Halosulfonium Salts. IX. Halogen-Induced Ring Cleavages of 1,3-Oxathiolanes

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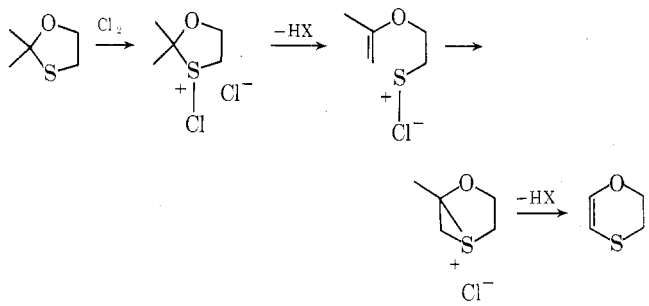
Halogenation of the 1,3-oxathiolanes derived from benzophenone, diisopropyl ketone, and cycloheptanone provides a route to regenerate the ketone in good yield. For diisopropyl ketone an additional product, α-(2-haloethylthiol)isopropyl isopropyl ketone, is obtained.

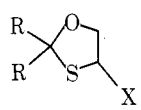
Chlorination of 1,3-oxathiolanes derived from ketones and aldehydes having an α-methylene provides 1,4-oxathienes as the primary product.[1] This reaction has been considered to proceed through the sequence of steps shown below for 2,2-dimethyl-1,3-oxathiolane. The work reported



here was undertaken to confirm this mechanism. The basic approach was to block the sequence at successive steps by use of appropriately substituted oxathiolanes.

Results and Discussion

The absence of protons on the side chain β to the sulfur atom was expected to block the initial dehydrohalogenation and lead to α-halogenation[2] of the ring to form 1 in



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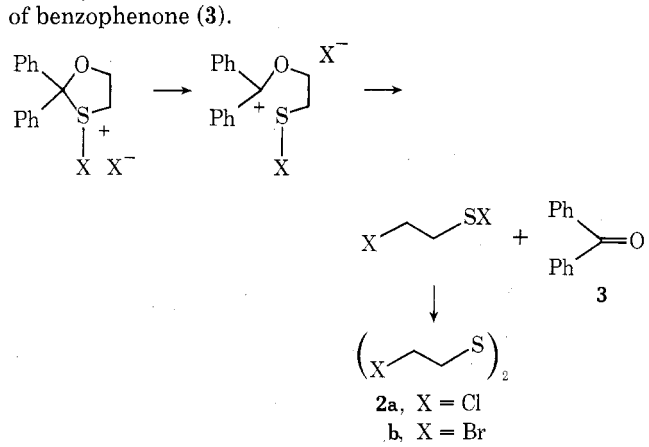
analogy to the halogenation of tetrahydrothiophene;[3] however, an alternative route was followed. Thus, chlorination of 2,2-diphenyl-1,3-oxathiolane in carbon tetrachloride provided β-chloroethyl disulfide (**2a**), verified by spectral identity with authentic material,[4] and a quantitative yield of benzophenone (**3**).



2a, X = Cl
b, X = Br

The cleavage of halosulfonium salts to provide stabilized carbonium ions is well known.[5] The reaction described produced none of the expected hydrogen halide, and required only 0.5 equiv of chlorine. The reaction with bromine paralleled the chlorination and provided **2b** which was spectrally identical with authentic material.

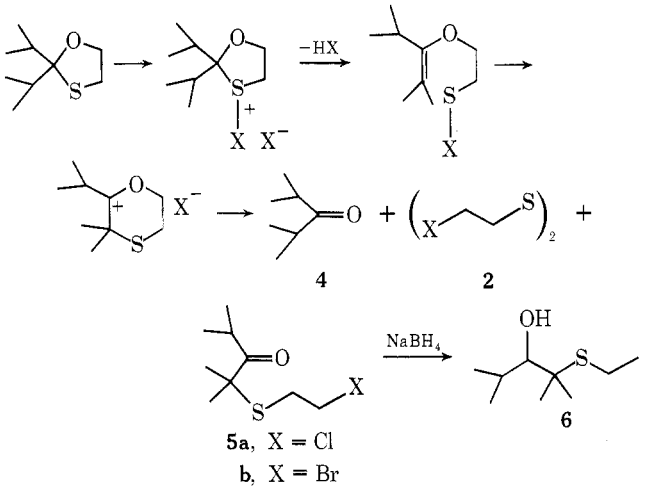
The origin of disulfide could involve either disproportionation of the sulfenyl halide to form the corresponding disulfide plus halogen or attack of the sulfenyl halide on the oxathiolane giving a thiosulfonium salt which would be subject to halide attack to afford the disulfide and benzophenone. The latter course was shown to be possible by a control experiment in which β-bromoethylsulfenyl bromide was generated in situ by the bromination of β-bromoethyl disulfide at low temperature, and allowed to react with oxathiolane. NMR analyses of the brominated solution of disulfide showed only one peak assignable to the accidentally degenerate methylene protons of the sulfenyl bromide. Upon addition of solid 2,2-diphenyl-1,3-oxathiolane, benzophenone and disulfide were formed as evidenced by NMR analysis of the final solution. This reaction is similar to that observed for the reaction of benzyl sulfenyl bromide with dibenzyl sulfide.[7]

