Studies on the Synthesis of Heterocyclic Compounds. XIV. Cleavage of 1,3-Benzoxathioles by Magnesium Bromide-Acetic Anhydride

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The cleavage reaction of some 1,3-benzoxathioles with magnesium bromide and acetic anhydride has been studied. In all the 1,3-benzoxathioles studied, the opening of the heterocyclic ring occurs first with cleavage of the C-O bond and formation of bromides and their corresponding products of hydrolysis. Successively also the cleavage of the C-S bond can occur. The competitive electrophilic substitution on the benzene ring becomes appreciable only in the 1,3-benzoxathioles-2,2-disubstituted with sterically demanding groups. The structure of newly prepared compounds has been determined by analytical and spectroscopic data and when possible by comparison with authentic samples.

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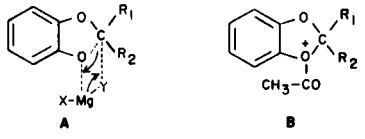
We have previously shown that 1,3-benzodioxoles react with magnesium bromide and acetic anhydride at room temperature with cleavage of one or both ethereal bonds [1].

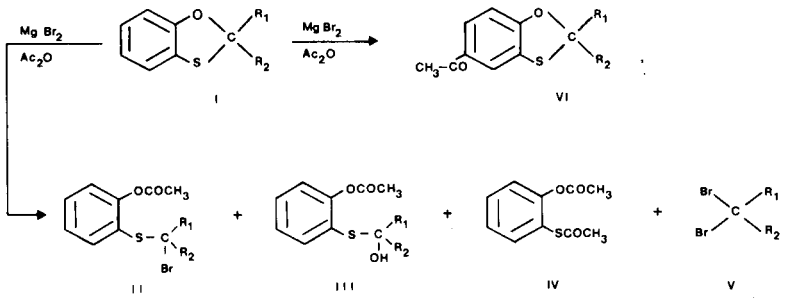
In this work we extend our research to 1,3-benzoxathiole derivatives in order to establish the relative case of cleavage of C-O and C-S linkage by acyl halides or acetic anhydride, and in order to obtain monoesters with the acyl group linked either to the oxygen or to the sulphur atom.

Recently the cleavage of 1,3-benzodioxole and 1,3-benzoxathiole derivatives by Grignard reagents [2] and aluminum and magnesium bromide [3] has been studied; the low attitude of magnesium halides to cleave the ethereal bonds and their inability to cleave the thioethereal one has been shown. The addition of anhydride or acyl chloride makes the cleavage reaction much easier. In fact it has been postulated that the cleavage of the heterocyclic ring ether bond by Grignard reagents or magnesium halides occurs first with coordination of the heterocycle to the reagent and formation of an intermediate **A** [2], while with magnesium bromide-acetic anhydride the initial attack is much easier because of the acyl ion, which has a stronger electrophilic character and leads to the intermediate **B** [3].



Surprisingly, working at room temperature no reaction occurred: after 48 hours in all the reactions the unaltered starting material was isolated except 1-methoxy-2-methyl-

Scheme



Table

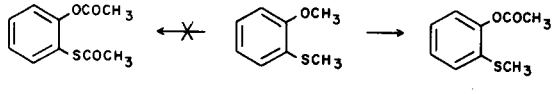
Action of Magnesium Bromide-Acetic Anhydride on the 1,3-Benzoxathioles for 24 Hours at Reflux Temperature

Starting Material	% Cleavage	% Products II	III	IV	VI
2,2-Dimethyl-1,3-benzoxathiole Ia	82	28	36	10	traces
2-Methyl-2-isopropyl-1,3-benzoxathiole Ib	63	16	26	6	8
Spiro[1,3-benzoxathiole-2,1'-cyclopentane] Ic	80	18	37	10	traces
Spiro[1,3-benzoxathiole-2,1'-cyclohexane] Id	70	20	23	7	10
2,2-Diisopropyl-1,3-benzoxathiole Ie	—	—	—	—	15

From 2-methoxymethylthiobenzene only 2-acetoxymethylthiobenzene was obtained in a yield of 91%.

thiobenzene which gave 91% of the reaction product. However by refluxing for 24 hours, the expected reaction products were obtained. Analyzing the reaction crude products, the predominant presence of derivatives II: 2-(α-bromoalkylthio)-1-acetoxybenzene has been noted. After reaction mixture treatment with a basic solution, we have noted the formation of the carbinolic compound III; the quantity of this product increases with the increase of the basic treatment (see Table). Maintaining the basic solution for some time (24 hours), the bromo derivative becomes insignificant while there is a strong increase in carbinolic derivative. The formation of ethylenic derivatives, which is always present in the cleavage of the analogous 1,3-benzodioxole derivatives, was never observed (Scheme).

