Facile Bridge Expulsion of Sulfur Heterocycles. The 7-Thiabicyclo[2.2.1]hepta-2,5-diene and 7-Thiabicyclo[4.1.0]hepta-2,4-diene Systems in Thiepin Synthesis

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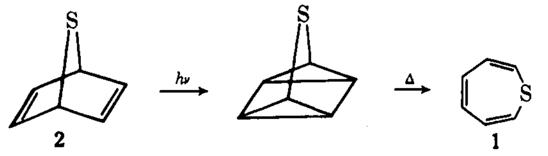
Dehydrohalogenation of bis-*endo*-1,5-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) and 3,4-dibromo-7-thiabicyclo-[4.1.0]heptane (**9**) was attempted with a variety of rather nonnucleophilic bases. From **3** the desired 7-thianorbornadiene (**2**) was not observed but benzene was formed presumably from this intermediate. From **9** benzene was also formed and this is postulated to arise from sulfur extrusion from thiepin or thianorcaradiene.

Despite the syntheses of several substituted derivatives,[1] the parent thiepin (**1**) is yet unknown. As the parent oxepin is now known and its behavior well established,[2] it would be of considerable interest to prepare and investigate the thiepin in order to compare the properties of these two basic heterocyclic ring systems. The successful synthesis of the stable thiepin 1,1-dioxide by Mock[3] lends further impetus to this goal as does the recent report of SCF–MO calculations which indicate that **1**, if planar, would be antiaromatic.[4] We decided to attack this problem from two different directions, both of which involved elimination of two molecules of hydrogen halides from key intermediates.

The first route employed was to adapt the Prinzbach[5] method for oxepin and azepin synthesis to the synthesis of thiepin as illustrated in eq 1.



(1)

While the most obvious choice for the synthesis of 7-thiabicyclo[2.2.1]hepta-2,5-diene (**2**) would be a Diels–Alder reaction between thiophene and acetylene, the well-established lack of reactivity of thiophenes in this addition[6] makes this an unlikely route. However, the ready availability of bis-*endo*-1,5-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) from the addition of sulfur dichloride to 1,4-dihydrobenzene[7] afforded a likely starting material. Unfortunately, the elimination of two molecules of hydrogen chloride from **3** proved rather frustrating in that the usual techniques afforded either no reaction or no isolable sulfur-containing products. Sodium 2-*n*-butylcyclohexoxide (BCO) had been shown to be a uniquely effective base for the elimination of hydrogen halides from endo-substituted norbornyl halides.[8] Under conditions mild enough to possibly provide an opportunity to observe thiepin, BCO proved ineffective as respectable recoveries of starting material were realized. Other bases employed for the dehydrochlorination of **3** were potassium *tert*-butoxide, 1,5-diazobicyclo[4.3.0]non-5-ene (DBN), 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU), and bis-1,8-dimethylaminonaphthalene (BDMAN), the latter being a particularly good nonnucleophilic base.[9] The results of these attempted dehydrochlorinations are summarized in Table I. While BCO proved to be rather unreactive to **3**, potassium *tert*-butoxide, DBN, and BDMAN each afforded benzene in low yield. In addition, the reaction of **3** with BDMAN yielded a large amount of 1,4-dihydrobenzene. The formation of this latter product likely proceeds through cyclic episulfonium ions and is analogous to the recently reported eliminations of 4-chlorobenzenesulfenyl chloride from chloroalkyl 4-

TABLE I

Halide	Base[a]	Solvent	Temp, °C	Products identified (yield, %)[b]
3	BCO	Et_2O	0	**3** (61)
3	BCO	Et_2O–BCOH	23	**3** (75)
3	KO-*tert*-Bu (3 *N*)	*tert*-BuOH	82	Benzene (6)
3	DBN (3 *N*)	CD_3CN	50[c]	Benzene (19)
3	BDMAN	CH_3CN	65–70[c]	Benzene (10); 1,4-dihydrobenzene (57)
3	DBU	DMSO-d_6	73 ± 3	Benzene (68)
5	DBU	CD_3CN	70 ± 5	Benzene (45); 1,4-dihydrobenzene (1)
9	KO-*tert*-Bu (3 *N*)	*tert*-BuOH	30	Benzene (4)
9	DBN (3 *N*)	DMSO	23	Benzene (4)
9	BDMAN	CH_3CN	24	Benzene (36)
9	DBU (3 *N*)	Neat	25 ± 3	Benzene (38)

