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SYNTHESIS AND PROPERTIES OF 4- AND 4,5-SUBSTITUTED 2,7-DI-*tert*-BUTYLTHIEPINS1)

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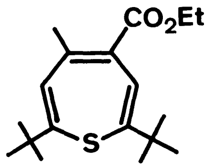
Various 4- and 4,5-substituted 2,7-di-*tert*-butylthiepins such as 4-ethoxycarbonyl- (**6**), 4-formyl- (**7**), 4-hydroxymethyl- (**8**), 4-methyl- (**12**), 4-methyl-5-hydroxymethyl- (**13**), and 4,5-dimethyl derivatives (**16**), and so on, were synthesized by functional group transformation and some of their properties were examined.

As a part of our continuous study on the thiepin chemistry,2) we have reported the first example of a remarkably stable monocyclic thiepin, 2,7-di-*tert*-butyl-4-ethoxycarbonyl-5-methylthiepin (**1**), the stability of which is shown to arise from the two bulky *tert*-butyl groups at 2,7-positions.3) However, since **1** possesses both an electron-donating methyl and an electron-withdrawing ethoxycarbonyl group at the adjoined positions, we could not eliminate completely the possibility that push-pull electronic effect also plays an important role in regulating the thermal stability of **1**.



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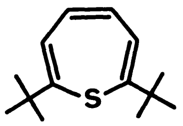

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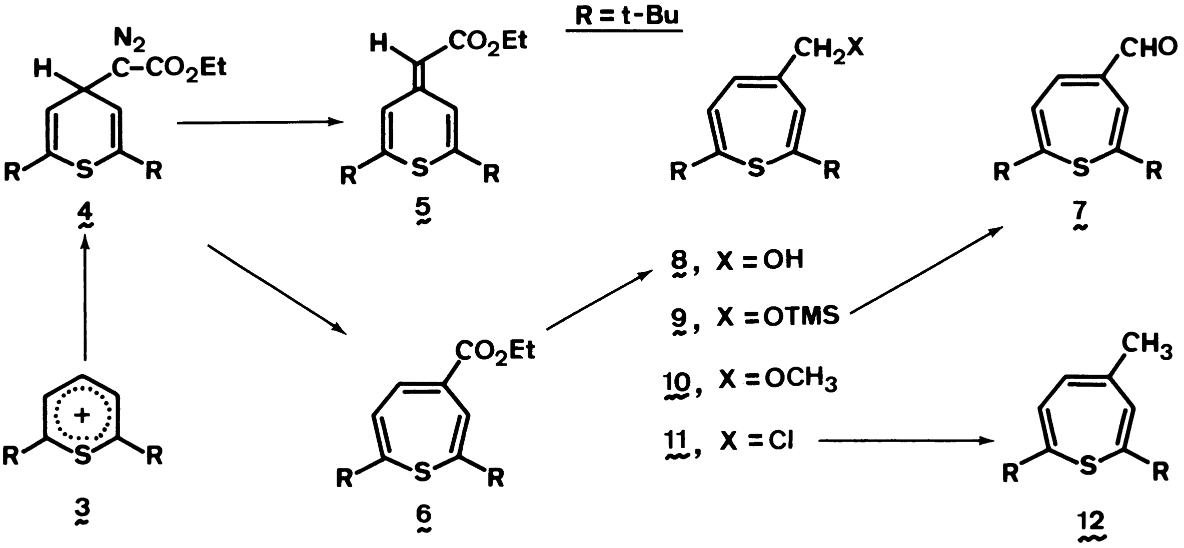
To clarify this ambiguity, we have recently described the synthesis and some properties of the simplest isolable thiepin, 2,7-di-*tert*-butylthiepin (**2**), together with its X-ray structure analysis.1) The substantial thermal stability of **1** and **2** clearly revealed that the presence of two bulky groups at 2,7-positions is indispensable to isolation of monocyclic thiepins.

