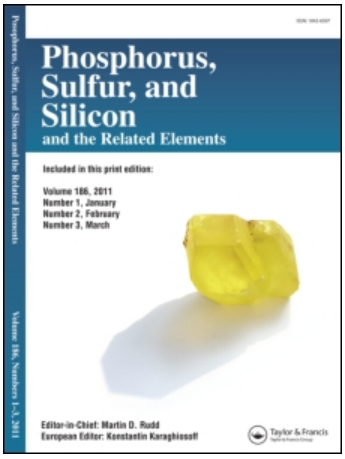

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COMPARATIVE STUDIES ON SYNTHESIS AND PROPERTIES OF PHOSPHORUS AND SULFUR HETEROCYCLES: THE HETERONIN OXIDE SYSTEM

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COMPARATIVE STUDIES ON SYNTHESIS AND PROPERTIES OF PHOSPHORUS AND SULFUR HETEROCYCLES: THE HETERONIN OXIDE SYSTEM

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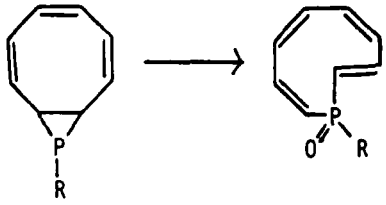
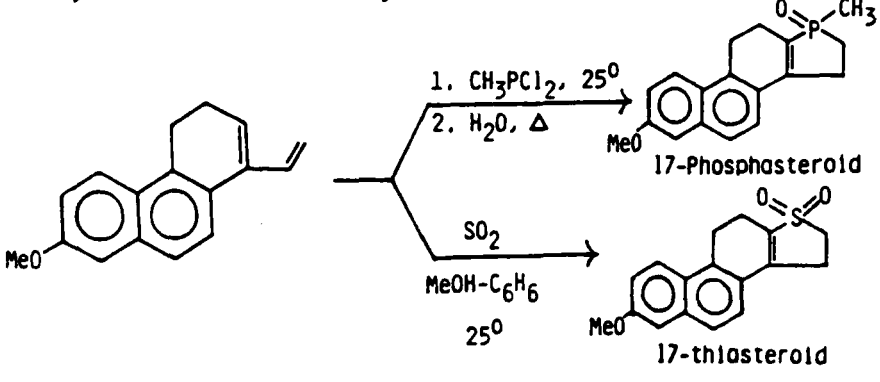
Phosphonin oxides are the first recognizable product on reaction of 9-phosphabicyclo[6.1.0]nona-2,4,6-trienes with peroxides at −15°C.

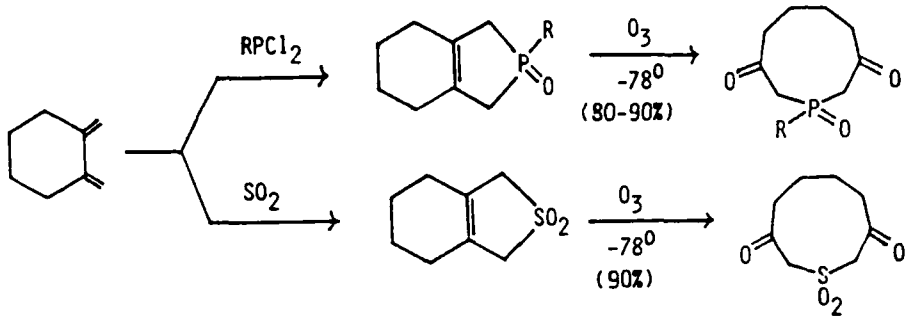


These compounds (R = C_{6H5} or t-C_4H_9) are stable below −15°C, but undergo intramolecular cycloaddition to give *trans*-3a,7a-dihydrophosphindoles on warming to room temperature. The reaction applied to the sulfur counterpart of the phosphine gave only the 9-thiabicyclo[4.2.1]nonatriene system, but oxidation with sodium periodate at −15°C gave a 34% yield of a product identified conclusively as *cis*-3a,7a-dihydrobenzo[b]thiophene oxide, which must have arisen from a thionin oxide. This is the first evidence for the formation of a noncyclic thionin derivative.

