chromophores. Also, in preliminary experiments, neither 13-*cis*-I, 9-*cis*-, nor 9-*cis*,13-*cis*-II gave detectable pigment analogues when incubated with a digitonin solution of cattle opsin[16]—the last two results being distinctly different from the parent retinal.[15,17] The twisted chromophores presumably no longer meet the longitudinal requirements of the binding site.[18] These results and conformational properties of I and II will be examined in detail.

**Acknowledgment.** The work was supported by a grant from the U.S. Public Health Services (AM 17806) and partially by the U.H. Biomedical program.

**Supplementary Material Available:** $^1$H and $^{19}$F NMR data (Figures 1-3) of 13-*cis*-I, 9-cis-II, and 9-*cis*,13-*cis*-II (4 pages). Ordering information is given on any current masthead page.

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(16) Following a procedure similar to that described in Matsumoto et al. (Matsumoto, H.; Asato, A. E.; Denny, M.; Baretz, B.; Yen, Y.-P.; Tong, D.; Liu, R. S. H. *Biochemistry* **1980**, *19*, 4589-4594).

(17) Crouch, R.; Purvin, V.; Nakanishi, K.; Ebrey, T. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 1538-1542.

(18) Matsumoto, H.; Liu, R. S. H.; Simmons, C.; Seff, K. *J. Am. Chem. Soc.* **1980**, *102*, 4259-4262.

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# Fused Thiirene Sulfoxides. Synthesis via [2 + 4] Cycloaddition of Thiiranoradialene Sulfoxide and Structural Characterization

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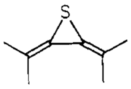
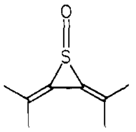
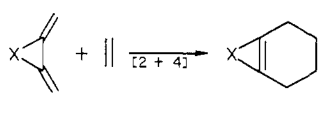
Recently we have synthesized the first hetero [3] radialenes, i.e., thiiranoradialene and its sulfoxide (**1** and **2**).[1] Although much attention has focused on the [2 + 4] cycloaddition of radialenes with dienophiles, no examples are known for [3] radialene[2] and its analogue.[3] The addition would be synthetically useful as a means of introducing a double bond into a three-membered ring fused to a six-membered ring, thereby giving a highly strained compound (eq 1). Both **1** and **2** can be regarded as potential precursors for the syntheses of six-membered rings fused to thiirene and thiirene sulfoxide units, respectively.



1



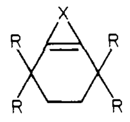
2



(1)

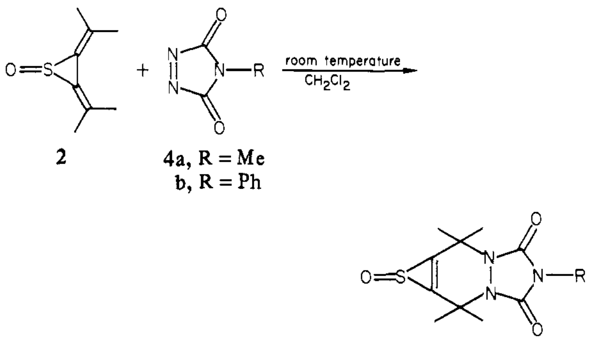
We now report the first syntheses of alkyl-substituted thiirene sulfoxides by [2 + 4] cycloaddition of thiiranoradialene sulfoxide with 4-substituted 1,2,4-triazoline-3,5-diones (TAD) and further to demonstrate the unique structural features of the novel thiirene sulfoxide so formed.

The annelated cyclopropene **3a** and cyclopropenone **3b** are the only cases reported of bicyclo[4,1,0]hept-1,6-enes.[4,5] The heteroatom analogues **3d** and **3e** as well as **3c** are unknown. Thus, it seems that the fused six-membered ring system represents the lower synthetic limits for a cyclopropene fused to a ring.



3a, X = $CMe_2$
b, X = C=O
c, X = $C{=}CR_2$
d, X = S
e, X = S=O

When thiiranoradialene sulfoxide **2** was treated with an equimolar amount of TAD (**4a**) in $CH_2Cl_2$ at room temperature (eq 2), the red color due to TAD rapidly disappeared and thiirene sulfoxide **5a** was immediately formed as colorless crystals in quantitative yield.[6] The addition proceeds equally well with phenyl-substituted TAD (**4b**) to give **5b**. However, the reaction of thiiranoradialene (**1**) with TAD gave no simple addition product but a complex product mixture, even at −50 °C,[7] although the reaction was as fast as that of **2**.[8] Apart from diaryl thiirene sulfoxide **6**,[9] thiirene sulfoxides **5a** and **5b** are the first alkyl-substituted cases. Cycloadducts **5a** and **5b** are extraordinarily stable (104-107 °C dec) just like **6**[9] and cyclopropenone **3b** (R = Me).[5] Their structures were fully determined by elemental analyses, spectroscopies,[11] and X-ray analysis.