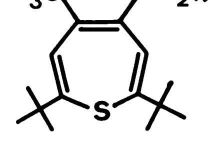
To evaluate the substituent effects on thermal stability of monocyclic thiepins, the synthesis and some properties of various 4- and 4,5-substituted 2,7-di-*tert*-butylthiepins were examined and the results are reported herein.4)

Our first effort is to synthesize 2,7-di-*tert*-butylthiepins having either an electron-withdrawing or an electron-donating group at 4-position. 2,6-Di-*tert*-butylthiopyrylium salt (**3**)3) was treated with ethyl lithiodiazoacetate (generated *in situ* at -110 °C) for 15 h at -78 °C to give the diazo ester **4**. Although reaction of **4** with a catalytic amount of π-allylpalladium dichloride gave the exomethylene compound **5** [98% yield, yellow oil, IR (neat) $\nu_{C=O}$ 1680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.28 (s, 9H), 1.36 (s, 9H), 1.27 (t, 1H, J = 7.0 Hz), 4.10 (s, 1H), 4.14 (q, 2H, J = 7.0 Hz), 6.37 (s, 1H), 8.22 (s, 1H)],3) treatment of **4** with dry hydrogen chloride in ether at -20 °C provided, though in low yield, 13%, 2,7-di-*tert*-butyl-4-ethoxycarbonylthiepin (**6**)5) as a yellow oil [IR (neat) $\nu_{C=O}$ 1710 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.25 (s, 9H), 1.26 (s, 9H), 1.32 (t, 3H, J = 7.0 Hz), 4.25 (q, 2H, J = 7.0 Hz), 6.40 (d, 1H, J = 6.0 Hz), 6.76 (s, 1H), 7.43 (d, 1H, J = 6.0 Hz); ^{13}C NMR (CDCl$_3$) δ 14.2, 30.3, 30.4, 40.1, 40.4, 68.8, 126.0, 127.0, 134.0, 140.0, 151.0, 158.2, 166.8; UV (c-hexane) λ_{max} nm (log ε) 234 (4.00), 388 (3.17), 402 (3.17)]. An alternate derivative having an electron-withdrawing formyl group, 2,7-di-*tert*-butyl-4-formylthiepin (**7**), was obtained through the sequential transformation of the ethoxycarbonyl group of **6**. On mild reduction with DIBAH in hexane at -30 °C the ester **6** was converted into the alcohol **8** [IR (CCl$_4$) ν_{OH} 3300-3350 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.23 (s, 9H), 1.25 (s, 9H), 1.68 (s, 1H, -OH), 4.17 (s, 2H), 6.30 (s, 3H)]. Trimethylsilyl ether **9** derived from **8** was oxidized with triphenylmethyl tetrafluoroborate in dichloromethane at room temperature to give **7** in 68% yield [yellow oil, IR (neat) $\nu_{C=O}$ 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.26 (s, 18H), 6.51 (d, 1H, J = 6.1 Hz), 6.68 (s, 1H), 6.98 (d, 1H, J = 6.1 Hz), 9.43 (s, 1H)].



While attempts to effect direct reductive transformation of **7** or **8** into 2,7-di-*tert*-butyl-4-methylthiepin (**12**) by LiAlH$_4$-AlCl$_3$ complex were unsuccessful, on treatment with trihexylphosphine-6) carbon tetrachloride at -10 °C for 5 min, **8** was smoothly converted to the chloride **11**, which, without isolation, was reduced with LiAlH$_4$ in ether at room temperature to afford **12** [66% yield, yellow oil, IR (neat) ν 1620 cm^{-1} (w); ^{1}H NMR (CDCl$_3$) δ 1.23 (s, 18H), 1.92 (s, 3H), 6.14 (pseudo s, 3H); ^{13}C NMR (CDCl$_3$) δ 25.1, 30.5, 30.6, 39.4, 39.7, 126.9, 129.1, 130.8, 141.3, 148.7, 149.1; UV (c-hexane) λ_{max} nm (log ε) 224 (4.03), 252 (3.51), 348 (2.60)].

