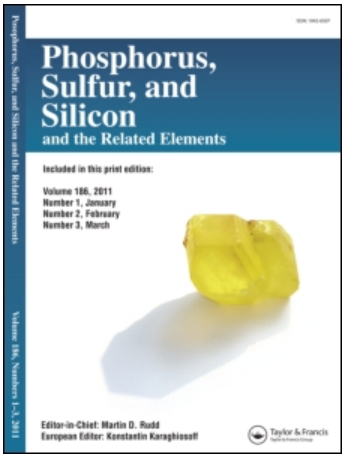

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Some New Aspects of Thiepine and Thiazepine Chemistry

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SOME NEW ASPECTS OF THIEPINE AND THIAZEPINE CHEMISTRY

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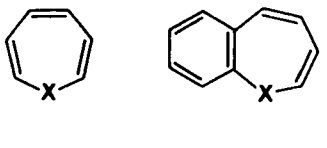
Abstract 1) 1-Benzothiepineiron tricarbonyl was synthesized as a first example of thiepine-metal complex. On oxidation and decomplexation the complex gave 1-benzothiepine 1-oxide as thermally labile compound. 2) Thermolysis of a stable monocyclic thiepine gave the sulfur extruded benzene derivative together with the sulfurated product, the structure of which was confirmed by X-ray analysis. 3) The ring expansion reaction of 2,6-di-tert-butyl-4-azido-4-R-thiopyrans resulted in the formation of 1,3-thiazepine derivatives instead of the expected 1,4-thiazepines.

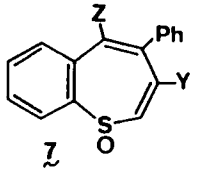
THIEPINE-METAL COMPLEX[1]

It is well accepted that unlike thiepine dioxide (**3**),[2] which has been isolated as a stable crystalline compound, thiepine itself (**1**) and its oxide (**2**) are considered to be extremely unstable molecules.[3] On the other hand, in an annelated thiepine series, 1-benzothiepine (**4**)[4-5] and its dioxide (**6**)[6-8] are well characterized, however, 1-benzothiepine 1-oxide (**5**) has never been



1: X = S
2: X = SO
3: X = SO_2

4: X = S
5: X = SO
6: X = SO_2

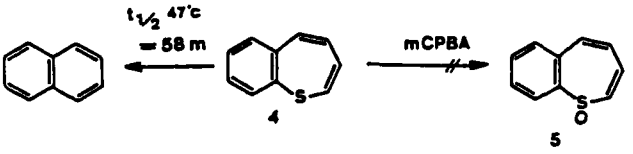


7

a: Y = $OCOCH_3$, Z = OCH_3
b: Y = Z = OCH_3
c: Y = OCH_3, Z = $OCOCH_3$
d: Y = Z = $OCOCH_3$

synthesized. Hitherto known thiepine oxides, which are confined to heavily substituted 1-benzothiepine oxides such as **7a-7d**,[9] are thermally less stable than the corresponding 1-benzothiepines. Although 1-benzothiepine (**4**) can be handled below 0 °C without serious decomposition, **4** easily extrude sulfur with half-life of 58 min at 47 °C[4b] to give naphthalene. In view of the precedents, the oxide **5** would be less stable than **4** (Scheme 1). Therefore,

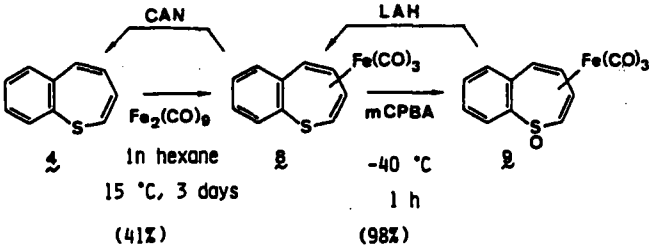
SCHEME 1



synthesis of **5** has to be done using an appropriate precursor under very mild conditions. Lack of success in our previous attempts[7] to obtain **5** by direct oxidation of **4** with m-chloroperbenzoic acid (mCPBA) prompted us to take advantage of a transition metal complexation strategy[10] for the synthesis of **5**.

On treatment with iron ennacarbonyl in hexane at 15 °C for 3 days, 1-benzothiepine (**4**) was converted into its iron tricarbonyl complex (**8**) in 41% yield as stable yellow needles of mp 83.5 °C. Oxidation of **8** with an equivalent mCPBA in chloroform at -40 °C gave its oxide **9** quantitatively. Inversely, **9** was reduced with LAH to give **8** which can be decomplexed with ceric ammonium nitrate (CAN) to the starting **4** in good yield (Scheme 2).

SCHEME 2



The η^4-complexation at the diene moiety of the thiepine ring in **8** was confirmed based on its ^{1}H-NMR spectrum (500 MHz, Figure

1) which exhibited substantially high field chemical shifts of H-2 and H-5 at δ 3.89 and 4.29, respectively, together with two ddd signals at δ 5.04 and 5.24 assignable to H-4 and H-3, respectively. The complex **8** provides a first example of thiepine-transition metal complex.