While the chemistry of heterocyclic phosphorus and sulfur compounds lacks similarity in some respects and has developed along different lines, it has proved possible to capitalize on synthetic advances with one element so as to gain access to analogous compounds based on the other element. This is particularly true in syntheses based on the formation of 5-membered rings by cheletropic cycloaddition processes. In phosphorus chemistry, this reaction involved cycloaddition of dienes with P(III) halides (the McCormack reaction),[1] followed by hydrolysis of the halogen-containing cycloadducts. In sulfur chemistry, the cycloadduct is formed with sulfur dioxide.[2] Several years ago we employed the McCormack reaction to generate the 5-membered ring of the 17-phosphasteroid system,[3] and later used the same diene to generate the previously unknown 17-thiasteroid system.[4]

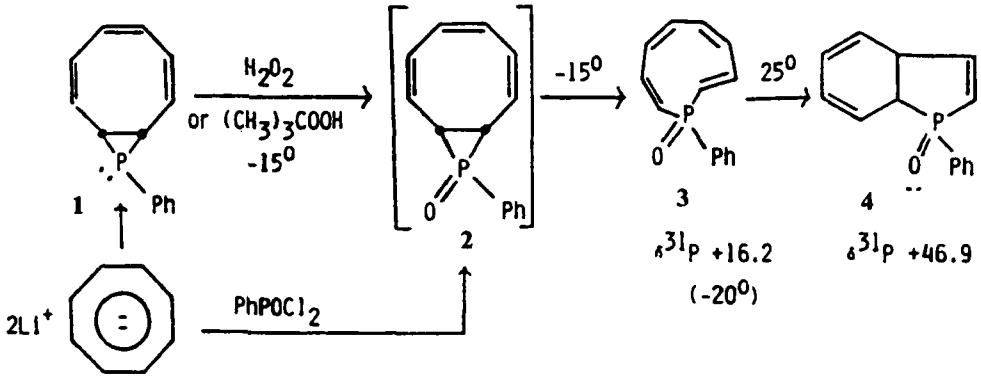


Similarly, a synthesis making available the phosphonane-3,8-dione system[5] led to the creation of the corresponding sulfur heterocycle;[6] both systems have great promise as a source of other 9-membered ring derivatives.

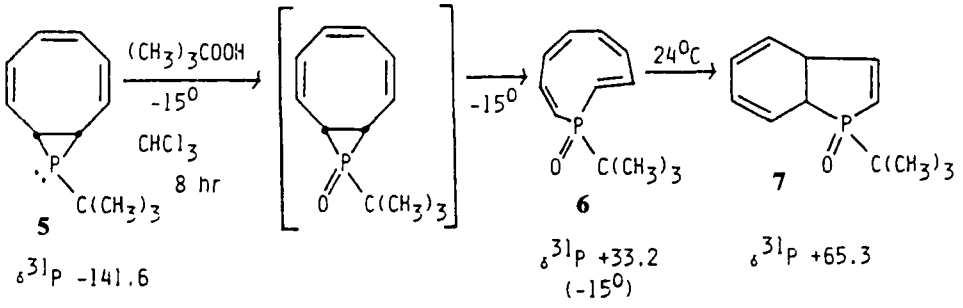


More recently, we discovered[7] a process for the generation of a fully unsaturated, 9-membered ring system containing the phosphine oxide group. This ring system (phosphonin) is of considerable interest, for when phosphorus has an electron pair available, the possibility of cyclic delocalization in a 10 π-electron (aromatic) system is present. Monocyclic phosphonins allowing the test of this possibility have yet to be prepared, and the similarly valuable sulfur (thionin) system has never been created. In this paper, further work in the phosphonin oxide system is described, as is the successful application of the synthetic technique to the sulfur analogue. The results point out the usefulness of the concept that success with one heterocyclic family can indeed guide research in the other.

The phosphonin oxide synthesis[7] is outlined below; its starting point is 9-phenyl-9-phosphabicyclo[6.1.0]nonatriene (**1**) first synthesized by Katz, *et al.*, in 1966.[8] We found that oxidation with peroxides at low temperatures (−15°C) gave, as the first recognizable product, 1-phenylphosphonin oxide (**3**) with one *trans*-double bond. Apparently the increase in coordination of phosphorus in going from **1** to its oxide **2** created additional strain in the 3-membered ring, rendering it unstable even at −15°C. This oxide was also approached by replacing $PhPCl_2$ in the Katz procedure with $PhP(O)Cl_2$. The phosphonin oxide was quite stable below −15°C, allowing the ^{31}P and ^{13}C NMR spectra to be recorded. However, on warming to room temperature, the compound underwent an intramolecular cycloaddition to give a 3a,7a-dihydrophosphindole oxide derivative (**4**).