The synthesis of 2,7-di-*tert*-butyl-4,5-dimethylthiepin (**16**) was achieved as follows: Reduction of the ester group of **1** was effected with LiAlH$_4$ to give the alcohol **13** which was then converted to methyl ether **14** (CH$_3$I/DME). While reduction of the corresponding methyl ether **10** [^{1}H NMR (CDCl$_3$) δ 1.23 (s, 9H), 1.24 (s, 9H), 3.32 (s, 3H), 3.97 (s, 2H), 6.26 (s, 3H)] with DIBAH in hexane resulted in formation of a complicated product mixture, the thiepin **16** [pale yellow plates, mp 59.5-61 °C, IR (KBr) ν 1620 cm^{-1} (w); ^{1}H NMR (CDCl$_3$) δ 1.22 (s, 18H), 1.85 (s, 6H), 6.08 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 20.9, 30.7, 39.2, 131.4, 135.0, 148.5; UV (c-hexane) λ_{max} nm (log ε) 206 (4.26), 226 (4.00), 253 (3.58), 336 (2.68)] was formed in 10% yield, when **14** was reduced with DIBAH in hexane at 10 °C for 6 h. Alternatively, **16** was obtained in 36% yield from **13** through chlorination ((C$_6$H$_{13}$)$_3$P/CCl$_4$) to form **15** followed by reduction (LiAlH$_4$/ether).



13, X = OH **15**, X = Cl

14, X = OCH$_3$ **16**, X = H

In the ^{1}H NMR spectra the ring proton signals of a series of monocyclic thiepins appeared at δ 6.1-6.9. As mentioned previously,1,3) these chemical shifts leave no doubt that the thiepin is not a paratropic7) but an atropic molecule.

An interesting point worth mentioning is the substituent effect of methyl group at 4- and 5-

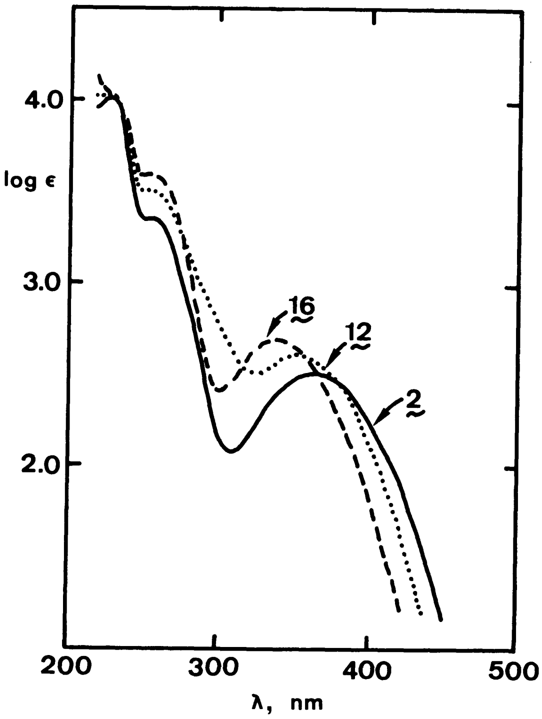


Figure 1. Ultraviolet Absorption Spectra of **2** (——), **12** (···), and **16** (---) in c-Hexane.

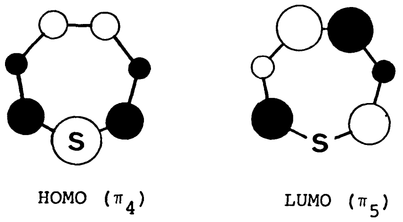


Figure 2. Frontier MO's of Thiepin.

positions of thiepin ring on the electronic spectral band shift. The electronic spectra of **12** and **16** together with that of the parent **2** are shown in Figure 1. It is quite clear that the longest wavelength bands of the thiepins, which were assigned to be π_4 (HOMO) → π_5 (LUMO) transitions,[8) having methyl group(s) at 4- (**12**) and 4,5-positions (**16**) display the successive blue shift by 12 and 26 nm, respectively, with increasing number of methyl substitution. The implication may be that the AO coefficients[8) at 4- and 5-positions in the LUMO of the thiepin are greater than those at the same positions in the HOMO so that the HOMO-LUMO gap increases with increasing methylation which causes the blue shift to the extent proportional to the number of methyl groups (Figure 2).

