A Novel Synthesis of 1,4-Benzoxathians[1]

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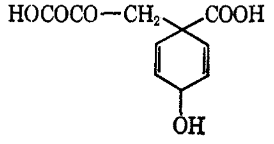
In a proposed synthesis of prephenic acid (**1**), 4-carbethoxycyclohexanone (**2**) was prepared and brominated to give 2,6-dibromo-4-carbethoxycyclohexanone (**3**). It was assumed that the ketone function of **3** could be protected for further reactions in the proposed scheme by the formation of a hemithioketal on treatment with β-mercaptoethanol. A large quantity of acidic gas was formed when **3** was subjected to this treatment and the major product isolated from the reaction was found to be 6-carbethoxy-1,4-benzoxathian (**4**).



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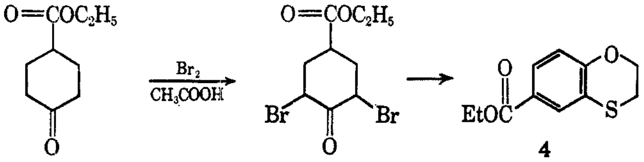

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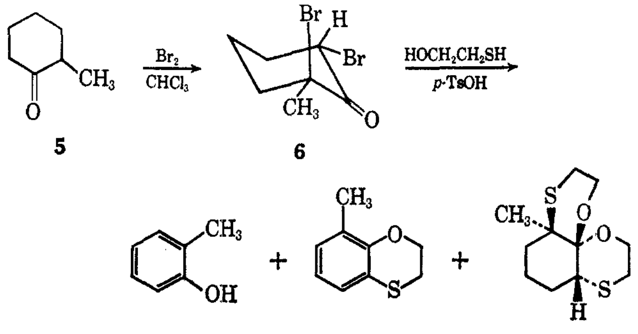
The mechanism of formation of this material posed an interesting problem and in addition led to speculation as to how general such a reaction may be since the literature indicates that 1,4-benzoxathians are not readily available. The model compound which was chosen for the mechanism study was 2,6-dibromo-2-methycyclohexanone (**6**). This bromo ketone was prepared by bromination of 2-methylcyclohexanone (**5**). Treatment of the bromo ketone **6** with β-mercaptoethanol led to a mixture of products as was shown by gas–liquid partition chromatography (glpc). Among the products formed was *o*-cresol (**7**), 8-methyl-1,4-benzoxathian (**8**), which was present in 30–40% yield, and the bisoxathian **9**. The benzoxathian was identified by desulfurization to *o*-ethoxytoluene followed by sulfonation and amide formation to give 3-methyl-4-ethoxybenzenesulfonamide.