It has also been observed that cleavage reactions preferably occur on the C-O rather than on the C-S bond. The second step of the reaction occurs much more slowly and therefore by interrupting the reaction after a certain time it is possible to obtain only the products with selective cleavage of C-O. On the contrary in the case of 1-methoxy-2-methylthiobenzene the only cleavage product obtained is 1-acetoxy-2-methylthiobenzene, even prolonging reaction times for several days.



The course of the cleavage reactions has been monitored by isolating small samples from the reaction mixture at regular intervals and analyzing them by glc. The starting materials were employed as comparison terms, thus determining the amount of the reacted compound. On the other hand the course of spiranic reactions was monitored by hplc.

EXPERIMENTAL

Boiling points were uncorrected and obtained from distillation or by means of a boiling point apparatus. The infrared spectra were recorded on a Perkin-Elmer model 157 G spectrophotometer. Samples were examined as potassium bromide pellets or as thin films in the case of liquids; absorption frequencies are quoted in reciprocal centimeters. The nmr spectra were determined on a Varian FT-80A spectrometer; chemical shifts were measured in ppm (δ) using tetramethylsilane as internal standard. Exchangeable protons were detected by deuterium oxide addition. The glc analyses were performed on a Perkin-Elmer 881 instrument equipped with Apiezon L column (2 m × 0.5 cm, 4% chromosorb W 60/80). The hplc analyses were performed using a Perkin-Elmer 601 liquid chromatograph. A Merck Lichrosorb Si-100 column was used (250 × 4 mm id; mobile phase 80:20 *n*-hexane-dichloromethane; flow-rate: 1 ml min^{-1}, detector UV/visible Perkin-Elmer LC 55, λ = 225 nm). Microanalyses for CHN were carried out on a Carlo Erba model 1106 Elemental-Analyzer. Analyses for bromine were performed according to literature procedure [4].

Starting Materials.

The following compounds were obtained according to literature procedures: 2-hydroxythiophenol [5], 2-hydroxythiophenol diacetic ester [6], 2,2-dimethyl-1,3-benzoxathiole [7,8], 2-methyl-2-isopropyl-1,3-benzoxathiole [1,8], 2,2-diisopropyl-1,3-benzoxathiole [1,8], spiro[1,3-benzoxathiole-2,1'-cyclopentane] [7,8], spiro[1,3-benzoxathiole-2,1'-cyclohexane] [7,8], 2-methoxy-1-methylthiobenzene [8]. All products were identified by comparison with authentic samples or by analytical and spectroscopic data.

Authentic Samples.

Acetone, 3-methyl-2-butanone, 2,4-dimethyl-3-pentanone, cyclopentanone, cyclohexanone, 2,2-dibromopropane as well as all the solvents were commercial products and were used without further purification; 3,3-dibromo-2-methylpropane, 1,1-dibromocyclopentane, 1,1-dibromocyclohexane were prepared according to established procedures [1].

Compounds VIa-e were prepared by the following general method.

2,2-Dialkyl-5-acetyl-1,3-benzoxathiole.

A cooled solution of acetyl chloride (10 mmoles) in dry 1,2-dichloroethane (10 ml) was added dropwise at 0° to a solution of 2,2-dialkyl-1,3-benzoxathiole I (10 mmoles), and aluminium chloride (10 mmoles) in dry 1,2-dichloroethane (30 ml). After 3 hours at 0°, the mixture was decomposed by shaking with ice and dilute hydrochloric acid for 1 hour. The organic layer was washed in 10% sodium hydroxide, in water, then dried over anhydrous sodium sulphate and evaporated. The oily residue wa distilled under reduced pressure, then chromatographed on a silica gel column using petroleum ether-diethyl ether (5:1).

2,2-Dimethyl-5-acetyl-1,3-benzoxathiole (VIa).

This compound was obtained in a yield of 60% (1.25 g), bp 160-163° (20 mm Hg); n_D^{20} 1.5775; ir (film): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.78-6.80 (m, 3H aromatic), 2.49 (s, 3H, $COCH_3$) and 1.82 ppm (s, 6H, $2CH_3$).