Nucleophilic substitution by halide ion at C-4 leading to irreversible cleavage of the oxathiolane ring might be expected to give way to the formation of 2-halo- or 4-halo-1,3-oxathiolane by generating the halosulfonium salt at low temperature and thus preventing its decomposition. Addition of a base such as triethylamine to the halosulfonium salt at this temperature might then favor the Pummerer rearrangement leading to **1**. To test this possibility, a solution of triethylamine in carbon tetrachloride was introduced into a −70°C suspension of the halosulfonium salt. The products, after filtration of triethylammonium bromide (78% yield), contained 93% of benzophenone, 7% of disulfide, and 9% of the starting oxathiolane. Evidently, the acidity of the protons in the oxathiolane ring is so low that they play no role in the determination of the reaction products.

Blockage of the second dehydrohalogenation could be effected by employing an oxathiolane with no protons γ to the sulfur atom. Reaction of 2,2-diisopropyl-1,3-oxathiolane with bromine under the conditions used for the bromination of diphenyl oxathiolane gave, after isolation and characterization, diisopropyl ketone (**4**, 41%), the bis(2-bromoethyl) disulfide, and α-(2-bromoethylthio)isopropyl isopropyl ketone (**5b**, 40%). Structure **5b** was confirmed by spectral data and by reduction to **6**.

Chlorination of 2,2-diisopropyl-1,3-oxathiolane under similar conditions gave, in addition to diisopropyl ketone, four other products as shown by VPC analysis. A quantitative estimation and characterization of each individual peak was not possible since the peaks overlapped badly in the VPC. After repeated distillations and column chromatography the pure major product, α-(2-chloroethylthio)-isopropyl isopropyl ketone (**5a**), was obtained in 41% yield. The ir and NMR spectra of the **5a** also isolated are similar to those of **5b**. Sodium borohydride reduction gave the al-

cohol **6** identical in every respect with that obtained from the reduction of **5b**.



5a, X = Cl
b, X = Br

We have also observed predominant ketone formation upon bromination of the oxathiolane derived from cycloheptanone. In each case cycloheptanone was obtained in approximately 97% yield. This result probably arises because oxathiene formation is more difficult in this case owing to steric restraints on proton loss from the sulfocarbonium ion rather than because of lowered activation energy for ketone formation.

Experimental Section.

Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrometer. NMR spectra were recorded with a Varian Associates Model A-60 spectrometer in carbon tetrachloride solution with Me_4Si as an internal standard at 0 ppm unless otherwise stated. VPC analyses were carried out on Aerograph Models 1520 and 220 vapor phase chromatographs employing helium as the carrier gas and columns of either XF1150 or DC11 or 60/80 mesh Chromosorb P. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were obtained on a Hitachi Model RMU-6E single-focusing mass spectrometer.

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Chlorine. To a solution of 7.26 g (30 mmol) of 2,2-diphenyl-1,3-oxathiolane in 80 ml of methyl chloride, precooled at −78° with a dry ice–acetone bath, was added 0.8 ml (ca. 16 mmol) of chlorine over a 5-min period. The resulting yellow solution was retained at −78 °C for 5 h and at room temperature for 24 h. NMR analysis of this solution showed only signals corresponding to benzophenone and bis(2-chloroethyl) disulfide (**2a**). Identification of the NMR signals of **2a** was made by comparison of chemical shifts of the signals with those obtained from an authentic sample.[6] VPC analysis of the reaction mixture also confirmed the presence of benzophenone and **2a**. The residue remaining after evaporation of the solvent was placed on a column of 140 g of silica gel and eluted with a methylene–carbon tetrachloride (4:1) mixture. The progress of the elution was followed by NMR and VPC analyses. The early fractions containing 1.58 g (56%) of **2a** were combined. The isolated **2a** was identical in every respect with an authentic sample. The rest of the eluents were combined and evaporated to give 5.48 g (100%) of benzophenone. Compound **2a** gave ir absorptions at ν_{max} (neat) 2960, 1440, 1412, 1280, 1205, and 850 cm^{-1}, and NMR analysis showed two multiplets of an AA′BB′ pattern centered at 3.00 and 3.76 ppm (area ratio 1:1).