^{31}P NMR provides a convenient tool for monitoring this conversion, as the shifts are quite different. An approximate half-life for **4** of 4 min. at 24°C was determined by making ^{31}P measurements over a 15 min. period. The low stability of phosphonin oxide **4** interferes with the performance of chemical reactions, especially those designed to remove the oxygen so as to synthesize the highly desired parent phosphine. Attempts to improve the stability by using other P-substituents, or by including C-substituents, are now in progress. At this time it can be reported that replacing P-phenyl by P-*tert*-butyl does double the half life (to 8 min.) but the instability is still too high as to permit successful deoxygenation reactions.



Nevertheless the new phosphonin oxide **6**, prepared from the recently synthesized[9] P-*tert*-butyl phosphirane **5**, is of value in providing a particularly well-resolved ^{13}C NMR spectrum (Figure 1) which convincingly reveals the presence of the *trans* double bond that is expected from orbital symmetry considerations for thermal opening of the 3-membered ring.[10] Tentative assignments of the signals are shown on the spectrum.

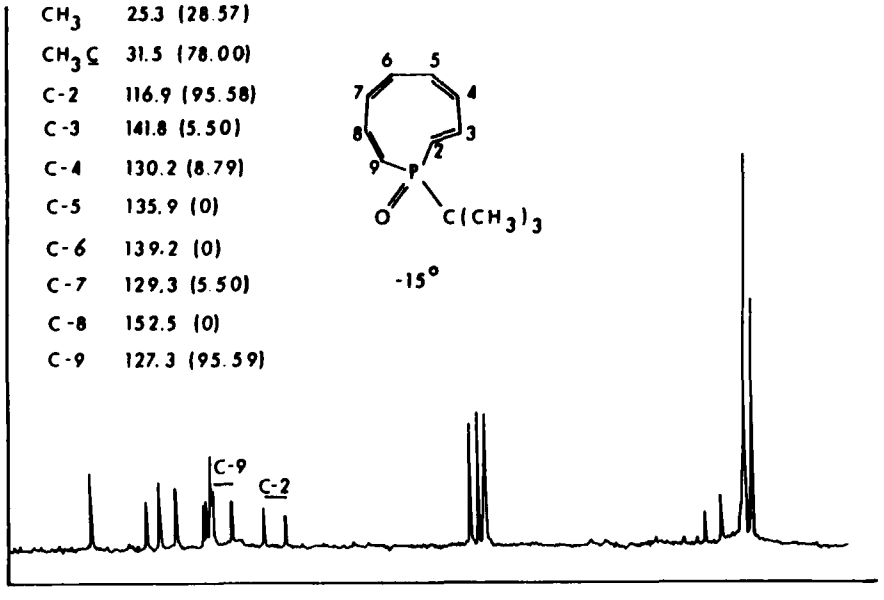
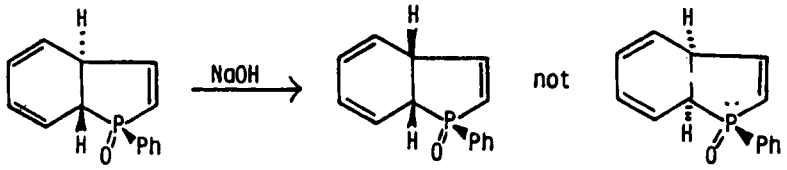


FIGURE 1 ^{13}C NMR spectrum of 1-*tert*-butylphosphonin oxide.

The stereochemistry of the ring fusion in the dihydrophosphindole cycloadducts is of importance; it is expected to be *trans*, based on orbital symmetry as well as on results obtained for the cycloaddition of *cis*[3],*-trans*-cyclononatetraene[11] and *cis*[3],*trans*-oxonin.[12] A particularly useful spectral property for establishing this stereochemistry is the size of the coupling constant for the protons on the ring fusion carbons (H-3a, H-7a). As seen in Table I, the constant is of unusually large size for *trans* derivatives, and significantly smaller for *cis* derivatives. Values for the products from the phosphonin oxides were clearly of the size (~ 20 Hz) for the *trans* structure.