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81. Found: C, 63.37; H, 5.83.

2-Methyl-2-isopropyl-5-acetyl-1,3-benzoxathiole (VIb).

This compound was obtained in a yield of 75% (1.77 g), bp 170-172° (20 mm Hg); n_D^{20} 1.5685; ir (film): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.80-6.80 (m, 3H aromatic), 2.46 (s, 3H, $COCH_3$), 2.30-1.90 (m,

1H, CH_3-C*H*-CH_3), 1.75 (s, 3H, ≡C-CH_3) and 1.05-0.80 ppm (d, 6H, CH_3-CH-CH_3).

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.08; H, 6.83. Found: C, 66.28; H, 6.79.

5-Acetylspiro[1,3-benzoxathiole-2,1'-cyclopentane] (VIc).

This compound was obtained in a yield of 78% (1.8 g), mp 59-60°; ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.78-6.73 (m, 3H aromatic), 2.51 (s, 3H, $COCH_3$), 2.47-1.56 (m, 8H, -$(CH_2)_4$-).

Anal. Calcd. for $C_{13}H_{14}O_2S$: C, 66.65; H, 6.02. Found: C, 66.67; H, 6.05.

5-Acetylspiro[1,3-benzoxathiole-2,1'-cyclohexane] (VId).

This compound was obtained in a yield of 80% (2 g), bp 215-218° (20 mm Hg); n_D^{20} 1.6338; ir (film): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.78-6.75 (m, 3H aromatic), 2.49 (s, 3H, $COCH_3$) and 2.41-0.73 ppm (m, 10H, -$(CH_2)_5$-).

Anal. Calcd. for $C_{14}H_{16}O_2S$: C, 67.73; H, 6.50. Found: C, 67.75; H, 6.51.

2,2-Diisopropyl-5-acetyl-1,3-benzoxathiole (VIe).

This compound was obtained in a yield of 85% (2.3 g), mp 43-44°; ir (potassium bromide): 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.80-6.68 (m, 3H aromatic), 2.45 (s, 3H, $COCH_3$), 2.49-1.90 (m, 2H, 2 CH_3-C*H*-CH_3), 1.11-0.95 (d, 6H, S-C-CH(CH_3)$_2$) and 0.95-0.89 ppm (d, 6H, O-C-CH(CH_3)$_2$).

Anal. Calcd. for $C_{15}H_{20}O_2S$: C, 68.16; H, 7.36. Found: C, 68.25; H, 7.39.

General Procedure for the Cleavage of 1,3-Benzoxathioles.

1,2-Dibromoethane (1.87 g, 10 mmoles) was added dropwise, stirring and under nitrogen, to magnesium turnings (0.24 g, 10 mmoles) and dry diethyl ether (20 ml). When all the magnesium had disappeared the ether was distilled under reduced pressure and replaced with dry acetonitrile (20 ml). To this suspension, stirred and cooled in an ice-water bath dry 1,3-benzoxathiole derivative (10 mmoles) and acetic anhydride (2.04 g, 20 mmoles) were added. The reaction was allowed to stir for 24 hours at room temperature and was then heated at reflux for an additional 24 hours. Succesively the reaction mixture was neutralized with a saturated sodium carbonate solution and extracted with diethyl ether. The ethereal solution was dried over anhydrous magnesium sulphate and evaporated. The oily residue was distilled under reduced pressure or chromatographed by column on silica gel.

Cleavage of 2,2-Dimethyl-1,3-benzoxathiole (Ia).

The cleavage of **Ia** (1.66 g, 10 mmoles) under the previously described conditions after column chromatography on silica gel using *n*-hexane-ethyl acetate (5:1), gave a mixture of 2-(α-bromoisopropylthio)-1-acetoxybenzene (IIa) and 2-(α-hydroxyisopropylthio)-1-acetoxybenzene (IIIa). A fraction of the mixture analyzed by glc, also showed the presence of 2-hydroxythiophenol diacetic ester (IV), 2,2-dibromopropane (Vc) and traces of 2,2-dimethyl-5-acetyl-1,3-benzoxathiole (VIa). The glc analysis of the mixture showed the ratio of II to III, IV and V to be 2.8:3.6:1:1.