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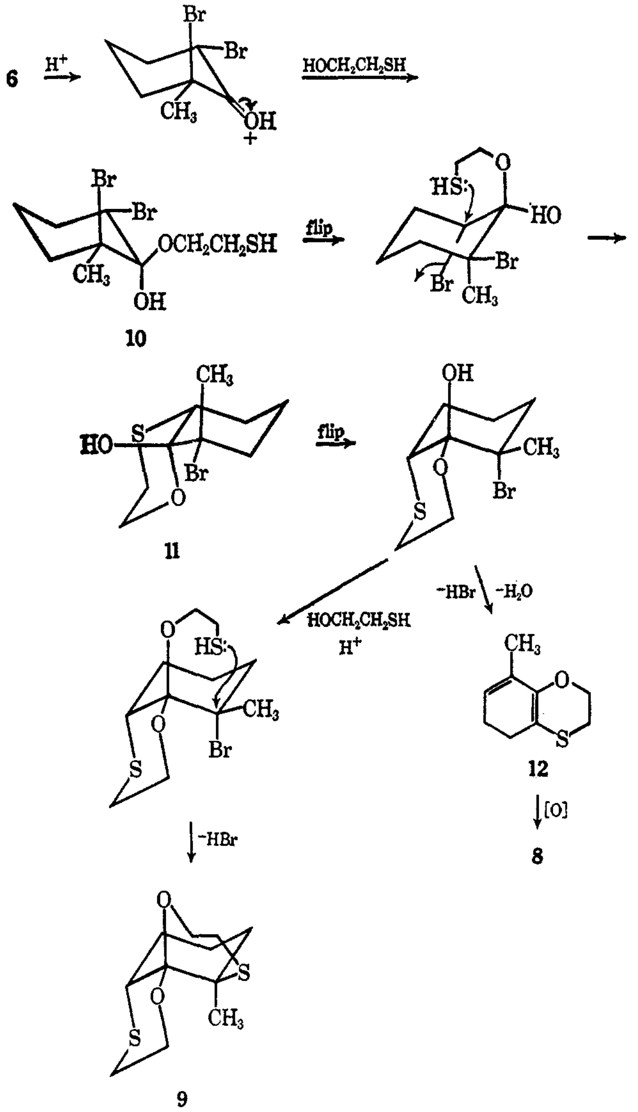
In order to eliminate the possibility of *o*-cresol (**7**) acting as an intermediate, it was subjected to the reaction conditions used in the synthesis of the benzoxathian, **8**. No benzoxathian was formed. In addition it was shown that *p*-toluenesulfonic acid was necessary to initiate the reaction. Hydrogen bromide also catalyzed the condensation but gave reduced quantities of **8**. The fact that an acid catalyst was necessary suggested that the first step was not nucleophilic attack by the sulfur on the carbon bearing a halogen. If such an attack were to occur, hydrogen bromide would be generated and the reaction should continue without the addition of acid. Therefore, it would appear that the first step was protonation of the ketone followed by hemiketal formation (**10**) (Scheme I). Nucleophilic displacement would then give **11**. Dehydration and dehydrohalogenation would give the dihydroaromatic system, **12**, which would be oxidized readily to the aromatic benzoxathian, **8**, under the reaction conditions employed. If a second molecule of β-mercaptoethanol reacts with the cyclic hemiketal, **11**, and a second nucleophilic displacement occurs, the tricyclic system **9** would be formed.

Scheme I



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[2] Taken in part from the dissertation presented by T. L. Lemke, Jan 1966, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

A reaction similar to the one investigated herein was reported utilizing 4,5-epoxy-3-keto steroids, polyphosphoric acid, and either ethanedithio, β-mercaptoethanol, or ethyl mercaptan.[3] Tomoeda and coworkers observed no thioketalization with any of their systems.

Experimental Section[4]

4-Carbethoxycyclohexanone (**2**) was prepared by the procedures described by Smissman, Lemke, and Creese.[5]

2,6-Dibromo-4-carbethoxycyclohexanone (**3**).—To a solution of 1.6 g (0.0094 mole) of ketone **2** dissolved in 25 ml of CCl_4 and maintained at 20° was added, while stirring, 3.2 g (0.02 mole) of Br_2 in 25 ml of CCl_4.[6] The addition took approximately 1.5 hr and was followed by an additional 0.75 hr of stirring. The CCl_4 solution was washed with a 10% solution of $NaHCO_3$ and dried (Na_2SO_4). Removal of the solvent left a residue of 3.17 g of a thick brown oil which by nmr appeared to be a mixture of isomers: nmr, 1.30 (3 H, triplet, J = 7.0 cps), 1.35 (3 H, triplet, J = 7.0 cps), 2.0–3.6 (10 H, broad multiplet), 4.20 (4 H, multiplet), 4.75 (1 H, broad triplet, $W_{1/2}$ = 9.0 cps), 5.40 (2 H, broad quartet, $W_{1/2}$ = 24 cps).

The dibromide was analyzed as the ethylene ketal.

Anal. Calcd for $C_{11}H_{16}O_4Br_2$: C, 35.51; H, 4.34. Found: C, 35.59; H, 4.22.