Further confirmation came in the case of the P-phenyl derivative by showing that the ^{31}P NMR spectrum was different from those of the two known[13] isomers with *cis*-fusion, and also by epimerization of the phosphonin product to form one of the *cis*-isomers. The epimerization must occur at C-3a, if it is assumed that no change in the configuration at phosphorus takes place and since the relative configurations at C-7a and at P are known[7] in **4**. In a very recent paper, it has also been reported[14]

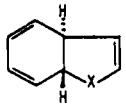
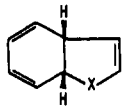


4

that thermal treatment (refluxing toluene) of the phosphiranes (e.g., **5**) caused rearrangement to the dihydrophosphindole phosphine system with *trans*-fusion ($^3J_{HH}$ = 20 Hz), probably as a result of the intermediacy of the *cis*[3],*trans*-phosphonin. We had previously tried to effect the conversion of phosphirane **1** to the phosphonin under flash vacuum pyrolysis conditions (400°C, 1.5 mm) with immediate trapping of the volatile product on a dry ice condenser, but received only

TABLE I

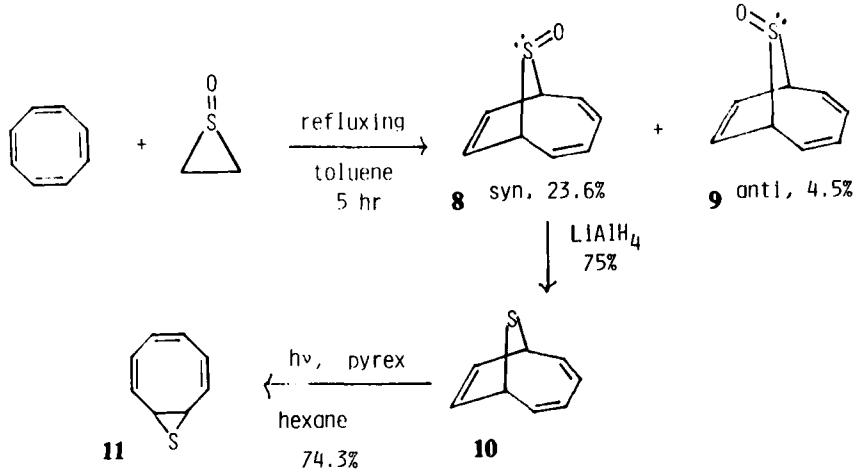
H-3a,H-7a Coupling Constants

	CR_2	O	$N—CO_2Et$	S	P(Ph)O	P(Bu-t)O
	12[a]	7[b]	—	12[c]	12	—
	20[a]	23.5[d]	24[b]	—	~ 20	18

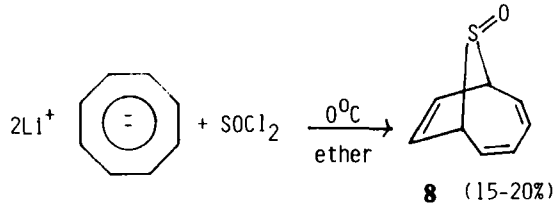
[a] S. W. Staley and J. J. Henry, *J. Am. Chem. Soc.*, **91**, 1239 (1969).
[b] A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 1969, 1521.
[c] Ref.[15b].
[d] Ref.[12].

derivatives containing another ring system (9-phosphabicyclo[4.2.1]nona-2,4,7-triene) encountered also by Katz[8] in solution reactions.

Since the thiirane containing the ring system of the phosphiranes **1** and **5** is a known compound,[15] an entry into the thionin system seemed possible if the phosphorus-sulfur analogy prevailed. Accordingly, thiirane **11** was synthesized by the published procedure.