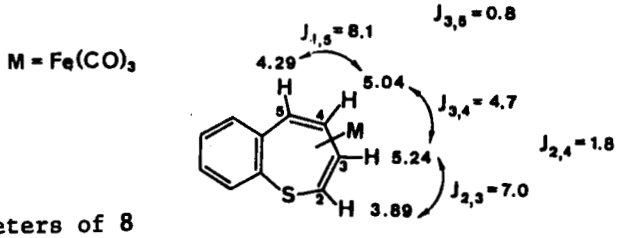
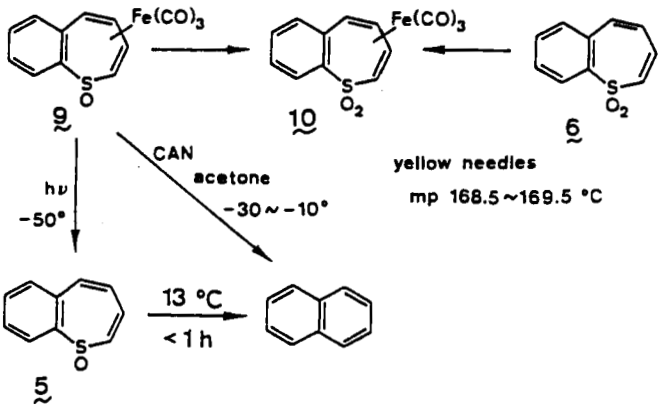


FIGURE 1

^{1}H-NMR parameters of **8**

The structure of **9** was unequivocally established through its spectral data along with the chemical reactions as shown in Scheme 3. Thus, further oxidation of **9** with mCPBA gave the dioxide complex **10** which was identical in all respects with the authentic sample prepared from the known 1-benzothiepine dioxide (**6**).[6,7]

SCHEME 3



In order to obtain free oxide **5** by oxidative decomplexation, **9** was treated with CAN in acetone at -30 °C. The TLC monitoring of the reaction mixture reveals that a new polar spot appears with decreasing less polar spot due to **9**. However, after 3 h at -10 °C the reaction mixture exhibited neither polar nor less polar spot

on TLC examination. Work-up of the reaction mixture afforded naphthalene quantitatively suggesting that the species responsible for the new polar spot might be assigned to 1-benzothiepine oxide (**5**) which extrudes sulfur oxide under the reaction conditions. On the other hand, irradiation of a dilute THF solution of **9** with a 400-W high pressure mercury lamp at -50 °C resulted in the formation of **5** which could be isolated and purified by low temperature column chromatography on silica gel with hexane at -40 °C.

The desired oxide **5** forms pale yellow needles at -40 °C. The indication of its structure came from the 200 MHz ^{1}H-NMR spectrum at -30 °C in CD_2Cl_2 (Figure 2) which exhibited two doublets at δ 6.08 (H-2) and 7.38 (H-5), two doublet of doublets at δ 6.38 (H-3) and 6.69 (H-4) along with aromatic proton multiplet at δ 7.4-8.0 in a ratio of 1:1:1:1.2:6.1 suggesting small contamination with naphthalene. The observed chemical shifts and coupling

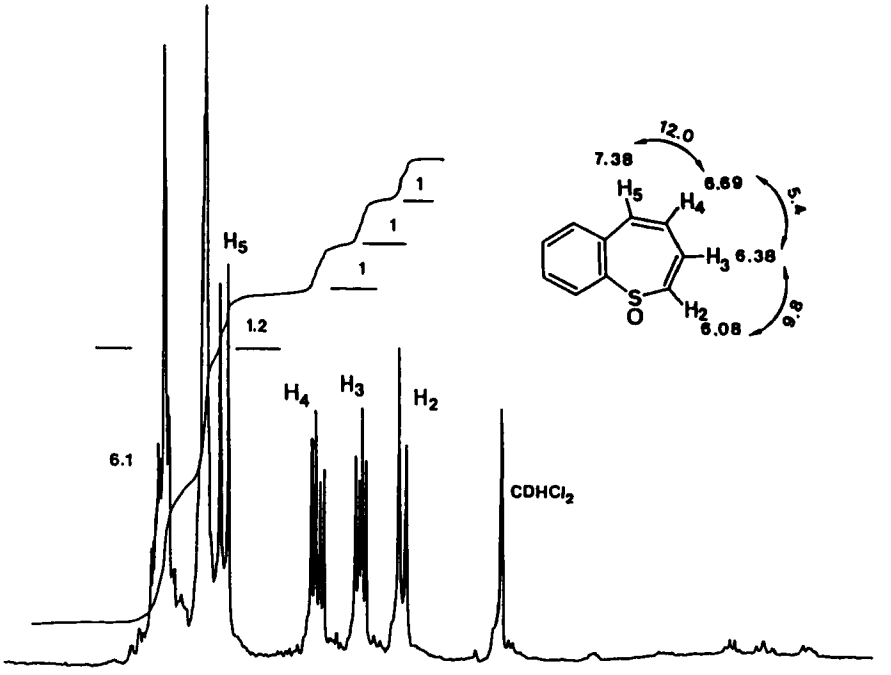
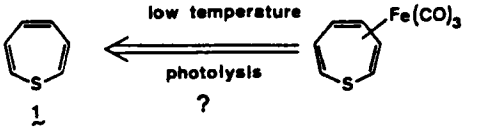


FIGURE 2. ^{1}H-NMR spectrum of **5** (200 MHz, at -30 °C)

constants are quite similar to those of 1-benzothiepine (**4**).[5] This implies no appreciable change in electronic and geometrical structures on going from **4** to its oxide **5**. As would be expected, **5** was found to be substantially less stable than **4** and the ^{1}H-NMR signals due to **5** were completely replaced by those of naphthalene within 1 h at 13 °C.