[a] Unless otherwise noted, 2 equiv of base were employed. [b] Benzene and 1,4-dihydrobenzene were identified by comparison and enrichment using a combination of gc and nmr spectroscopy. The gc was performed on columns of either 3% SE-30 on 100/120 Varaport 5 ft × 0.25 in. or 10% SE-30 on 60/80 Chromosorb W 10 ft × 0.25 in. Yields were calculated using the integration ratios of portions of reaction mixtures as distillates of known weights. [c] No reaction occurred at room temperature.

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[1] (a) G. P. Scott, *J. Amer. Chem. Soc.*, **75**, 6332 (1953); (b) W. E. Truce and F. J. Lotspeich, *ibid.*, **78**, 848 (1956); (c) K. Dimroth and G. Lenke, *Angew. Chem.*, **68**, 519 (1956); (d) E. D. Bergmann and M. Rabinowitz, *J. Org. Chem.*, **25**, 828 (1960); (e) K. Dimroth and G. Lenke, *Chem. Ber.*, **89**, 2608 (1956); (f) R. H. Schlessinger and G. S. Ponticello, *J. Amer. Chem. Soc.*, **89**, 7138 (1967); (g) R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 3017 (1968), 4361 (1969); (h) H. Hofmann and H. Westernacher, *Angew. Chem., Int. Ed. Engl.*, **5**, 958 (1968); (i) J. M. Hoffman, Jr., and R. H. Schlessinger, *J. Amer. Chem. Soc.*, **92**, 5263 (1970).

[2] (a) E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem., Int. Ed. Engl.*, **3**, 510 (1964); (b) E. Vogel, and W. A. Böll, and H. Gunther, *Tetrahedron Lett.*, 609 (1965); (c) E. Vogel and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **6**, 385 (1967).

[3] W. L. Mock, *J. Amer. Chem. Soc.*, **89**, 1281 (1967).

[4] M. J. S. Dewar and N. Trinajstic, *ibid.*, **92**, 1453 (1970).

[5] H. Prinzbach, M. Arguelles and E. Druckrey, *Angew. Chem., Int. Ed. Engl.*, **5**, 1039 (1966).

[6] J. F. Scully and E. V. Brown, *J. Amer. Chem. Soc.*, **75**, 6329 (1953).

[7] E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

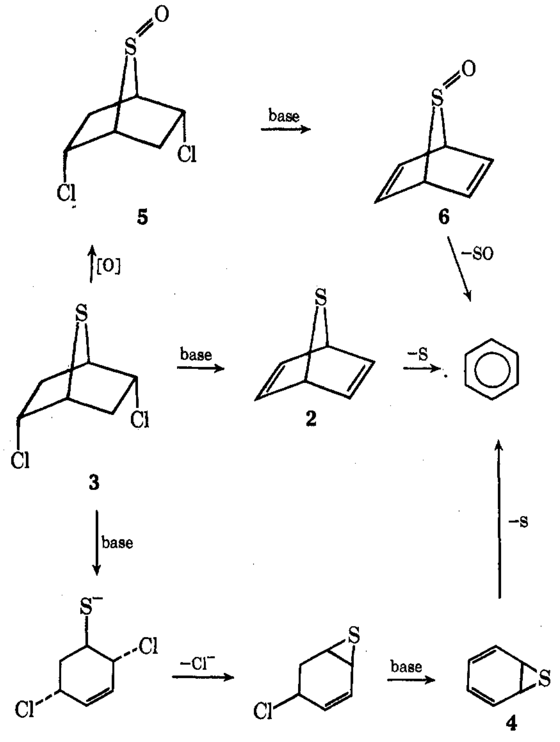
[8] (a) M. Hanack, H. Eggensperger, and R. Hähnle, *Justus Liebigs Ann. Chem.*, **652**, 96 (1962); (b) M. Hanack and R. Hähnle, *Chem. Ber.*, **95**, 191 (1962).

[9] R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Commun.*, 723 (1968).

chlorophenyl sulfides;[10] however, the reason for this singular departure is not understood at present.

