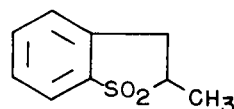
The fact that no additional chlorosulfonation of the benzene nucleus occurred as in the case of propiophenone may be explained by the field effect, *i.e.*, the positive charge on the amino nitrogen prevents further attack of HOSO_2^+ at the 6-position.

The free bases (IX) and (X) were somewhat unstable on prolonged standing. IX decomposed to a brown gum within a few months. IX was very stable toward acid treatment. The hydrochloride of IX was recovered unchanged after 24 hours boiling in constant boiling hydrochloric acid. The base (IX) was also converted to the methiodide.

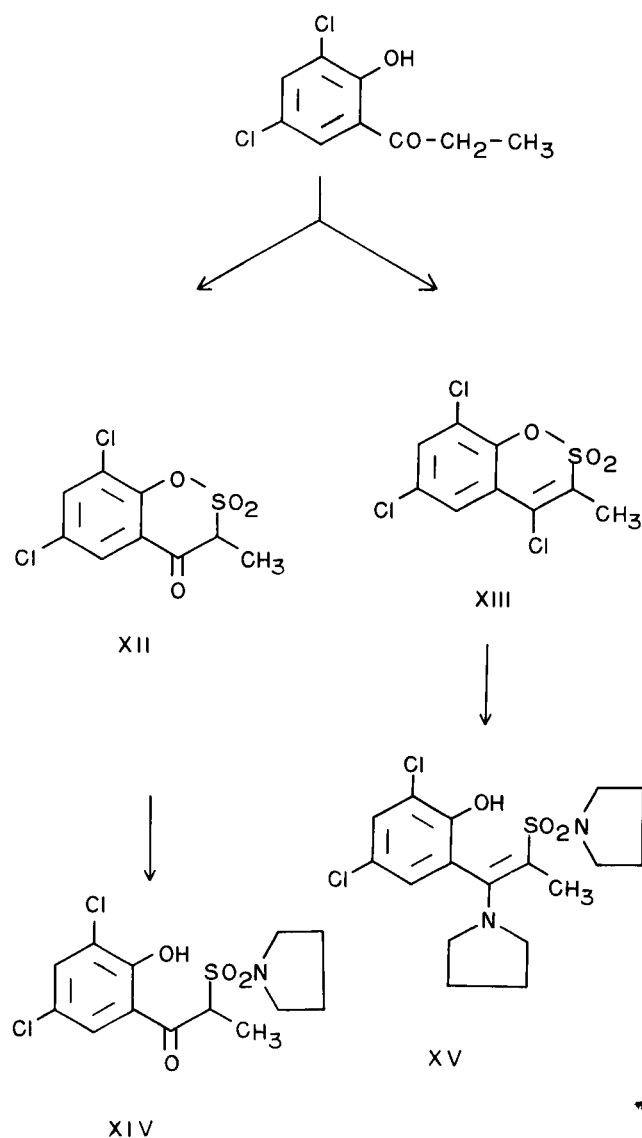
When IX or its methiodide was treated with an excess of hydrazine hydrate a retro Mannich reaction occurred from which the only product isolated was benzothiophen-3(2*H*)-one, hydrazone-1,1-dioxide (XI). The following mechanism is proposed:



On catalytic hydrogenation both VIII and IX gave the known 2-methyl 1-thiaindanesulfone (3):



Some interesting sulfones are formed by the chlorosulfonation of 3,5-dichloro-2-hydroxypropiophenone. If the chlorosulfonation is carried out at steam-bath temperature for 1 hour a mixture is obtained which is easily separated into its components, to give after purification a yield of 26.5% of XII and 25.8% of XIII. Both products were subjected to aminolysis with pyrrolidine to give XIV and XV, respectively.



EXPERIMENTAL (4)

3,6-Dichloro-2-methylbenzothiophene-1,1-dioxide (I).

To 800 ml. (12 moles) of chlorosulfonic acid was added with stirring 336 g. (2 moles) of *p*-chloropropiophenone. The solution was heated on the steam bath for 3 hours. After cooling the reaction mixture was poured with stirring on an excess of ice. The light tan solid was collected on a filter and washed with ice water. The crude product melted about 130°. Some dark impurities were removed by adding the crude, still-wet product to about 1 l. of concentrated ammonia. The product was filtered from the dark solution, washed with water and recrystallized from ethanol (charcoal) to give a white crystalline solid, 321 g. (64%), m.p. 136-137°.