SCHEME 4

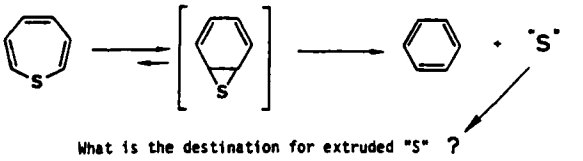


The success in decomplexation of **9** by means of low temperature photolysis suggests the possibility to detect an elusive parent thiepine (**1**) through its transition metal complex (Scheme 4). Efforts to achieve this goal are now in progress.

DESULFURATION AND SULFURATION OF MONOCYCLIC THIEPINES[11]

One of the most significant characteristics of thiepine is ready sulfur extrusion reaction to produce the corresponding aromatic compound.[3] A question which has to be answered is that what is the destination for extruded sulfur atom ?

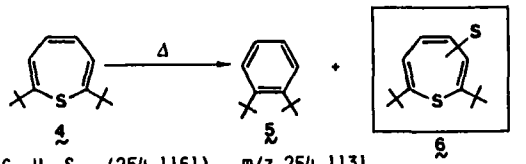
SCHEME 5



When 2,7-di-tert-butyl-4,5-dimethylthiepine (**1**)[12] was thermolyzed in decalin at 150 °C, 4,5-di-tert-butyl-o-xylene (**2**) was obtained along with a small amount of by-product **3**. The exact mass measurement showed that the by-product **3** contained two sulfur atoms ($C_{16}H_{26}S_2$) implying that **3** must be a sulfurated thiepine.

The similar transformation was also observed in the thermolysis of 2,7-di-tert-butylthiepine (**4**).[13] Thus, the products were found to be o-di-tert-butylbenzene (**5**) and a sulfurated product **6** (Scheme 6). The ^{1}H-NMR spectrum of **6** required the presence of equivalent

SCHEME 6

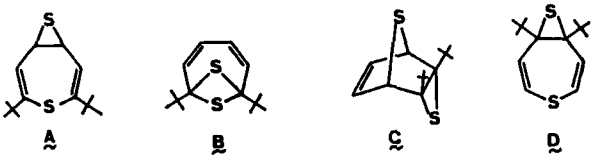


$C_{14}H_{22}S_2$ (254.1161), m/z 254.1131

^{1}H-NMR : δ = 1.17 (s, 18H), 5.14 (AA'BB', 4H)

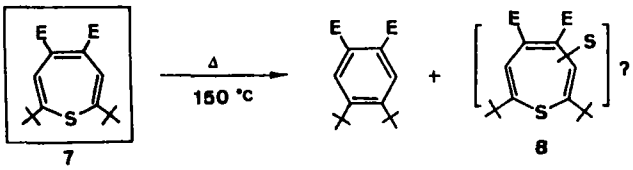
^{13}C-NMR : δ = 30.3 (q), 34.6 (s), 60.7 (d), 115.7 (d), 155.2 (s)

"Tow-fold symmetry"



tert-butyl groups at δ 1.17 and a narrow AA'BB' multiplet centered at δ 5.14 implying at least a two-fold symmetry, the situation also confirmed by the ^{13}C-NMR spectrum which showed only five carbon resonances. At first glance, structures (**A**) to (**D**) might be considered as the possible candidates for **6**. However, the observed NMR data are inconsistent with any of the structures **A** - **D**. Final structural proof can be obtained by a single crystal X-ray analysis of a well crystallized derivative. For this purpose we have chosen 2,7-di-tert-butyl-4,5-bis(ethoxycarbonyl)thiepine (**7**)[14] as a precursor for the sulfurated sample. The thiepine **7**

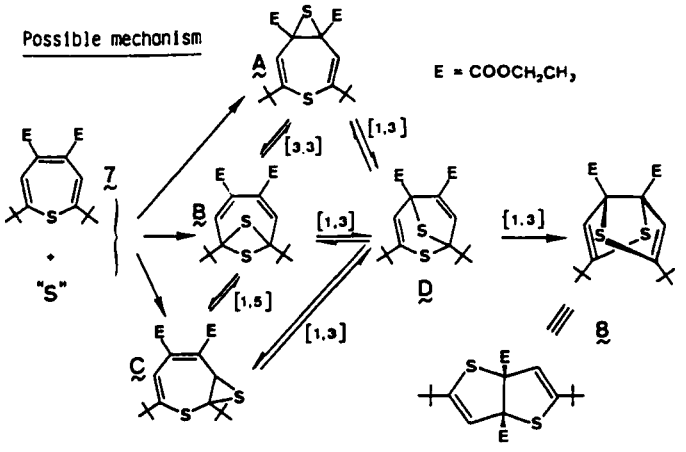
SCHEME 7



was thermolyzed in toluene at 150 °C to give di-tert-butylphthalic ester accompanied by a sulfurated product **8** as pale yellow crystals, mp 90-92 °C (Scheme 7), which are suitable for X-ray analysis. As the ORTEP drawing shown in Figure 3, the basic skeleton of **8** was found to be a 2,6-dithiabicyclo[3.3.0]octadiene. The methylene protons of the ethyl esters in the ^{1}H-NMR spectrum of **8** were nonequivalent and appeared as part of an ABX_3 pattern. Such diastereotopic behavior exhibited by ethyl group is well known[15] and may be explained by the presence of a proximal chiral center.