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Bromine. To a solution of 3.63 g (15 mol) of 2,2-diphenyl-1,3-oxathiolane in carbon tetrachloride at 0 °C was added 2.56 g (15.5 mmol) of bromine in carbon tetrachloride. The mixture was allowed to warm to room temperature and then kept at 40–43 °C for an additional 18 h. NMR analyses of the cooled solution indicated the presence of benzophenone and bis(2-bromoethyl) disulfide (**2b**). The solvent was evaporated, and the residual material was put on a column of 50 g of silica gel and eluted with 2:1 chloroform–carbon tetrachloride. The first 150 ml of eluent was evaporated to yield 1.2 g (64%) of brown oil ($n^{26}D$ 1.6164, mp 25–26 °C) identified as **2b** by comparison of ir, NMR, and VPC spectra with those of an authentic sample. The final 325 ml of the eluent, after the discarding of 50 ml of an intermediate fraction, were concentrated to give 2.6 g (96%) of benzophenone. Compound **2b** gave ir absorption at ν_{max} (neat) 2960, 1432, 1250, 1185, 1095, and 615 cm^{-1}, and the NMR showed two multiplets centered at 3.16 and 3.50 ppm in a ratio of 1:1.

Bis(2-chloroethyl) Disulfide (2a). To 15.6 g (0.2 mol) of β-mercaptoethanol at room temperature was added 20 ml (ca. 0.175 mol) of 30% hydrogen peroxide dropwise with ice–water cooling. The resulting clear solution was maintained at 50–60 °C for 2 h and then 70 ml of concentrated hydrochloric acid was added at room temperature with constant stirring. The solution was then heated at 100 °C until two layers were observed. The organic layer was obtained by extracting twice with 100 ml of methylene chloride and dried. Vacuum distillation of the residue afforded 14.4 g (75.5%) of bis(2-chloroethyl) disulfide (**2a**), $n^{25}D$ 1.5641 (lit.[6] $n^{20}D$ 1.5656).

Bis(2-bromoethyl) Disulfide (2b). To a solution of 31.2 g (0.4 mol) of β-mercaptoethanol in 80 ml of chloroform was added 52.4 g (0.44 mol) of thionyl chloride in 30 ml of chloroform over a 1-h period. The clear solution was stirred at room temperature for 16 h, then solvent was removed in vacuo. Distillation gave 38.2 g (77%) of 1,2,3-oxadithiolane 2-oxide, bp 57–58 °C (0.5 mm), $n^{26}D$ 1.5757 (lit.[7] $n^{24}D$ 1.5782). A solution of 24.8 g (0.2 mol) of 1,2,3-oxadithiolane 2-oxide in 200 ml of carbon tetrachloride at 0 °C was brominated with 32 g (0.2 mol) of bromine. The final dark red solution was stirred at room temperature for 18 h, concentrated, and vacuum distilled to give 21.9 g (78%) of bis(2-bromoethyl) disulfide (**2b**), $n^{25}D$ 1.6203 (lit.[7] $n^{19}D$ 1.6190), bp 107–109 °C (0.5 mm).

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Bromine in the Presence of Triethylamine. To a solution of 2.42 g (0.01 mol) of 2,2-diphenyl-1,3-oxathiolane in a mixture of 20 ml of methylene chloride and 30 ml of carbon tetrachloride maintained at −65 °C was added as quickly as possible 1.6 g (0.01 mol) of bromine in 10 ml of the solvent mixture. To the orange paste formed was then added 1.01 g (0.01 mol) of triethylamine rapidly at this temperature. The final yellow suspension was allowed to warm to room temperature. A solid material was removed by filtration, washed with cold carbon tetrachloride, and dried to give 1.34 g (78%) of triethylammonium bromide, mp 250–252 °C. The mother liquor was taken to dryness, giving a yellow oil. The oil was placed on 100 g of silica gel and eluted with carbon tetrachloride, the progress of elution being followed by NMR analysis. From the early fractions totaling 1 l. of eluent, 0.09 g (7%) of **2b** was obtained. The next fractions totaling 600 ml were combined and evaporated under vacuum, yielding 0.23 g (9%) of recovered starting material. The rest of the fractions were combined, and evaporation of the solvent left 1.54 g (93%) of benzophenone.