Anal. Calcd. for $C_9H_6Cl_2SO_2$: C, 43.39; H, 2.43; Cl, 28.47. Found: C, 43.40; H, 2.46; Cl, 28.29.

6-Chloro-3-methoxy-2-methylbenzothiophene-1,1-dioxide (II).

To a solution of 25 g. (0.1 mole) of I in 500 ml. of absolute methanol was added a methanolic solution of 5.7 g. (0.105 mole) of sodium methoxide. It was heated at reflux temperature for 5 hours. The reaction mixture was neutralized with a few drops of acetic acid. The solvent was evaporated and the crude product was taken up in ether and washed with water. Recrystallization from 2-propanol gave 12.6 g. (51%) of a white crystalline solid, m.p. 155-156°, λ max (KBr), 6.1 μ (C=C-O).

Anal. Calcd. for $C_{10}H_9ClO_3S$: C, 49.08; H, 3.71. Found: C, 49.32; H, 3.95.

6-Chloro-3-(*p*-chlorophenylthio)-2-methylbenzothiophene-1,1-dioxide (III).

To a suspension of 50 g. (0.2 mole) of I in 1 l. of absolute ethanol was added 31 g. (0.21 mole) of *p*-chlorothiophenol and with ice cooling an alcoholic solution of 11.5 g. (0.21 mole) of sodium methoxide. It was heated at reflux temperature for 5 hours. The filtrate was evaporated, the crude solid slurried with water and recrystallized from ethanol to give 59 g. (82%) of a white crystalline product, m.p. 114-115°.

Anal. Calcd. for $C_{15}H_{10}Cl_2S_2O_2$: C, 50.42; H, 2.82. Found: C, 50.34; H, 2.91.

6-Chloro-3-(2-diethylaminoethylthio)-2-methylbenzothiophene-1,1-dioxide Hydrochloride (IV).

It was prepared as above from 50 g. (0.2 mole) of I, 35.5 g. (0.21 mole) of diethylaminoethanethiol hydrochloride and 23 g. (0.425 mole) of sodium methoxide. The crude product was taken up in ether, washed with water, the organic layer extracted with dilute hydrochloric acid and washed with ether. Regeneration of the free base gave 41 g. (59%) of a light tan oil. A sample was converted to the hydrochloride, which was recrystallized from 2-propanol. The white crystalline solid melted at 169-171°.

Anal. Calcd. for $C_{15}H_{21}Cl_2NS_2O_2$: C, 47.11; H, 5.54; N, 3.66. Found: C, 47.24; H, 5.53; N, 3.85.

6-Chloro-3-(2-diethylaminoethylamino)-2-methylthiophene-1,1-dioxide (V).

To 25 g. (0.1 mole) of I was added 23.2 g. (0.2 mole) of *N,N*-diethylethylenediamine. The mixture was heated carefully on the steam bath. After the mild exothermic reaction had subsided it was heated for another 10 minutes. The reaction mixture was washed with water, the gummy solid recrystallized repeatedly from 2-propanol to give 8.5 g. (13%) of a light tan solid, m.p. 136-137°, λ max (KBr), 3.0 μ (N-H), 6.02 μ (C=C-N).

Anal. Calcd. for $C_{15}H_{21}Cl_2N_2O_2S$: C, 54.78; H, 6.44; N, 8.52. Found: C, 54.99; H, 6.46; N, 8.32.

6-Chloro-2-methyl-3-pyrrolidinobenzothiophene-1,1-dioxide (VI).

A solution of 50 g. (0.2 mole) of I and 50 ml. (0.6 mole) of pyrrolidine in 500 ml. of methanol was heated at reflux temperature for 4 hours. The suspension was cooled, the solid collected by filtration, washed with water and recrystallized from alcohol to give 17.2 g. (30%) of a white crystalline solid, m.p. 216-217°, λ max (KBr), 6.1 μ (C=C-N).

Anal. Calcd. for $C_{13}H_{14}ClNO_2S$: C, 55.02; H, 4.98; N, 4.94. Found: C, 55.17; H, 5.08; N, 4.93.

6-Chloro-2-methylbenzothiophen-3(2*H*)one-1,1-dioxide (VII).

To 50 ml. of 18% aqueous hydrochloric acid was added 14.1 g. (0.05 mole) of VI. A clear solution was obtained, but on warming a gum

separated. It was heated at reflux temperature for 0.5 hours, cooled, decanted and crystallized from 2-propanol. The product, 10.1 g. (88%) melted at 107-109°, λ max (KBr), 5.82 μ (C=O).