A likely mechanism for the formation of **8** was shown in Scheme 8. The thermally extruded sulfur, which is in a highly reactive monomeric form,[16] adds to **7** in 1,2- and/or 1,6-fashion to produce intermediates **A**,**C**, and **B**, respectively, all of which can be convertible through [1,3]shift of the C-S bond into **D**. The initial sulfur addition to **7** in a 1,4-fashion would produce **D** also. Consecutive [1,3]shift may afford the final product **8**.[17]

SCHEME 8



The structural elucidation of **8** provides a concrete evidence for the destination of the sulfur atom liberated thermally from the thiepine.

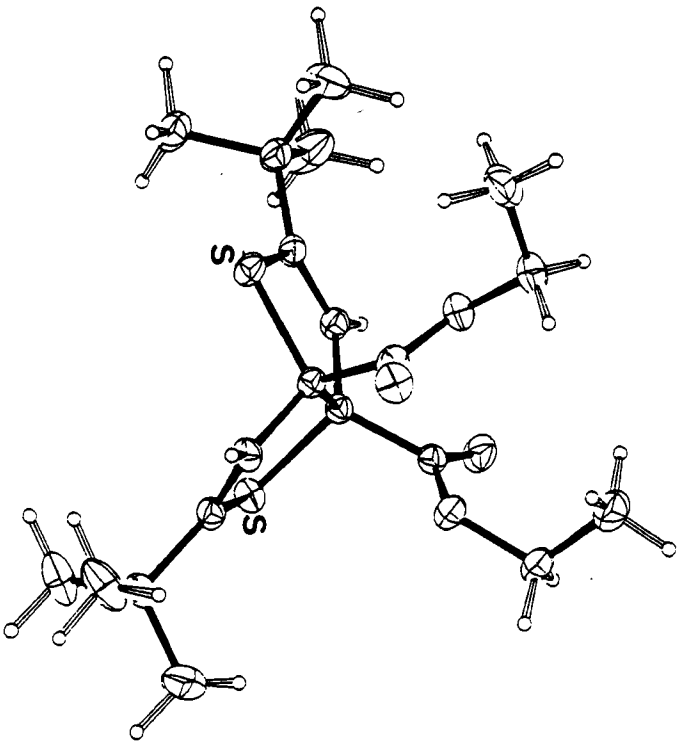
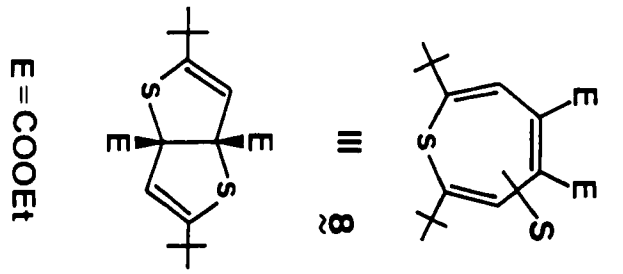


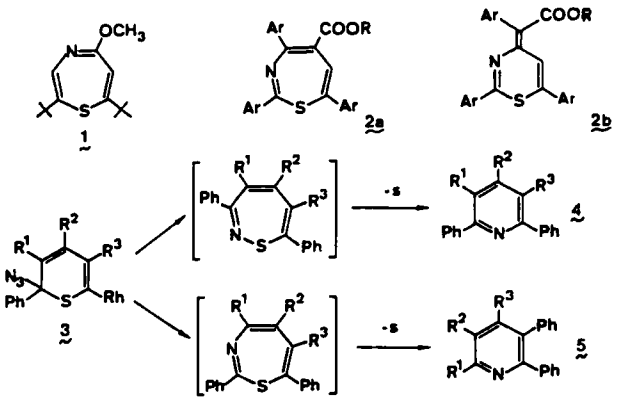
FIGURE 3. ORTEP drawing of 8.



MONOCYCLIC THIAZEPINES[18]

Like thiepines, thiazepines are also thermally unstable and the reported examples are confined to the annelated derivatives.[19-20] Although the synthesis of some monocyclic 1,3-thiazepine derivatives **2a** has been reported,[21] both the spectroscopic data and their thermal stabilities arouse the suspicion on their thiazepine structures.[22] A most likely alternative would be a structure **2b** which is consistent with the reported properties. Furthermore, ring expansion reactions of the azide **3** resulted in the formation of the pyridine derivatives, **4** and **5**, instead of the expected 1,2- and 1,3-thiazepines[23] (Scheme 9). This reflects the thermal

SCHEME 9

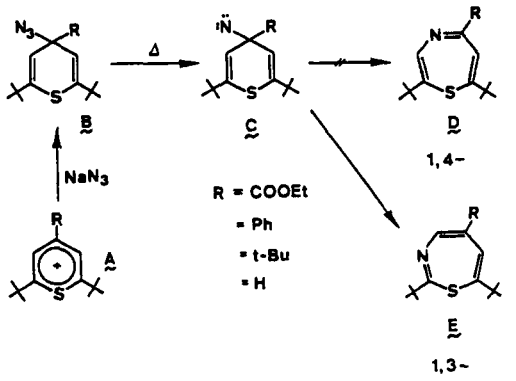


instability of monocyclic thiazepine ring system. The great stability of monocyclic thiepine caused by 2,7-di-tert-butyl substitution has already been confirmed by the synthesis of a monocyclic 1,4-thiazepine **1**.[24] To obtain further insight into thiazepine chemistry, we examined the synthesis of monocyclic thiazepines.