Reaction of 2,2-Diisopropyl-1,3-oxathiolane with Bromine. A solution of 34.9 g (0.2 mol) of 2,2-diisopropyl-1,3-oxathiolane in 200 ml of methylene chloride was brominated with 33.5 g (0.2 mol) of bromine in 100 ml of methylene chloride. After the reaction was complete and solvent removed in vacuo, the residual oil on VPC analysis showed two peaks corresponding to 41% of diisopropyl ketone and 59% of another product. Vacuum distillation of the residue gave in addition to low-boiling diisopropyl ketone, 20.1 g (40%) of α-(2-bromoethylthio)isopropyl isopropyl ketone (**5b**): bp 90–92 °C (0.3 mm); $n^{24}D$ 1.5004; ν_{max} (neat) 2970, 1690, 1378, 1361, 1029, 610 cm^{-1}; NMR (CCl_4) δ 1.08 (d, J = 6.6 Hz, 7 H), 1.45 (s, 6 H), 2.70 (m, 2 H), 3.33 ppm (m, 2 H).

Anal. Calcd for $C_9H_{17}OSBr$: C, 42.69; H, 6.77; S, 12.67; mol wt, 253. Found: C, 42.74; H, 6.82; S, 12.79; mol wt, 254 (mass spectrum, molecular ion), 252 (osmometric).

Reduction of α-(2-Bromoethylthio)isopropyl Isopropyl Ketone (5b). To a solution of 5 g (19.7 mmol) of the ketone **5b** in absolute ethanol was added 1.5 g (400 mmol) of sodium borohydride portionwise at 0 °C with constant stirring. After the addition was complete, the solution was stirred for an additional 30 min and then heated under reflux for 1 h. The resulting yellow suspension was cooled, the excess sodium borohydride was destroyed with 10% hydrochloric acid, the solution was made basic with 10% aqueous sodium carbonate, and finally the solid was removed by filtration. The organic layer was extracted twice with 80 ml of ethyl acetate, washed, and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. Distillation of the residue gave 1.90 g (55%) of α-ethylthioisopropyl isopropyl alcohol (**6**): bp 55–57 °C (0.4 mm); $n^{25}D$ 1.4761; ν_{max} (neat) 3350, 2960, 1460, 1380, 1360, and 1260 cm^{-1}; NMR (CCl_4) δ 3.15 (d, J = 3.0 Hz, 1 H), 248 (s, –OH), 2.50 (q, J = 15 Hz, 2 H), 2.0 (m, 1 H), 1.34 (s, 3 H), 1.17 (s, 3 H), 1.0 (m, 9 H).

Anal. Calcd for $C_9H_{20}OS$: C, 61.33; H, 11.44; S, 18.20; mol wt, 176. Found: C, 61.57; H, 11.60; S, 18.39; mol wt, 176 (mass spectrum, molecular ion).

Reaction of 2,2-Diisopropyl-1,3-oxathiolane with Chlorine. A solution of 17.4 g (0.1 mol) of 2,2-diisopropyl-1,3-oxathiolane in 150 ml of methylene chloride at −70 °C was chlorinated with 7.8 g (0.11 mol) of chlorine according to the procedure previously described. VPC analysis of the solution after the reaction was complete showed the presence of isopropyl ketone and five other products. Quantitative analysis of the product ratio was not possible owing to overlapping of the peaks on the VPC trace. The crude residue was fractionally distilled to give 8.6 g (41%) of major product, bp 85–90 °C (1.0 mm). Repeated distillation of the crude distillate did not remove the impurities. The analytical sample of this product was obtained by column chromatography on 100 g of silica gel using benzene–hexane (3:1) as eluent. The impurities were eluted in the early fractions. The later fractions were combined and concentrated to afford a pure liquid oil identified as α-(2-chloroethylthio)isopropyl isopropyl ketone (**5a**): $n^{25}D$ 1.4821; ν_{max} (neat) 2970, 2940, 2880, 1692, 1468, 1380, 1365, 1035 cm^{-1}; NMR (CCl_4) δ 1.07 (d, J = 7.0 Hz, 6 H), 1.40 (s, 6 H), 2.64 (m, 2 H), 3.42 (m, 2 H); mass spectrum m/e 208 (2.65), 139 (96.25), 137 (66.25), 63 (24.43), 59 (27.08), 43 (100), 41 (92.50), 39 (26.14), 27 (46.78).