All the thiepins described in this paper are sufficiently stable and show no indication to extrude sulfur at room temperature. The thermal stability of these thiepins was examined at 130 °C in decalin-d_{18} monitored by ^{1}H NMR spectroscopy and the results are summarized in Table 1.[9) It is interesting to note that thiepins having two substituents, regardless of electron-donating or -withdrawing groups, at 4,5-positions such as **1** and **16** are found to be less stable than those having none or a single substituent at 4-position. A decisive explanation for these substituent effect on the thermal stability of thiepin will require additional investigation. We are now in the process of seeking preparation of 4,5-bis(ethoxycarbonyl)-2,7-di-*tert*-butylthiepin which will provide useful information concerning this point.

Table 1. Thermal Stability of 2,7-Di-tert-butylthiepins

compd.	substituents		$t_{1/2}^{130°C}$ (h)
	4-	5-	
1	COOEt	CH_3	7.1[a)]
2	H	H	195[b)]
6	CO_2Et	H	b,c)
9	CH_2OTMS	H	b,c)
12	CH_3	H	b,c)
16	CH_3	CH_3	13[b)]

a) Measured in toluene-d_8.
b) Measured in decalin-d_{18}.
c) No sulfur extrusion product could be detected within 20 h.

References

1) Thiepins 16. For part 15 in this series, see K. Yamamoto, S. Yamazaki, Y. Kohashi, I. Murata Y. Kai, N. Kanehisa, K. Miki, and N. Kasai, *Tetrahedron Lett.*, 23, 3195 (1982).

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3) K. Nishino, S. Yano, Y. Kohashi, K. Yamamoto, and I. Murata, *J. Am. Chem. Soc.*, 101, 5059 (1979); I. Murata, K. Nishino, S. Yano, Y. Kohashi, and K. Yamamoto, *Croat. Chem. Acta*, 53, 615 (1980).

4) All new compounds described in this paper gave satisfactory elemental analyses and suitable spectral data.

5) Acid catalyzed ring expansion reactions, **4**→**6**, by using *p*-toluenesulfonic acid in benzene instead of dry hydrogen chloride in ether were examined without any reproducible results, although in some cases the yield of **6** was improved up to 40%.

6) The alcohol **8** was found to be inert toward chlorination by means of Ph_3P/CCl_4 instead of $(C_6H_{13})_3P/CCl_4$.

7) J. Hoffman, Jr. and R. H. Schlessinger, *J. Am. Chem. Soc.*, 92, 5263 (1970); R. H. Schlessinger. "Aromaticity, pseudo-aromaticity, anti-aromaticity", The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Eds. E. D. Bergmann and B. Pullman, The Israel Academy of Sciences and Humanities, p. 158 (1971).

8) A. Tajiri, M. Hatano, K. Yamamoto, and I. Murata, *Chem. Phys. Lett.*, in press.

9) Thermolysis of 2,7-di-*tert*-butyl-4,5-dimethylthiepin (**16**) gave 1,2-di-*tert*-butyl-4,5-dimethylbenzene as a major product along with a small amount (less than 5%) of an unidentified by-product ($C_{16}H_{26}S_2$, presumably a sulfurated product of **16**). Although we have reported the quantitative formation of o-di-*tert*-butylbenzene on thermolysis of **2**, careful examination of the products reveals that a slight amount of sulfurated product, $C_{14}H_{20}S_2$, was also formed in this reaction. After completion of this manuscript we learned that Reinhoudt and co-workers reported the similar desulfuration and sulfuration of 2-thiabicyclo[3.2.0]hepta-3,6-dienes. R. H. Hall, H. J. den Hertog, Jr., D. N. Reinhoudt, S. Harkema, T. J. van Hummel, and J. W. H. M. Uiterwijk, R. *J. Org. Chem.*, 47, 977 (1982).

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