Anal. Calcd. for $C_9H_7ClSO_3$: C, 46.87; H, 3.06. Found: C, 47.04; H, 3.22.

3-Chloro-2-methylbenzothiophene-1,1-dioxide (VIII).

To 200 ml. (3 moles) of chlorosulfonic acid was added 67 g. (0.5 mole) of propiophenone. The solution was heated for 3 hours to 65-75°, cooled, and poured on ice. The gummy solid was washed with ice water, slurried with petroleum ether (to remove unreacted propiophenone) and crystallized from 2-propanol to give a white crystalline solid, m.p. 162-163°.

Anal. Calcd. for $C_9H_7ClSO_2$: C, 50.36; H, 3.29. Found: C, 50.37; H, 3.37.

3-Chloro-2-(dimethylaminomethyl)-benzothiophene-1,1-dioxide (IX).

To 450 ml. (6.8 mole) of chlorosulfonic acid was added with stirring 127.8 g. (0.6 mole) of ω -dimethylaminopropiophenone hydrochloride. The solution was heated on a steam bath for one hour, cooled, and poured on ice. The pale yellow solution was added with efficient cooling at $< 10^\circ$ to 2 l. of ammonium hydroxide. The granular, pink precipitate was collected by filtration, washed well with ice water and air-dried. The crude product melted at about 90°. It was recrystallized from benzene (charcoal) to give 71 g. (46%) of pale tan solid, m.p. 96-97°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2S$: C, 51.26; H, 4.69; N, 5.44; Cl, 13.76. Found: C, 51.35; H, 4.89; N, 5.31; Cl, 13.55.

Hydrochloride.

To a solution of 25.8 g. (0.1 mole) of the above base (IX) in 200 ml. of warm 2-propanol was added 9 ml. of concentrated hydrochloric acid. The hydrochloride precipitated immediately. It was recrystallized from water to give 24 g. (82%) of a crystalline solid, m.p. 240-245°.

Anal. Calcd. for $C_{11}H_{13}Cl_2NO_2S$: C, 44.90; H, 4.45; N, 4.76. Found: C, 44.77; H, 4.57; N, 4.65.

Methiodide.

A solution of 51.6 g. (0.2 mole) of IX in 400 ml. of benzene was heated at reflux temperature with 30 ml. of methyl iodide for 5 hours. The product was filtered and washed with benzene to give 76.1 g. (95%) of a yellow crystalline solid, m.p. 190-195° (dec.). The product may be recrystallized from water or 95% alcohol.

Anal. Calcd. for $C_{12}H_{15}ClINO_2S$: C, 36.06; H, 3.78; N, 3.50. Found: C, 36.25; H, 3.73; N, 3.32.

3-Chloro-2-(1-morpholinomethyl)benzothiophene-1,1-dioxide (X).

A solution of 127.5 g. (0.5 mole) of ω -morpholinopropiophenone hydrochloride in 380 ml. (5.75 mole) of chlorosulfonic acid was treated as in the preparation of IX to give a product, m.p. 118-120°. Recrystallization from benzene gave 76.5 g. (51%), m.p. 121-122°.

Anal. Calcd. for $C_{13}H_{14}ClN_2SO_2$: C, 52.08; H, 4.71; N, 4.67. Found: C, 51.74; H, 4.92; N, 4.55.

Hydrochloride.

To a hot solution of 30 g. (0.1 mole) of X in 200 ml. of 2-propanol was added 9 ml. of concentrated hydrochloric acid. The hydrochloride crystallized from the solution in beautiful yellow platelets, m.p. 185-190°, dec.

Anal. Calcd. for $C_{13}H_{15}Cl_2NSO_3$: C, 46.44; H, 4.50; N, 4.17. Found: C, 46.64; H, 4.58; N, 4.06.

Benzothiophen-3(2*H*)-one, hydrazone-1,1-dioxide (XI).

A mixture of 10 ml. of 85% hydrazine hydrate and 5 g. of IX was heated on the steam bath. The reaction mixture turned brown, but on further warming a yellow solution was obtained. It was evaporated under reduced pressure and crystallized from aqueous 2-propanol to give 1.7 g., (44%) of a white crystalline solid, m.p. 175-180°, dec., λ max (KBr), 3.0 μ (NH₂), 6.1 μ (C=N). NMR (d₆ DMSO) showed 4 aromatic protons at 7.5-8 p.p.m., 2 protons (NH₂) at 7.3 p.p.m., 2 aliphatic protons at 4.3 p.p.m. The two -NH₂-protons washed out after addition of D₂O.