Our basic synthetic route and the compounds examined are shown in Scheme 10. Starting materials are the 4-substituted 2,6-di-tert-butylthiopyrylium cations (**A**) which are converted into the

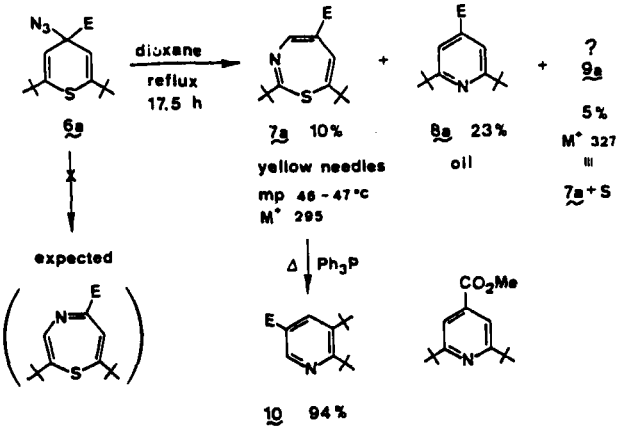
corresponding azides (**B**). In all cases, the site of the azide group was confirmed at 4-position through their symmetrical ^{1}H-NMR patterns. Thermolysis of **B** would lead to the ring expanded 1,4-thiazepines (**D**). Contrary to our expectation the products obtained were not 1,4-thiazepines (**D**) but 1,3-thiazepines (**E**).

SCHEME 10



Thus, on thermolysis in refluxing dioxane the azide **6a** is converted into three isolable products, **7a**, **8a**, and **9a** (Scheme 11). The structure of **8a** was found to be 2,6-di-tert-butyl-4-ethoxycarbonylpyridine. The product **7a** can be established as 2,7-di-tert-butyl-5-ethoxycarbonyl-1,3-thiazepine which was supported by the fact that the reaction **7a** with PPh_3 readily gave 2,3-di-tert-butyl-5-ethoxycarbonylpyridine (**10**) quantitatively. It

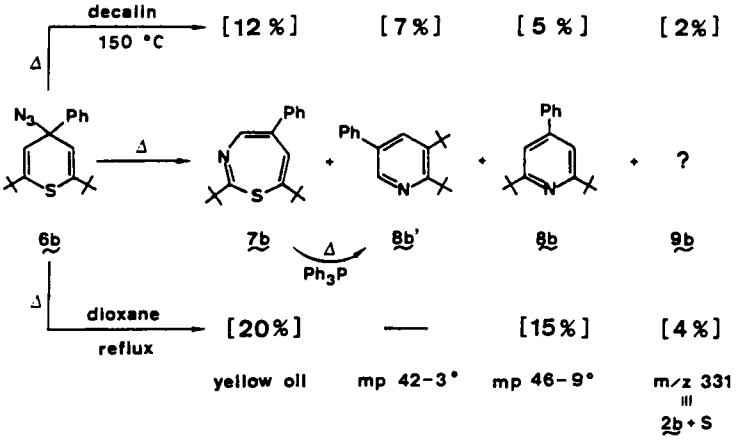
SCHEME 11



should be stressed that, in spite of the careful examination, no anticipated 1,4-thiazepine derivative could be detected in the reaction mixture. Elemental analysis and mass spectrometry showed that the minor product **9a** contained two sulfur atoms ($C_{16}H_{25}NO_2S_2$).

When 4-azido-2,6-di-tert-butyl-4-phenylthiopyran (**6b**) was thermolyzed in refluxing dioxane, again 2,7-di-tert-butyl-5-phenyl-1,3-thiazepine (**7b**), 2,6-di-tert-butyl-4-phenylpyridine (**8b**), and sulfurated product **9b** were obtained in 20%, 15%, and 4% yields, respectively (Scheme 12). However, when the thermolysis was carried out in decalin at 150 °C, 2,3-di-tert-butyl-5-phenyl-pyridine (**8b'**) was obtained with the decreasing yield of **7b**. Under the reaction conditions, **7b** extruded sulfur atom to give **8b'**.