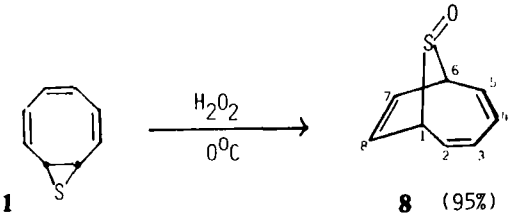


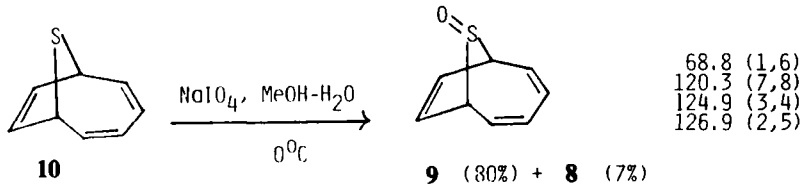
We also devised a new scheme for obtaining intermediate product **8**, which involved the reaction of thionyl chloride with the dianion of cyclooctatetraene. Although the



yield is only 15–20%, this process is advantageous in that a single isomer is formed, and is easily isolated by column chromatography or silica gel (elution by ethyl acetate).

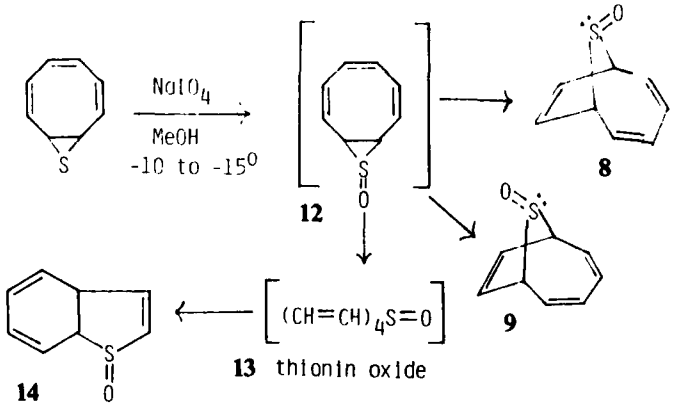
Application of the low-temperature peroxide reaction to thiirane **11** resulted only in a high yield of the 9-thiabicyclo[4.2.1]nonatriene derivative **8**. Its ^{13}C NMR spectrum was identical to that for **8** obtained in the SO transfer to COT, and quite different from that of the *anti*-isomer **9**, which was prepared by oxidation of the bridged sulfide **10** with $NaIO_4$.





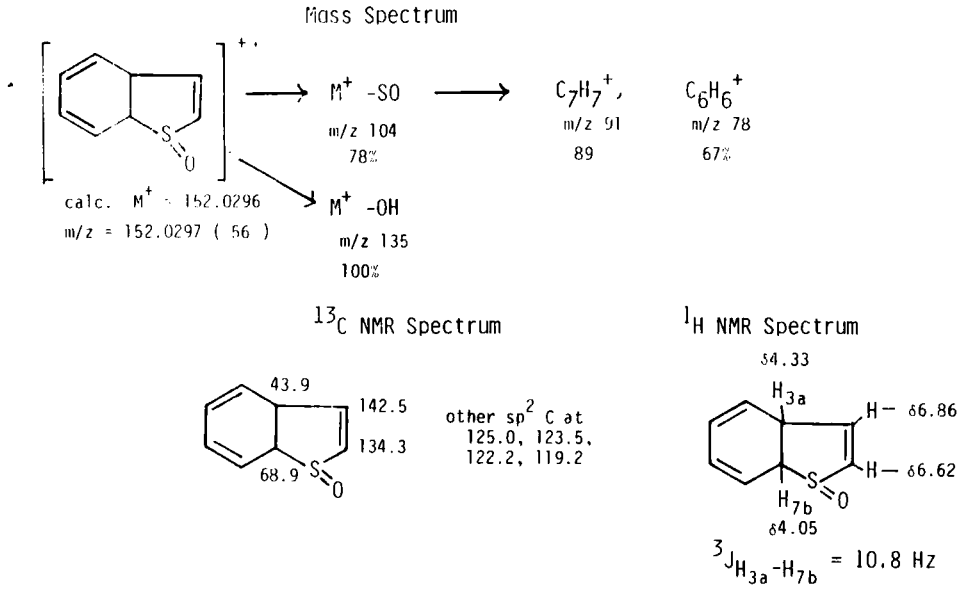
10 **9** (80%) + **8** (7%)