2-(α-Bromoisopropylthio)-1-acetoxybenzene (IIa).

This compound was obtained in a yield of 28% (0.8 g), bp 185° (760 mm); n_D^{20} 1.5298; ir (film): 1760 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.53-6.50 (m, 4H aromatic), 2.20 (s, 3H, $OCOCH_3$) and 1.75 ppm (s, 6H, $2CH_3$).

Anal. Calcd. for $C_{11}H_{13}BrO_2S$: C, 45.69; H, 4.53; Br, 27.64. Found: C, 45.76; H, 4.49; Br, 27.59.

2-(α-Hydroxyisopropylthio)-1-acetoxybenzene (IIIa).

This compound was obtained in a yield of 36% (0.8 g), bp 120° (7 mm); n_D^{20} 1.4850; ir (film): 3400 (OH), 1770 cm^{-1} (O-C-C=O); nmr (deuteriochloroform): δ 7.35-6.40 (m, 4H aromatic), 2.21 (s, 3H, $OCOCH_3$), 1.90 (s, 1H, OH deuterium oxide exchanged) and 1.76 ppm (s, 6H, $2CH_3$).

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.39; H, 6.23. Found: C, 58.29; H, 6.21.

Cleavage of 2-Methyl-2-isopropylthio-1,3-benzoxathiole (Ib).

The cleavage of Ib (1.94 g, 10 mmoles) under the previously described conditions after distillation gave a mixture of 2-(α-bromo-α,β-dimethylpropylthio)-1-acetoxybenzene (IIb) and 2-(α-hydroxy-α,β-dimethylpropylthio)-1-acetoxybenzene (IIIb). A fraction of the mixture analyzed by glc also showed the presence of 2-hydroxythiophenol diacetic ester (IV), 3,3-dibromo-2-methylpentane (Vb) and 2-methyl-2-isopropylthio-5-acetyl-1,3-benzoxathiole (VIb). The glc analysis of the mixture showed the ratio of II to III to IV and V to be: 1.6:2.6:0.6:0.6.

2-(α-Bromo-α,β-dimethylpropylthio)-1-acetoxybenzene (IIb).

This compound was obtained in a yield of 16% (0.5 g), bp 115-118° (7 mm); n_D^{30} 1.5325; ir (film): 1760 cm^{-1} (O-C=O), nmr (deuteriochloroform): δ 7.30-6.50 (m, 4H aromatic), 2.16 (s, 3H, $OCOCH_3$), 2.30-1.92 (m, 1H, CH_3-C*H*-CH_3), 1.65 (s, 3H, ≡C-CH_3) and 1.21-1.09 ppm (d, 6H, CH_3-CH-CH_3).

Anal. Calcd. for $C_{13}H_{17}BrO_2S$: C, 49.22; H, 5.40; Br, 25.19. Found: C, 49.20; H, 5.38; Br, 25.30.

2-(α-Hydroxy-α,β-dimethylpropylthio)-1-acetoxybenzene (IIIb).

This compound was obtained in a yield of 26% (0.65 g), bp 98-100° (10 mm); n_D^{30} 1.5195; ir (film): 3400 (OH), 1760 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.25-6.50 (m, 4H aromatic), 2.98 (s, 1H, OH deuterium oxide exchanged), 2.18 (s, 3H, $OCOCH_3$), 2.28-1.88 (m, 1H, CH_3-C*H*-CH_3), 1.69 (s, 3H, ≡C-CH_3) and 1.18-1.05 ppm (d, 6H, CH_3-CH-CH_3).

Anal. Calcd. for $C_{13}H_{18}O_3S$: C, 61.40; H, 7.14. Found: C, 61.51; H, 7.12.

Cleavage of Spiro[1,3-benzoxathiole-2,1'-cyclopentane] (Ic).

The cleavage of Ic (1.92 g, 10 mmoles) under the previously described conditions after distillation gave a mixture of 2-(α-bromocyclopentylthio)-1-acetoxybenzene (IIc), 2-(α-hydroxycyclopentylthio)-1-acetoxybenzene (IIIc). A fraction of the mixture analyzed by hplc and glc also showed the presence of 2-hydroxythiophenol diacetic ester (IV), 1,1-dibromo cyclopentane (Vc) and traces of spiro-5-acetyl-[1,3-benzoxathiole-2,1'-cyclopentane] (VIc). The hplc and glc analysis of the mixture showed the ratio of II to III to IV and V to be 1.8:3.7:1:1.