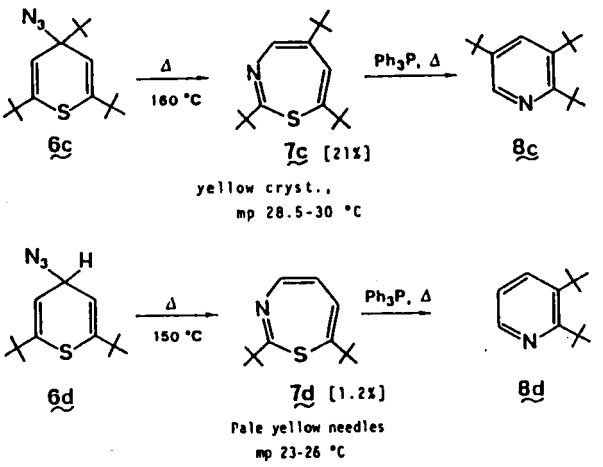
SCHEME 12



On thermolyses in decalin at 150 - 160 °C, 4-azido-2,4,6-tri-tert-butylthiopyran (**6c**) and 4-azido-2,6-di-tert-butylthiopyran (**6d**) gave the corresponding 1,3-thiazepines, **7c** and **7d**, respectively, without any other isolable products (Scheme 13). The formation of 2,7-di-tert-butyl-1,3-thiazepine (**7d**), though very low yield, provides a simplest example of 1,3-thiazepine.

The ^{1}H-NMR spectrum (500 MHz) of the simplest 1,3-thiazepine **7d** (Figure 4) exhibited well separated AMX signals at δ 7.13 (H-

SCHEME 13



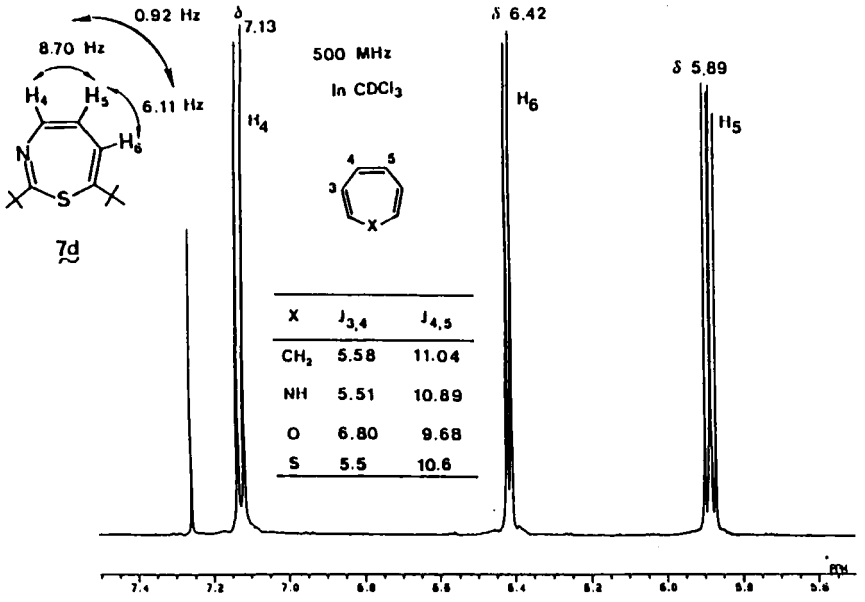


FIGURE 4. ^{1}H-NMR spectrum of **7d** (500 MHz, $CDCl_3$).

4), 5.89 (H-5), and 6.42 (H-6) with the coupling constants of $J_{4,5}$ = 8.70 Hz, $J_{5,6}$ = 5.89 Hz, and $J_{4,6}$ = 0.92 Hz. The difference between two vicinal coupling constants, $J_{4,5}$ and $J_{5,6}$, is smaller than those of cycloheptatriene,[25] azepine,[25-26] oxepine,[25] and thiepine[13] suggesting that the geometrical structure of 1,3-thiazepine system was perturbed by an additional nitrogen atom to some extent.

The electronic spectra of 2,7-di-tert-butyl-1,3-thiazepine derivatives compared with that of 2,7-di-tert-butylthiepine are illustrated in Figure 5. Both spectra of **7d** and the corresponding thiepine are essentially the same and the longest absorption bands exhibited slight hypsochromic and hyperchromic effects on going from the thiepine to the thiazepine similar to those of benzene and pyridine.[27]

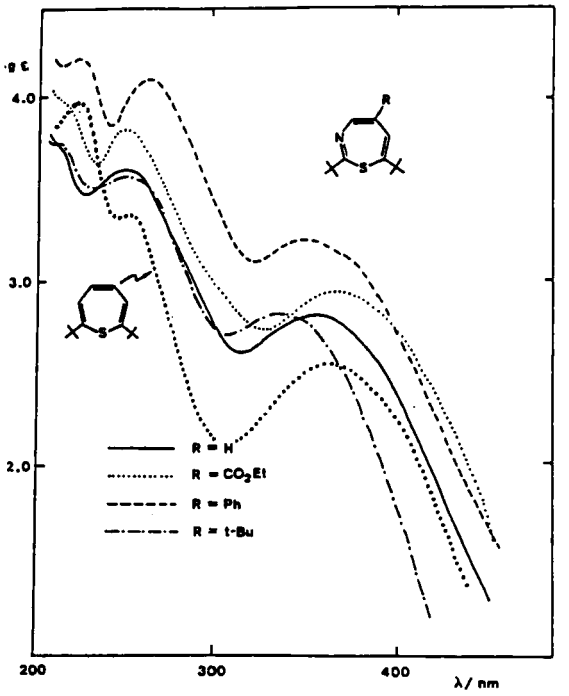
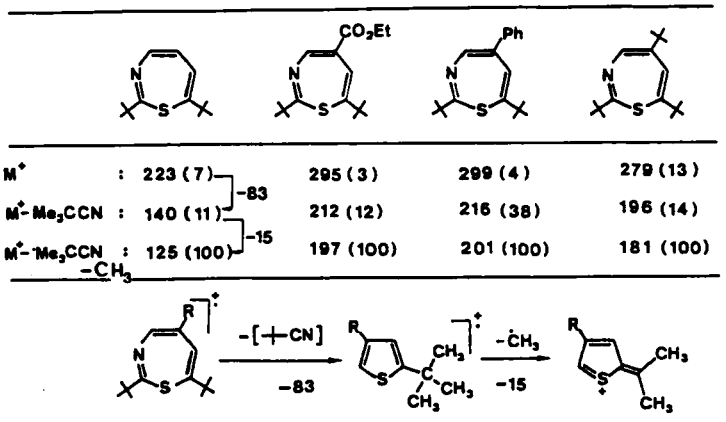