When the bromination was performed according to the procedure of Yanagita,[7] which consisted of using glacial acetic acid as the solvent, an impure oil was isolated which appeared to be a single isomer: nmr, 5.45 (1 H, doublet of doublets, $W_{1/2}$ = 22 cps), 4.73 (1 H, multiplet, $W_{1/2}$ = 7.0 cps), 4.18 (2 H, quartet, J = 7.0 cps), 2.0–3.8 (5 H, broad band), 1.30 (3 H, triplet, J = 7.5 cps).

6-Carbethoxy-1,4-benzoxathian (**4**).—To a flask containing 50 ml of dry benzene was added 0.60 g (0.0076 mole) of β-mercaptoethanol, 50 mg of *p*-toluenesulfonic acid, and 2.40 g (0.0073 mole) of 2,6-dibromo-4-carbethoxycyclohexanone (**3**). The mixture was heated under reflux for 5 hr and the water formed was collected in a Dean–Stark trap. The benzene was removed on a flash evaporator and the oil which remained (2.0 g) was chromatographed on 50 g of silica gel (Brinkmann) using petroleum ether (bp 63–68°)–$CHCl_3$ (3:1) as eluting solvent. The first six fractions (640 mg) were found to be the benzoxathian, **4** (40%): infrared, 5.84 (s), 6.25 (m), 6.73 μ (s); nmr, 1.34 (3 H, triplet, J = 7.2 cps), 3.08 (2 H, multiplet), 4.31 (2 H, multiplet), 4.31 (2 H, triplet, J = 7.0 cps), 6.91 (1 H, broad doublet of doublets), 7.50 (1 H, doublet of doublets), 7.70 (1 H, singlet); $\lambda_{\max}^{CH_3OH}$ 237 mμ (ϵ 35,000), 268 (10,000), 3.12 (5000).

The oil was treated with 10 ml of 10% NaOH and heated at reflux temperature. Acidification of the basic layer resulted in precipitation of 6-carboxy-1,4-benzoxathian which after recrystallization from EtOH–H_2O melted at 175–182°: infrared (KBr), 5.93 (s), 6.25 (s), 6.39 (w), and 6.7 μ (w); $\lambda_{\max}^{CH_3OH}$ 218, 264, 272, 310 mμ.

Anal. Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; S, 16.34. Found: C, 54.88; H, 3.93; S, 16.30.

To a flask containing 50 ml of benzene and two small scoops of freshly prepared Raney nickel (W-4) was added 196 mg of 6-carbethoxy-1,4-benzoxathian (**4**). The contents were stirred for 2 hr and the benzene was decanted. The Raney nickel was washed with benzene. The benzene layers were combined and the solvent removed leaving 140 mg of an oil: infrared, 5.82 (s), 6.21 (s), 6.6 μ (m); nmr, 1.35 (3 H, triplet, J = 7.0 cps), 1.38 (3 H, triplet, J = 7.0 cps), 4.02 (2 H, quartet, J = 7.0 cps), 4.23 (2 H, quartet, J = 7.0 cps), 7.35 (4 H, quartet, J = 8 and 6.5 cps); $n^{25}\text{D}$ 1.5192 (lit.[8] $n^{25}\text{D}$ 1.5065). This material proved to be ethyl 4-ethoxybenzoate by comparison with an authentic sample.

2,6-Dibromo-2-methylcyclohexanone (**6**).—To a solution of 50 ml of $CHCl_3$ and 11.2 g (0.1 mole) of 2-methylcyclohexanone (**5**) cooled to 10° was added, while stirring, 32 g (0.2 mole) of Br_2 in 50 ml of $CHCl_3$. The addition took 1 hr; the mixture was then allowed to stand an additional 0.5 hr. Removal of the solvent *in vacuo* left a green solid which was recrystallized from 59% EtOH. A total of 17 g (63%) of white needles, mp 42°, was recovered (lit.[9] mp 42–43°).