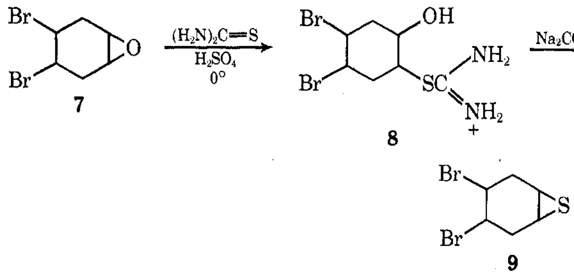
Formation of benzene from **3** may be explained as either proceeding by thermal extrusion of sulfur from **2** or initial anionic ring opening eventually leading to the thianorcaradiene **4** from which sulfur extrusion may take place. This latter pathway would be expected to lead also to thiophenol. Efforts to isolate this product were uniformly unsuccessful and if present it must be a very minor component.

If indeed benzene results from a bridge expulsion of sulfur from **2**,[11] an approach to a more stable diene could be the prior oxidation of **3** to the sulfoxide **5**. The resulting diene, **6**, would have to extrude sulfur monoxide if it were to decompose to benzene. However, reaction of **5** with DBU provides benzene as the sole isolable product in good yield (45%). This observation casts further doubt on a mechanism involving initial anionic ring opening, as the driving force of formation of the mercaptyl anion is removed in the case of **5**. Although likely and reasonable, the intermediacy of **2** cannot be said to be definite. Several of the reactions in Table I were performed in nmr tubes with continuous nmr monitoring. With the exception of BDMAN–acetonitrile system (which exhibited vinyl absorption for 1,4-dihydrobenzene), none of the nmr spectra of the reaction mixtures revealed any olefinic absorption indicative of **2** or **6**.



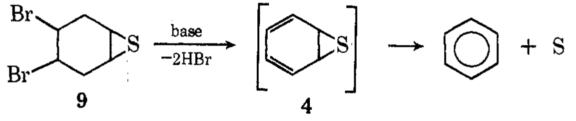
(2)

A much more straightforward route to thiepin synthesis is one similar to that used by Vogel in the synthesis of oxepin.[2] Indeed the final intermediate in Vogel's synthesis, 4,5-dibromocyclohexene oxide (**7**), can be utilized as a logical starting point for the synthesis of thiepin. Compound **7** was easily converted to the thiourium salt (**8**) in high yield by reaction with thiourea. Treatment of **8** with aqueous sodium carbonate resulted in good yields (85%) of white, crystalline 3,4-dibromo-7-thiabicyclo[4.1.0]heptane (**9**).



(3)

When **9** was treated with a variety of bases, including sodium methoxide, triethylamine, potassium *tert*-butoxide, DBN, DBU, and BDMAN in several solvents, isolation of any product even vaguely resembling thiepin could not be accomplished. Certain of these results are summarized in Table I and in each case benzene was the sole identifiable product. With the exception of the BDMAN–acetonitrile system, no olefinic products could be detected. Using BDMAN, an intermediate olefinic material(s) exhibiting complex absorptions at δ 5.5 and 4.75–4.4 was observed; it appeared to decompose to benzene. While the data do not absolutely demand the intermediacy of thianorcaradiene (**4**), it seems likely that this intermediate is formed and quickly eliminates sulfur to form benzene (eq 4). This type of elimination is well established for substituted thiepins, although the thermal stability strongly depends upon the nature of the substituents.[1,11]



(4)

Experimental Section[12]

2,5-Bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (**3**) was prepared by the method of Corey and Block using sulfur dichloride and 1,4-cyclohexadiene in methylene chloride.[7] Sulfide **3** was oxidized to sulfoxide **5**, mp 170–71.5°, in 92% yield through reaction with 1 equiv of *m*-chloroperbenzoic acid in chloroform for 1 week at 0°. The ir spectrum of **5** revealed a very intense band at 1055 cm^{-1} (S=O); the nmr spectrum (CD_3CN) showed absorptions at δ 5.0 (m, 1 H), 4.48 (m, 1 H), 3.69 (m, 2 H), 2.68 (m, 1 H), and 2.37 (m, 3 H); and the molecular weight was confirmed by the mass spectrum.