FIGURE 5. Electronic spectra of 1,3-thiazepines **7a-7d**.

The fragmentation behavior of 1,3-thiazepine (**7d**) in its mass spectrum is uncomplicated (Table I). **7d** exhibits weak molecular ion which decomposes by relatively few and easily rationalized pathways. The most characteristic feature in the spectrum is the pronounced loss of pivalonitrile (M-83) to form tert-butylthiophene. The remainder of the spectrum shows that the β-cleavage of a tert-butyl group with loss of methyl radical gives rise to the base peak (M-98). Such fragmentation can be seen to be favorable for all the molecular ions of 1,3-thiazepines, fully conjugated sulfonium ions being produced in all cases.

TABLE I. Mass spectral data of 1,3-thiazepines, m/z (%).



As the sulfurated products, **9a** and **9b**, obtained during the syntheses of thiazepines, we tentatively proposed structures shown in the Figure 6 in analogy with the case of the sulfurated thiepines. Although the observed ^{1}H-NMR data are fully consistent with these structures, the alternative structures shown in this Figure can not be ruled out. Final structural elucidation must await X-ray analysis.

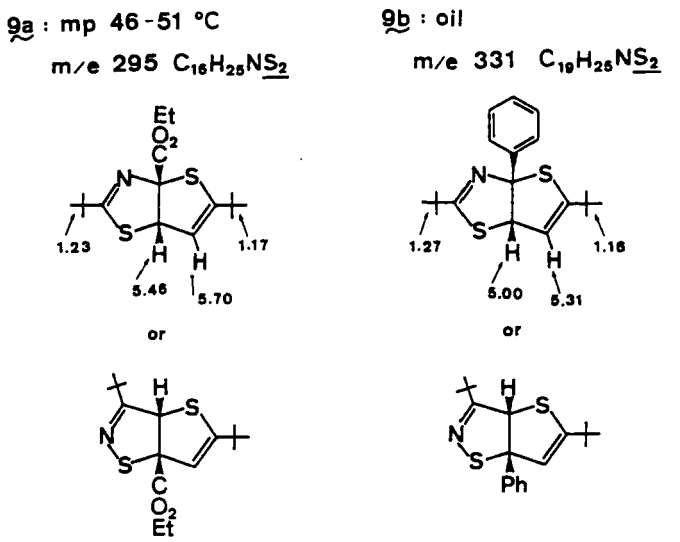
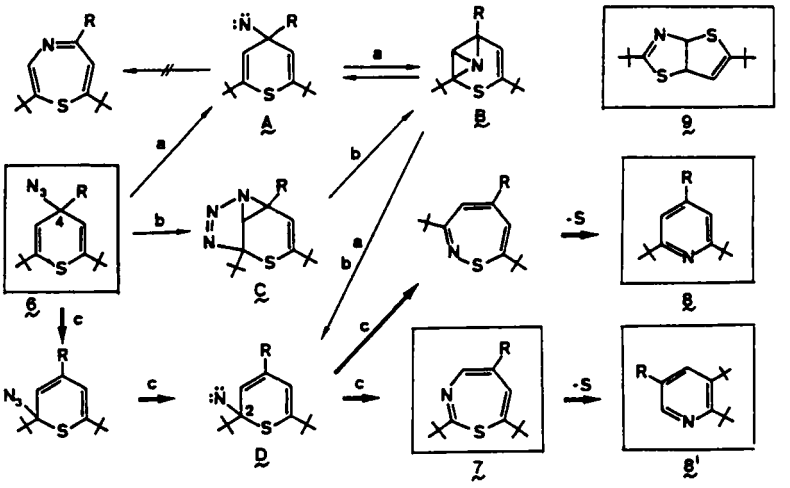


FIGURE 6. Possible structures of sulfurated 1,3-thiazepines.

Isolation of 1,3-thiazepine derivatives from the thermolysis of 4-azidothiopyrans strongly suggests that an intermediate (D), which contains nitrene center at 2-position of the thiopyran skeleton, does indeed produced during the thermolysis (Scheme 14).