Anal. Calcd for $C_9H_{17}OSCl$: C, 51.80; H, 8.21; S, 15.36; mol wt, 208.7. Found: C, 51.78; H, 8.07; S, 16.29; mol wt, 208 (mass spectrum, molecular ion).

Reduction of α-(β-Chloroethylthio)isopropyl Isopropyl Ketone (5a) with Sodium Borohydride. Six grams (28.8 mmol) of **5a** in 50 ml of absolute ethanol was reduced with 2.8 g (73 mmol) of sodium borohydride as previously described. The product, α-ethylthioisopropyl isopropyl alcohol (**6**), after work-up and distillation, was obtained in 77% yield.

Reaction of 1,4-Oxathiaspiro[4.6]undecane with Bromine. A solution of 34.4 g (0.2 mol) of 1,4-oxathiaspiro[4.6]undecane[8] and 33.6 g (0.21 mol) of bromine in 200 ml of carbon tetrachloride was allowed to react as above. After being refluxed for 24 h, the greenish solution was concentrated on the rotary evaporator and the residue was analyzed by VPC which showed mainly cycloheptanone and a small amount of high-boiling material. Distillation of the residue gave 20.7 g (93%) of cycloheptanone, identified by comparisons of the ir spectrum with that of commercial material, and 16.4 g of a gummy residue, apparently a polymeric material.

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Registry No.—1 (R = Ph; X = H), 33735-40-9; 1 (R = *i*-Pr; X = H), 16047-99-7; 1 (R, R = $(CH_2)_6$; X = H), 184-31-6; **2a**, 1002-41-1; **2b**, 1002-40-0; **3**, 119-61-9; **4**, 565-80-0; **5a**, 57738-71-3; **5b**, 57738-72-4; **6**, 57738-73-5; chlorine, 7782-50-5; bromine, 7726-95-6; β-mercaptoethanol, 60-24-2; 1,2,3-oxadithiolane 2-oxide, 57738-74-6; triethylammonium bromide, 636-70-4; cycloheptanone, 502-42-1.

References and Notes

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Kinetics of the Reactions of 2-Bromo-3,5-dinitrothiophene with Meta- and Para-Substituted Anilines in Methanol. The Application of Hammett and Ingold–Yukawa–Tsuno Equations[1a]

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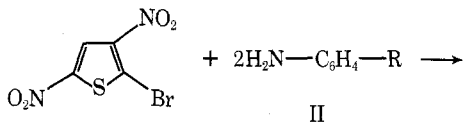
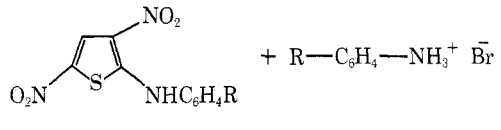
The rate constants of debromination of 2-bromo-3,5-dinitrothiophene by various meta- and para-substituted anilines have been measured in methanol at various temperatures and the Arrhenius parameters determined. The kinetic data have been analyzed, using the Ingold–Yukawa–Tsuno equation. The ρ (−3.00), r^- (0.99), and r^+ (0.38) values obtained are discussed.

The reactions of halogenonitroaromatic and heteroaromatic derivatives with substituted anilines have been studied by many research workers,[2] but no systematic quantitative studies, covering the whole range of substituent effects in the aniline moiety, have so far been carried out.

In the framework of our researches[3] on the applicability of linear free energy relationships to aromatic nucleophilic substitution reactions in the thiophene series, we now report kinetic data of the reaction of 2-bromo-3,5-dinitrothiophene (I) with various meta- and para-substituted anilines (II).





Results

2-Bromo-3,5-dinitrothiophene (I) gave the expected anilino derivatives (III) on treatment with anilines (II) in almost quantitative yields as shown by TLC and uv–visible spectral analysis. The relevant physical and analytical data are shown in Table I.

Rate constants and activation parameters for the anilino debromination reactions of I are shown in Table II. All the reactions were first order both in I and II.[6] An increase of the rate of substitution was observed on introduction of electron-repelling substituents into the nucleophile. On the