Sodium 2-*n*-butylcyclohexoxide (BCO) was prepared from sodium and 2-*n*-butylcyclohexanol according to the method of Hanack.[8]

Thiouronium Salt of 7 (8).—To a stirred, ice-cooled mixture consisting of 0.51 ml of concentrated sulfuric acid, 6.0 ml of water, 50 ml of ether, and 1.30 g (17 mmol) of thiourea was added a solution of 4.35 g (17 mmol) of **7** over 1.5 hr. A thick, milky mixture soon resulted and, after stirring for an addi-

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[10] G. H. Schmid and P. H. Fitzgerald, *J. Amer. Chem. Soc.*, **93**, 2547 (1971). See also ref 7 and T. Tsuji, T. Komeno, H. Itani, and H. Tanida, *J. Org. Chem.*, **36**, 1648 (1971).

[11] For reviews of the thermal extrusion of sulfur, see B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, Oxford, 1967; J. D. Louden in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Oxford, 1961, p 299; and R. Grigg, R. Hayes, and J. L. Johnson, *Chem. Commun.*, 1167 (1969).

[12] Elemental analysis was performed by Ilse Beetz, Kronach, West Germany. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were taken on a Varian Model A-60 or a Hatachi R20-B spectrophotometer using TMS as an internal standard. Mass spectra were obtained on an Atlas CH4 spectrometer. Gas chromatographic analysis was performed on either a Varian-Aerograph Hy Fi 600-C or a Varian-Aerograph 1700 using SE30 columns as indicated in the Experimental Section. Melting points are uncorrected.

tional 1 hr at 0–5°, the reaction mixture was allowed to warm to room temperature where stirring was continued for 12 hr. The white solid was then filtered, washed twice with 15 ml of absolute ethanol, and dried (5.24 g, 81%), mp 188° dec.

3,4-Dibromo-7-thiabicyclo[4.1.0]heptane (9).—A solution of sodium carbonate (0.56 g, 5.3 mmol) in 10 ml of water was added over a 30-min period to a slurry of **8** (4.00 g, 5.3 mmol) in 50 ml of water. Stirring was continued for 20 min after which the reaction temperature was raised to 50° for 15 min. After cooling, the mixture was filtered, washed three times with 25 ml of water, and dried. Recrystallization from ether–hexane afforded 2.43 g (85%) of the title compound: mp 59.5–60.5°; nmr (CCl_4) δ *ca.* 4.2 (complex m, 2 H), *ca.* 3.0 (very complex m, 6 H).

Anal. Calcd for $C_6H_8Br_2S$: C, 26.49; H, 2.96; Br, 58.76; S, 11.79. Found: C, 26.62; H, 3.08; Br, 58.60; S, 11.91.

Attempted Dehydrochlorination of 3 with BCO.—Dry nitrogen gas was bubbled through 4.40 ml (3.97 g, 25.6 mmol) of freshly distilled 2-*n*-butylcyclohexanol for *ca.* 15 min. Sodium metal (0.278 g, 12.4 mmol) was added. The magnetically stirred mixture was heated at 70° in a nitrogen atmosphere until all the sodium had reacted. Freshly distilled ethyl ether (9 ml, from $LiAlH_4$) was added to the stirred mixture followed by a solution of 1.00 g (5.5 mmol) of **3** in 4 ml of ether. After 2 days at room temperature, 5 ml of 2 *N* NaOH was added, followed by 12 ml of ether. The ether solution was extracted with 6–10-ml portions of 2 *N* NaOH. The combined alkaline extracts were acidified with HCl and extracted with three 25-ml portions of ether. After drying ($MgSO_4$), the ether was evaporated and the residue (38 mg) was analyzed by tlc (Brinkman PF_{254} and pentane). No thiophenol was observed in the many-component mixture.

The ether solution, after base extraction, was washed with water, washed with saturated NaCl solution, and dried over $MgSO_4$, and most of the ether was removed by distillation. The remaining liquid was analyzed by gc (Varian-Aerography Hy Fi 600-C) using a 5 ft × 0.125 in., 5% SE-30 on 60/80 Chromosorb W, column with a flame ionization detector. No benzene was seen. The mixture contained residual ether, 2-*n*-butylcyclohexanol, and **3**. The presence of **3** was confirmed by tlc. Dry column chromatography[13] on silica gel (pentane eluent) resulted in a 75% recovery of starting **3**.