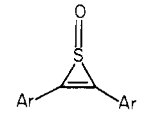


(2)

2

4a, R = Me
b, R = Ph

5a, R = Me
b, R = Ph



6 (Ar = Ph, *p*-FPh)

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(1) Ando, W.; Haniu, Y.; Takata, T. *Tetrahedron Lett.* **1981**, *22*, 4815-6.

(2) Kobrich, G.; Heinemann, H.; Zundorf, W. *Tetrahedron* **1967**, *23*, 565-84.

(3) Pasto, D. J.; Smorada, R. L.; Turini, B. L.; Wampfler, D. J. *J. Org. Chem.* **1976**, *41*, 432-8.

(4) Closs, G. L.; Boll, W. A.; Heyn, H.; Dev, V. *J. Am. Chem. Soc.* **1968**, *90*, 173-8.

(5) Suda, M.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1974**, 504-5.

(6) Attempt to prepare other [2 + 4] cycloadducts of **2** with some dienophiles such as maleic anhydride, maleinimide, ethylazodicarboxylate, etc., have failed at present time.

(7) This result may be due to the occurrence of the other reactions such as [2 + 2] cycloaddition and ene reaction, which should predominate over the [2 + 4] cycloaddition, where highly unstable thiirene can be formed.

(8) TAD, an extremely strong dienophile,[10] can react with **2** regardless of the presence of sulfoxide group (an electron-withdrawing group), because of the stabilization of the transition state.

(9) Carpino, L. A.; Chen, H.-W. *J. Am. Chem. Soc.* **1979**, *101*, 390-4.

(10) Burrage, M. E.; Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1325-34.

(11) **5a**: $^1$H NMR ($CDCl_3$) $\delta$ 3.10 (s, 3 H), 1.93 (s, 6 H), 1.87 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.0, 153.2, 64.7, 25.1, 23.3, 22.7; IR (cm$^{-1}$, KBr) 2975 (w), 2925 (w), 1698 (s), 1460 (s), 1115 (s) ($\nu_{S-O}$). Anal. Calcd for $C_{11}H_{15}N_3O_3S$: C, 49.05; H, 5.61; N, 15.60; S, 11.90. Found: C, 48.80; H, 5.56; N, 15.41; S, 12.07. **5b**: $^1$H NMR ($CDCl_3$) $\delta$ 1.97 (s, 6 H), 1.90 (s, 6 H), 7.55 (s, 5 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 153.5, 151.4, 130.4, 128.0, 125.4, 64.8, 23.0, 22.3; IR (cm$^{-1}$, KBr) 3050 (w), 2950 (w), 2900 (w), 1690 (s), 1400 (s), 1115 (s) ($\nu_{S-O}$).

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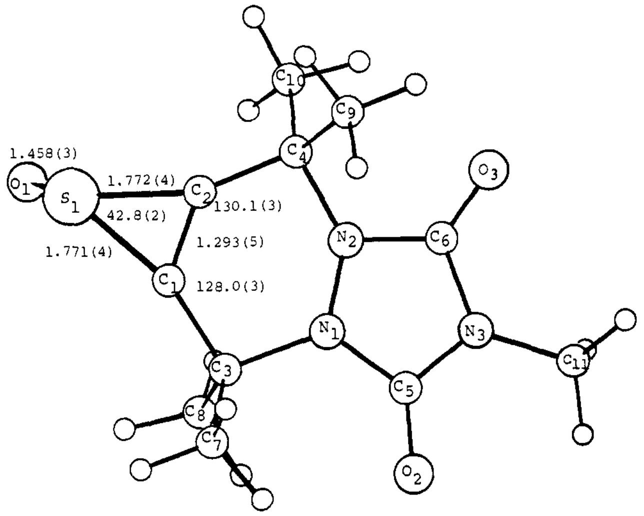

**Figure 1.** Molecular crystal structure of thiirene sulfoxide **5a**. Numerical values written out are bond lengths (Å) and angles (deg).