2-(α-Bromocyclopentylthio)-1-acetoxybenzene (IIc).

This compound was obtained in a yield of 18% (0.56 g), bp 180-182° (5 mm); n_D^{20} 1.5512; ir (film): 1755 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.28-6.48 (m, 4H aromatic), 2.16 (s, 3H, $OCOCH_3$) and 2.35-1.79 ppm (m, 8H, -$(CH_2)_4$-).

Anal. Calcd. for $C_{13}H_{15}BrO_2S$: C, 49.53; H, 4.79; Br, 25.35. Found: C, 49.51; H, 4.76; Br, 25.39.

2-(α-Hydroxycyclopentylthio)-1-acetoxybenzene (IIIc).

This compound was obtained in a yield of 37% (0.93 g), bp 150-152° (5 mm); n_D^{20} 1.4882; ir (film): 3350 (OH), 1760 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.35-6.48 (m, 4H aromatic), 3.45 (s, 1H, OH deuterium oxide exchanged), 2.18 (s, 3H, $OCOCH_3$) and 2.32-1.75 ppm (m, 8H, -$(CH_2)_4$-).

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.89; H, 6.39. Found: C, 61.78; H, 6.37.

Cleavage of Spiro[1,3-benzoxathiole-2,1'-cyclohexane] (Id).

The cleavage of Id (2.06 g, 10 mmoles) under the previously described conditions after distillation gave a mixture of 2-(α-bromocyclohexylthio)-1-acetoxybenzene (IId) and 2-(α-hydroxycyclohexylthio)-1-acetoxybenzene (IIId). A fraction of the mixture analyzed by hplc and glc also showed the presence of 2-hydroxythiophenol diacetic ester (IV), 1,1-dibromocyclohexane (Vd) and 5-acetylspiro[1,3-benzoxathiole-2,1'-cyclohexane] (VId). The hplc and glc analysis of the mixture indicated a ratio of II to III to IV and V to be 2:2.3:0.7:0.7.

2-(α-Bromocyclohexylthio)-1-acetoxybenzene (IId).

This compound was obtained in a yield of 20% (0.66 g), bp 220° (760 mm); n_D^{20} 1.5558; ir (film): 1760 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.28-6.48 (m, 4H aromatic), 2.18 (s, 3H, $OCOCH_3$) and 2.12-1.24 ppm (m, 10H, -$(CH_2)_5$-).

Anal. Calcd. for $C_{14}H_{17}BrO_2S$: C, 51.07; H, 5.20; Br, 24.27. Found: C, 51.15; H, 5.19; Br, 24.30.

2-(α-Hydroxycyclohexylthio)-1-acetoxybenzene (IIId).

This compound was obtained in a yield of 23% (0.62 g), bp 180-182° (10 mm); n_D^{20} 1.4213; ir (film): 3320 (OH), 1755 cm^{-1} (O-C=O); nmr (deuteriochloroform): δ 7.30-6.48 (m, 4H aromatic), 3.20 (s, 1H, OH deuterium oxide exchanged, 2.20 (s, 3H, $OCOCH_3$) and 2.11-1.35 ppm (m, 10H, $-(CH_2)_5-$).

Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.14; H, 6.81. Found: C, 63.19; H, 6.89.

Cleavage of 2,2-Diisopropyl-1,3-benzoxathiole (Ic).

The cleavage of Id (2.22 g, 10 mmoles) under the previously described conditions did not give any cleavage compound. The only reaction product obtained was 2,2-diisopropyl-5-acetyl-1,3-benzoxathiole (VIc), which was obtained in a yield of 15% (0.40 g).

Cleavage of 2-Methoxy-1-methylthiobenzene.

The cleavage of this compound gave 2-acetoxy-1-methylthiobenzene as the only product at room temperature. Even refluxing for two days, the cleavage of C-S bond did not occur.

2-Acetoxy-1-methylthiobenzene.

This compound was obtained in a yield of 91% (1.65 g), bp 89-90° (7 mm); mp 48-50°; ir (film): 1760 cm^{-1} (OCO); nmr (deuteriochloroform): δ 7.48-6.68 (m, 4H aromatic), 2.21 (s, 3H, $OCOCH_3$) and 2.13 ppm (s, 3H, SCH_3).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.33; H, 5.53. Found: C, 59.16; H, 5.56.

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