Dehydrochlorination of 3 with Potassium *tert*-Butoxide.—To 12 ml of freshly distilled *tert*-butyl alcohol was added a mixture of 1.0 g (5.5 mmol) of **3** and 1.7 g (15 mmol) of potassium *tert*-butoxide. The magnetically stirred solution was refluxed under nitrogen for 24 hr. The *tert*-butyl alcohol was distilled in five fractions over a range of 74–82°. By gc (Varian-Aerograph 1700, 5 ft × 0.25 in. column of 30% SE-30 on 100/200 Anaport, thermal detector) and nmr it was determined that 24 mg of benzene was present in the alcohol distillate. The distillation residue was treated with aqueous KOH and then extracted with four 15-ml portions of ether. The combined ether extracts were extracted with four 15-ml portions of 2 *N* NaOH. Acidification of this aqueous solution with HCl followed by ether extraction, drying ($MgSO_4$), and evaporation afforded 13.7 mg of solid material. Analysis of this material by tlc (Brinkman PF_{254} silica gel) indicated a mixture of at least nine components. The presence of thiophenol could not be detected. The ether fraction remaining after initial base extraction was evaporated to yield 0.41 g of residue. Tlc and nmr analysis of this material indicated that it contained *ca.* 0.20 g (20% recovery) of starting **3**.

Dehydrochlorination of 3 with Bis-1,8-dimethylaminonaphthalene (BDMAN).—A mixture of 2.47 g (13.6 mmol) of **3** and 5.94 g (28.0 mmol) of BDMAN (Aldrich) was dissolved in 18 ml of acetonitrile. This solution was heated under nitrogen at 68 ± 3° for 14 days. Analysis of the reaction mixture by gc (Varian-Aerograph 1700, 10 ft × 0.25 in. column of 10% SE-30 on 60/80 Chromosorb W) and nmr indicated that benzene (10%) and 1,4-dihydrobenzene (57%) were present. Positive identification was made with both gc and nmr by enrichment of the reaction mixture with authentic materials.

Dehydrobromination of 9 with Potassium *tert*-Butoxide.—A solution containing 1.01 g (3.7 mmol) of **9** and 1.3 g (11 mmol) of potassium *tert*-butoxide in 15 ml of freshly distilled *tert*-butyl alcohol was stirred under nitrogen at 30 ± 3° for 14 days. Analysis by tlc (PF_{254}) indicated no remaining **9** in a mixture of at least four components. The alcohol was removed by distillation at 80–82° and was shown by gc and nmr to contain 4% benzene. The residue from the distillation was mixed with water and filtered to obtain 0.30 g of solid material. Chromatography on a dry column of silica gel (chloroform eluent) afforded a major fraction of 0.22 g of a very complex mixture from which no pure materials were isolated.

Dehydrobromination of 9 with DBN.—To a solution of 1.8 g (14.6 mmol) of dry DBN in 20 ml of dry DMSO was added 1.00 g (3.65 mmol) of **9** in a dry nitrogen atmosphere (glove bag). The solution was stirred for 12.5 hr at room temperature at which time it was a wine red. The stirred reaction mixture was then immersed in a water bath (20 ± 2°) and a vacuum of 0.4 Torr was applied. Three Dry Ice–acetone traps were placed in the vacuum system and the vacuum was applied for 10.5 hr. After this period the nitrogen atmosphere was restored and stirring at room temperature was continued for 2.5 days with the above vacuum treatment being applied intermittently. Benzene (4%) was found in the first two traps using gc and nmr.

Dehydrobromination of 9 with DBU.—To 88 mg (0.32 mmol) of **9** in an nmr tube was added 0.155 g (1.0 mmol) of DBU. This was performed in a dry nitrogen atmosphere at room temperature. An exothermic reaction occurred immediately which afforded a brown gum. To this was added 0.23 g of DMSO-d_6 and the nmr spectrum of this solution indicated the presence of benzene and the absence of **9**. The presence of benzne was confirmed by gc analysis and the observed yield was calculated to be 38%.

Registry No.—**3**, 6522-40-3; **5**, 32846-51-8; **9**, 32861-43-1.

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[13] B. Loev and M. Goodman, *Chem. Ind.* (*London*), 2026 (1967).