SCHEME 14



Both the pathway-a and -b, which involve an azabicyclobutane intermediate (**B**), leading to (**D**) can be eliminated, since the expected 1,4-thiazepines were not observed in the product mixture. A most likely pathway (path-c) would involve [1,3]azide shift[28] followed by nitrogen evolution to give **D**. Sulfur shift to the nitrene center would generate 1,2-thiazepine which easily extrude sulfur to give pyridines **8**. On the other hand, vinyl shift to the nitrene would produce 1,3-thiazepines **7**. Although 1,3-thiazepines **7** are reasonably stable, they decompose to give pyridine **8'** under the high temperature conditions.

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REFERENCES

1. K. Nishino, S. Ishigami, Y. Tamura, Y. Ikutani, K. Imagawa, and I. Murata, submitted for publication.
2. W. L. Mock, J. Am. Chem. Soc., 89, 1281 (1967); H. L. Ammon and P. H. Watts, Jr., J. Am. Chem. Soc., 90, 4501 (1968).
3. I. Murata and K. Nakasuji, Top. Curr. Chem., 97, 33 (1983).
4. a) V. J. Traynellis, Y. Yoshikawa, J. C. Sih, and L. J. Miller, J. Org. Chem., 38, 3978 (1973); b) I. Murata, T. Tatsuoka and Y. Sugihara, Angew. Chem., 86, 161 (1974); Angew. Chem., Int. Ed. Engl., 13, 142 (1974).
5. N. Yasuoka, Y. Kai, N. Kasai, T. Tatsuoka, and I. Murata, Angew. Chem., 88, 295 (1976); Angew. Chem., Int. Ed. Engl., 15, 297 (1976).
6. V. J. Traynellis and R. F. Love, J. Org. Chem., 26, 2728 (1961).
7. T. Tatsuoka, Doctor Thesis, Osaka Univ. (1975).
8. N. Yasuoka, Y. Kai, and N. Kasai, Acta Crystallogr., B31, 2729 (1975).

9. H. Hofmann and H. Gaube, Angew. Chem., 87, 843 (1975); Angew. Chem., Int. Ed. Engl., 14, 812 (1975); H. Hofmann and H. Gaube, Chem. Ber., 112, 781 (1979); H. Hofmann, R. Bohme, and E. Wilhelm, Chem. Ber., 111, 309 (1978).
10. Cf. A. J. Pearson, Metallo-organic Chemistry (John Wiley and Sons, New York, 1985), p. 61.
11. I. Murata, K. Yamamoto, A. Matsukawa, K. Fukushima, and Y. Fukazawa, unpublished work.
12. K. Yamamoto, S. Yamazaki, Y. Kohashi, A. Matsukawa, and I. Murata, Chem. Lett., 1843 (1982).
13. K. Yamamoto, S. Yamazaki, Y. Kohashi, I. Murata, Y. Kai, N. Kanehisa, K. Miki, and N. Kasai, Tetrahedron Lett., 23, 3195 (1982).
14. K. Yamamoto, A. Matsukawa, and I. Murata, Chem. Lett., 1119 (1985).
15. For a review, see: W. B. Jennings, Chem. Rev., 75, 307 (1975).
16. T. Chivers and I. Drummond, Chem. Soc. Rev., 233 (1973).
17. For a related desulfuration and sulfuration reactions, see: R. H. Hall, H. J. den Hertog, Jr., D. N. Reinhoudt, S. Harkema, G. J. van Hummel, and J. W. H. M. Uiterwijk, J. Org. Chem., 47, 977 (1982).
18. I. Murata, K. Yamamoto, and S. Muramatsu, unpublished work.
19. W. Ried and W. Ochs, Chem. Ber., 107, 1334 (1974); W. Ried and E. König, Justus Liebigs Ann. Chem., 755, 24 (1972); M. S. Kulyk and D. C. Neckers, J. Org. Chem., 47, 3914 (1982).
20. For a review, see: K.-H. Wunsch and A. Ehlers, Z. Chem., 10, 361 (1970).
21. R. R. Schmidt and G. Berger, Synthesis, 187 (1974).
22. I. Murata, K. Yamamoto, and A. Matsumura, unpublished work.
23. K. Suzuki, Nippon Kagaku Kaishi, 101, 604 (1980).
24. K. Yamamoto, S. Yamazaki, H. Osedo, and I. Murata, Angew. Chem., 25, 635 (1986); Angew. Chem., Int. Ed. Engl., 25, 635 (1986).
25. H. Günther and H. H. Hinrichs, Tetrahedron Lett., 787 (1966).
26. E. Vogel, H. J. Altenbach, J. M. Drossard, H. Schmicher, and H. Stegelmeiner, Angew. Chem. Int. Ed. Engl., 19, 1016 (1981).
27. D. J. Pasto and C. R. Johnson, Organic Structure Determination, (Prentice-Hall, Inc., Englewood Cliffs, N.J., 1969), p. 101.
28. A. Gagneux, S. Winstein, and W. G. Young, J. Am. Chem. Soc., 82, 5956 (1960); C. A. van der Welf and V. L. Heasley, J. Org. Chem., 31, 3534 (1966); H. Priebe, Angew. Chem., 96, 728 (1984); Angew. Chem., Int. Ed. Engl., 23, 736 (1984); K. Banert, Angew. Chem., 97, 231 (1985);Angew. Chem., Int. Ed. Engl., 24, 216 (1985).