Anal. Calcd. for $C_8H_8N_2O_2S$: C, 48.96; H, 4.11; N, 14.28. Found: C, 49.05; H, 4.11; N, 14.37.

Catalytic hydrogenation of VIII or IX to give 2-methyl-1-thiaindane-sulfone.

A solution of 3.65 g. of VIII in 200 ml. of alcohol was hydrogenated in the presence of 0.3 g. of 20% palladium-charcoal and 2.4 g. of

sodium acetate. An almost quantitative yield of product, m.p. 115-116° (lit. (3), m.p. 115-115.5°) was obtained.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.30; H, 5.53. Found: C, 59.39; H, 5.54.

An identical product was obtained from the hydrogenation of a sample of IX in ethanol in the presence of palladium-charcoal.

3',5'-Dichloro-2'-hydroxypropiophenone-2-sulfonic acid α -sultone (XII).

A mixture of 300 ml. (4.5 moles) of chlorosulfonic acid and 100 g. (0.45 mole) of 3,5-dichloro-2-hydroxypropiophenone was heated on a steam bath for one hour. The brown reaction mixture was poured on ice, the gummy product taken up in ether and washed with water. Evaporation gave 111 g. of product. It was suspended in 500 ml. of water and 100 ml. of ammonium hydroxide added. After stirring for one hour the suspension was filtered and the filtrate acidified to pH 4 with hydrochloric acid. The product was collected by filtration, washed with water and recrystallized from 2-propanol to give 34 g. (26.5%) of a white crystalline solid, m.p. 100-101°, λ max (KBr), 5.85 μ (C=O).

Anal. Calcd. for $C_9H_6Cl_2O_4S$: C, 38.45; H, 2.15. Found: C, 38.36; H, 2.38.

2-Chloro-2-(3,5-dichloro-2-hydroxyphenyl)-1-methylethanesulfonic acid α -sultone (XIII).

The product of the previous preparation which was insoluble in ammonia was washed with water and recrystallized from 2-propanol twice to give 35.2 g. (25.8%) of a white crystalline solid, m.p. 131-132°, λ max (KBr), 6.2 μ (C=C), 6.41 μ (phenyl), 7.25 μ and 8.45 μ (SO_2).

Anal. Calcd. for $C_9H_6Cl_3O_3S$: C, 36.08; H, 1.68. Found: C, 36.18; H, 1.67.

3',5'-Dichloro-2'-hydroxy-2-(1-pyrrolidinylsulfonyl)propiophene (XIV).

A solution of 10 g. (0.356 mole) of ketosultone (XII) in 50 ml. of pyrrolidine was heated at reflux temperature for one hour. The yellow solution was evaporated under reduced pressure, the residue treated

with dilute acetic acid and crystallized from 2-propanol twice to give 7.2 g. (57%) of a yellow crystalline solid, m.p. 125-126°, λ max (KBr), 6.12 μ (C=O, bonded with OH).

Anal. Calcd. for $C_{13}H_{16}Cl_2NO_4S$: C, 44.33; H, 4.29; N, 3.98. Found: C, 44.41; H, 4.34; N, 4.13.

2',4'-Dichloro-6'-[1-(1-pyrrolidinyl)-2-(1-pyrrolidinylsulfonyl)propenyl]phenol (XV).

To 50 ml. of pyrrolidine was added gradually 10 g. (0.334 mole) of XIII. An exothermic reaction occurred. The excess of pyrrolidine was evaporated on the steam bath under reduced pressure. The residue was recrystallized twice from 2-propanol to give 10.5 g. (77%) of a white crystalline solid, m.p. 132-134°, λ max (KBr), 3.5-4.5 μ ($-OH \cdot N \rightleftharpoons$), 6.16 μ (C=C-N).

Anal. Calcd. for $C_{17}H_{22}Cl_2N_2O_3S$: C, 50.37; H, 5.47; N, 6.91. Found: C, 50.43; H, 5.65; N, 7.09.

Acknowledgment.

The author wishes to thank Dr. A. Burgstahler for a helpful discussion about mechanisms, Mr. C. E. Childs and co-workers for the microanalytical data and Mr. R. B. Scott and Mr. E. J. Schoeb for spectral data.

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- (4) Melting points were determined on a Fisher-Johns block with a calibrated thermometer.

Received March 30, 1966

Ann Arbor, Michigan 48106