This oxidation result is quite different from that experienced with the phosphiranes, and here the P,S analogy has not proved useful. However, the desire to attain the thionin system was strong enough to continue the investigation with the use of other oxidizing agents, and some success was achieved with the use of $NaIO_4$. When conducted by the slow addition of a water solution of the oxidant to a methanol solution of the thiirane at $-10°$ to $-15°C$, the formation of bridged sulfoxides **8** and **9** was repressed and another product predominated. The substance proved to be 3a,7a-dihydrobenzo[b]thiophene 1-oxide (**14**) and was isolated in 34% yield after medium pressure liquid chromatography (silica gel; ethyl acetate) to separate it from **8** (16%) and **9** (14%). The proportion of **14** was diminished if the reverse addition was made at 0°C, and indeed an earlier mention (as a footnote, without details[15b]) of the periodate oxidation of **11** did not include the observation of this product.



As for oxidation of the phosphirane, the initial product (sulfoxide **12**) must undergo spontaneous ring opening. But unlike the phosphorus system, where a phosphonin oxide can then be detected, the thionin oxide produced by the ring opening must also be quite unstable, at least under the conditions required before a product analysis is possible. (An advantage in working with the phosphorus compound is that ^{31}P NMR can be used immediately, at low temperature, to detect the initial product.) The intermediacy of a thionin oxide (**13**) is a *requirement* in an explanation of the formation of the dihydrobenzothiophene oxide **14**.

The structure proof of **14** rests on mass spectral, ^{13}C NMR, and ^{1}H NMR spectral evidence as summarized below. The ^{1}H NMR spectrum was complex even at 250 MHz and in order to determine the chemical shifts and coupling constant, it was necessary to employ computer simulation. The experimental and calculated spectra are shown in Figure 2, and gave the chemical shifts recorded above. The particularly



important coupling for stereochemical analysis is $^3J_{H\text{-}3a,H\text{-}7a}$, and was found to have a value of 10.8 Hz. This value is indicative of *cis*, rather than *trans* ring fusion, which was hardly expected in view of the *trans* stereochemistry clearly established for the dihydrophosphindoles from phosphonin-ring cycloaddition. The point is a critical one, and additional structure proof was required. This was first attempted by converting **14** (an oil) to a solid derivative **15** for X-ray analysis.

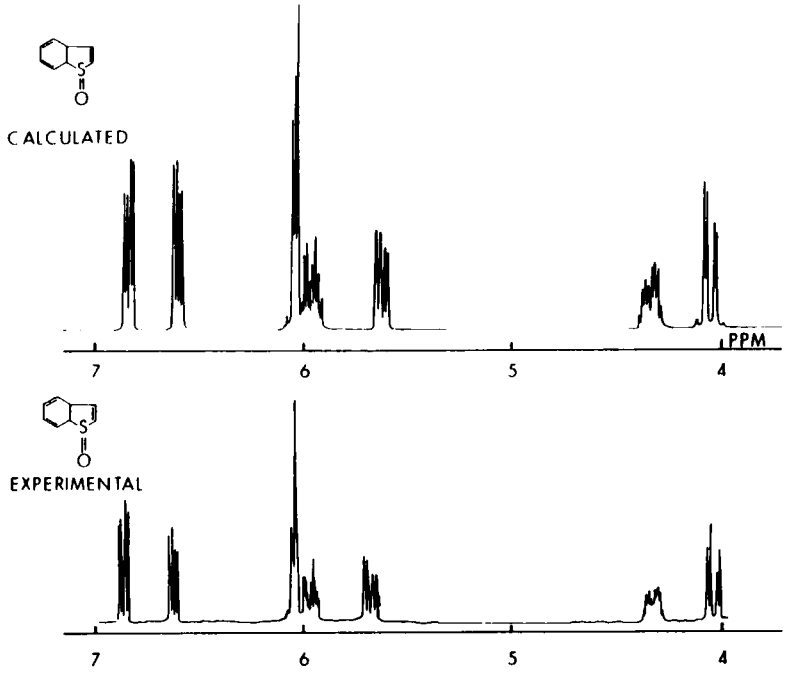
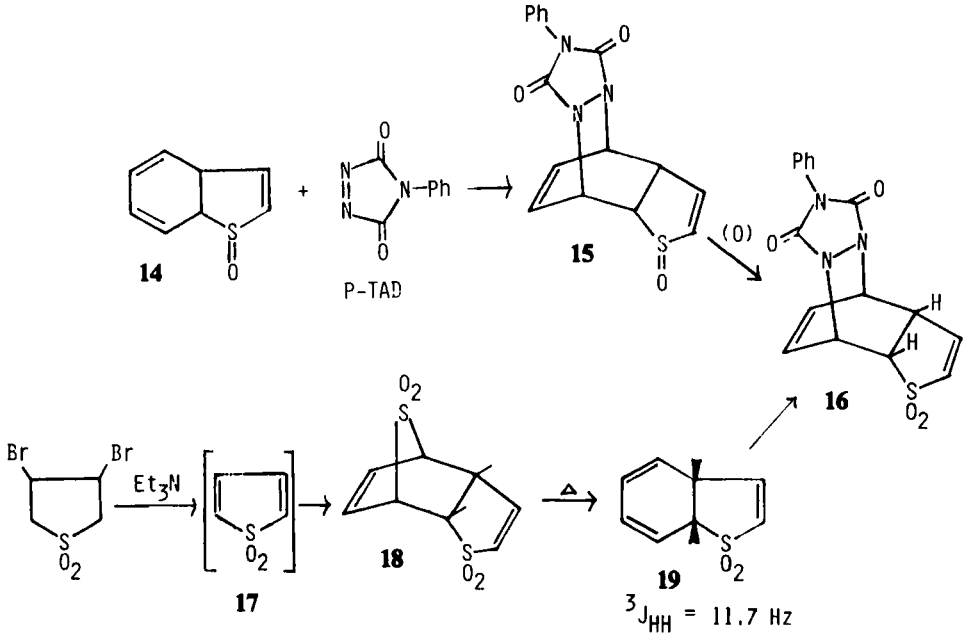
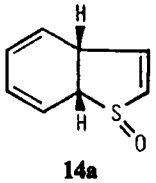