8-Methyl-14-benzoxathian (**8**).—A solution of 50 ml of benzene, 1.56 g of (0.02 mole) of β-mercaptoethanol, and 5.10 g (0.019 mole) of bromo ketone, **6**, was heated under reflux for 1.5 hr. Very little water was collected in the Dean–Stark trap and no hydrogen bromide could be detected. At this time 45 mg of *p*-toluenesulfonic acid was added to the reaction mixture and the system was again heated. An acidic gas was found to be evolved soon after the addition of the catalyst. The reaction was terminated after 3.5 hr. Removal of the solvent resulted in recovery of a thick oil which by glpc was shown to contain *o*-cresol (**7**) by rechromatography with a known added sample of this substance. The oil was chromatographed first on Al_2O_3 (Merck, reagent) using $CHCl_3$ as the eluting solvent, then on silica gel (Brinkmann) using petroleum ether (bp 63–68°)–benzene (6:1). The first oils collected contained a mixture of materials but later fractions contained pure **8**. A yield of 1.15 g (37%) of the benzoxathian, **8**, was obtained: infrared, 6.29 (s), 6.80 (s), 5.2 (w), 5.45 (w), and 5.65 μ (w); nmr, 2.12 (3 H, singlet), 2.99 (2 H, multiplet), 4.35 (2 H, multiplet), and 6.72 (3 H, broad singlet).

Anal. Calcd for $C_9H_{10}OS$: C, 65.02; H, 6.02; S, 19.29. Found: C, 65.27; H, 7.18; S, 19.30.

To a solution of 309 mg of the benzoxathian, **8**, in 50 ml of dry benzene was added approximately 5 g of freshly prepared W-4 Raney nickel. The mixture was stirred for 2 hr at 25°. The benzene was decanted and the Raney nickel was washed with benzene. The benzene extracts were combined and the solvent was removed. The *o*-ethoxytoluene thus formed was treated with chlorosulfonic acid followed by aqueous ammonia to give 3-methyl-4-ethoxybenzenesulfonamide, mp 148–150° (lit.[10] mp 149°).

In another experiment a white solid was isolated from the silica gel column when the column was washed with benzene. The material was recrystallized from ethanol–water and was identified as the bisoxathian, **9**: mp 112–114°; infrared (KBr), 6.97 (m), 7.73 (s), 8.40 (s), 8.66 (s), 9.17 (s), 9.52 μ (s); nmr, 3.90 (4 H, multiplet), 3.07 (3 H, multiplet), 0.97 (3 H, broad doublet), 1.1–2.6 (8 H, broad band).

Anal. Calcd for $C_{11}H_{18}O_2S_2$: C, 53.62; H, 7.36. Found: C, 53.62; H, 7.37.

Registry No.—**3**, 14789-67-4; **4**, 14789-68-5; free acid of **4**, 14789-69-6; **8**, 14789-70-9; **9**, 14789-71-0.

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[4] Melting points were obtained on a Thomas-Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR-5, IR-8, and IR-10 spectrophotometers and the ultraviolet data were recorded on a Cary 14 spectrophotometer. Nmr data were obtained from a Varian Associates Model A-60 spectrometer utilizing CCl_4 as a solvent, unless otherwise stated, with tetramethylsilane as an internal standard, and reported in parts per million as δ values. Elemental analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo., and by Drs. G. Weiler and F. B. Strauss, Oxford, England.

[5] E. E. Smissman, T. L. Lemke, and M. W. Creese, to be published.

[6] H. Plieninger, G. Ege, H. J. Grasshoff, G. Keilich, and W. Hoffmann, *Ber.*, **94**, 2115 (1962).

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[8] W. Emerson, J. Heyd, V. Lucas, E. Chapin, G. Owens, and R. Shortridge, *J. Am. Chem. Soc.*, **68**, 674 (1946).

[9] E. J. Corey, T. H. Topie, and W. A. Wozniak, *ibid.*, **77**, 5415 (1955).

[10] A. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co. Ltd., London, 1956, p 673.

A Deuterium Isotope Effect in a Nonaqueous Acid–Base System

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The purpose of this research was to determine if an isotope effect exists between hydrogen bromide and deuterium bromide in their interactions with the π-