FIGURE 2 250 MHz ^{1}H NMR spectrum of *cis*-3a,7a-dihydrobenzo[b]thiophene oxide.

No crystals suitable for the analysis could be obtained, however, but the product proved of value because it underwent clean oxidation with *m*-chloroperbenzoic acid to the sulfone **16**, which could be obtained independently and with *known* (*cis*) stereochemistry from the SO_2 elimination from the dimer (**18**) of thiophene sulfone.[16]

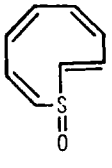


Identity of the P-TAD adducts was established by ^1H NMR spectra (in $(CD_3)_2SO$); melting points were not directly useful, since decomposition occurred, but the two products, and a mixture, all gave exactly the same tracing on differential scanning calorimetry.[17] The ring fusion in sulfoxide **14** is unequivocally established as *cis* (**14a**). It cannot be stated at this time how this ring fusion arises; it is possible that

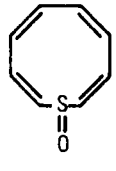


14a

the fusion is initially the expected *trans* and epimerization then occurs, or that the initially formed *cis*[3],*trans*-thionin oxide (**13a**) rearranges to the all-*cis* (**13b**) isomer, which would give a *cis*-fused cycloadduct.



13a



13b

Another point that requires further attention is the differing behavior of thiirane **11** on peroxide and on periodate oxidation. A very recent paper[18] has presented some kinetic results on the periodate oxidation of sulfides, and proposes a mechanism wherein a "one-step electrophilic oxygen transfer from IO_4^- to sulphide through a polar product-like transition state" occurs. Oxidations with peroxides are electrophilic oxygen-transfer reactions that proceed through a heterolytic splitting of the O—O bond that is promoted by proton transfer processes.[19] It is not possible yet to associate differences in oxidation mechanism with the differences in reaction pathway found for thiirane **11**. The differing behavior of the phosphirane and thiirane to peroxides also rests on a mechanistic difference; phosphine reactions with hydroperoxides may involve a pentacoordinate, dioxyphosphorane intermediate (as with dialkylperoxides), although an ionic intermediate is also a possibility.[20] Either would be quite different from the sulfide reaction mechanism. In any case, the results of our study in comparative phosphorus-sulfur heterocyclic chemistry have revealed sufficient analogy to encourage continuation of this line of research on synthetic methods, although subtle mechanistic or reactivity differences can exist and can lead to different results. The approach has given rise to the first demonstration of the existence of a thionin oxide, albeit of a transient nature.

ACKNOWLEDGMENT

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