In the $^{13}$C NMR spectra of **5a** and **5b**, the olefinic carbon resonances are assigned to the signals at 153.2 and 153.5 ppm, respectively, by comparison with those found for dipropylcyclopropenone (160.9 ppm), diphenylcyclopropenone (148.7 ppm),[12] and cyclopropenone **3b** (169.0 ppm).[5] Thiiranoradialene sulfoxide (**2**) showed an olefinic ring carbon resonance at 131.2 ppm.[1] A characteristic feature of both **5a** and **5b** is seen in the IR spectra, where the stretching vibrational absorption due to the S–O bond appears at the unusually high frequency of 1115 cm$^{-1}$.[13] The value indicates a surprisingly short S–O bond length, the shortest found for any type of sulfoxide.

The structure of **5a** was determined by X-ray analysis. The crystal has monoclinic space group $p2/n$ with $a$ = 15.208 (2) Å, $b$ = 6.083 (1) Å, $c$ = 16.139 (2) Å, and $\beta$ = 117.06 (1)° with $Z$ = 4. Intensity data were collected on a four-circle diffractometer with graphite monochromated Cu K$\alpha$ radiation. Of 2457 reflections obtained with $2\theta \leq 158°$, 1691 had intensities greater than $3\sigma|F_o|$ and were used for structure analysis. The structure was refined to a value of 0.058.

The molecular structure of **5a** is revealing (Figure 1). In the crystalline state the S–O bond length (1.458 Å) is substantially shorter than that of the diphenyl analogue **6** (1.467 Å),[5] as expected from the infrared spectra (1115 and 1061 cm$^{-1}$ for **5a** and **6**, respectively), but not shorter than those in thiirene sulfones.[14]

The short S–O bond length has repercussions on the length of the $C_1{=}C_2$ bond (1.293 Å) and the C–S bond (1.771 Å), which are both shorter than those in **6** (1.305 and 1.784 Å). Consequently, this is a considerable increase in $\pi$-bond character over the three-membered ring and the attached S–O bond, which may be attributed to the combined effects of ring fusion and alkyl substitution.[15] Although the bond angle of $C_1$–$S_1$–$C_2$ of **5a** (42.8°) is comparable to that of **6** (42.9°), the $C_4$–$C_1$–$C_2$ and $C_1$–$C_2$–$C_3$ angles (128.0 and 130.1°) are ~20° smaller than those in **6** (151.9 and 152.7°). Once again ring fusion accounts for this angular compression. The angle of deviation of the sulfoxide oxygen from the thiirene ring is 63.9°. Thus, the thiirene ring of our thiirene sulfoxide **5a** is significantly shortened in all bonds compared to that in **6**.

We hope the data reported here will stimulate theoretical studies on thiirenes. Furthermore, since [2 + 4] cycloadditions of [3] radialenes are uncommon, the successful [2 + 4] cycloaddition of hetero [3] radialene is correspondingly noteworthy.[16] The termini of the diene fragment of [3] radialene are far apart; therefore the dienophile has difficulty in spanning this distance in the transition state.

Success in the present instance is undoubtedly due to the unique structure of thiiranoradialene sulfoxide **2**.

**Acknowledgment.** We are indebted to Professor C. W. Jefford, University of Geneva, for his useful comments.

**Registry No. 2**, 81355-46-6; **4a**, 13274-43-6; **4b**, 4233-33-4; **5a**, 82613-75-0; **5b**, 82613-76-1.

**Supplementary Material Available:** Listings of atomic positional parameters, bond lengths, and bond angles for compound **5a** (5 pages). Ordering information is given on any current masthead page.

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(12) Stang, P. J.; Maas, G.; Smith, D. L.; McCloskey, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4837–45.

(13) Infrared spectrum of **5a** in CDCl$_3$ also showed $\nu_{S-O}$ at 1115 cm$^{-1}$.

(14) Ammon, H. L.; Fallon, L.; Plastas, L. A. *Acta Crystallogr., Sect. B* **1976**, *B32*, 2171–9.

(15) The influence of alkyl and aryl substituents on the dimensions of the three-membered ring has been noted in thiirene sulfone. X-ray analyses show that all bond lengths of the thiirene ring and the S–O bond of 2,3-dimethylthiirene sulfone are shorter than those in 2,3-diphenylthiirene sulfone.[11] This effect may be accounted for by the $\pi$-electron delocalization of the thiirene double bond with the benzene ring and the magnitude of the C–S bond $\pi$ character.

(16) To determine whether the cycloaddition proceeds concertedly (in Diels–Alder type) or stepwise is usually difficult in a [2 + 4] cycloaddition of TAD with dienes.[10] In our result on solvent effect, which is consistent with the previous report,[10] the rate of the [2 + 4] cycloaddition of **2** with **4a** is decreased in polar solvent; the rate constants are 110 M$^{-1}$ s$^{-1}$ in benzene, 54 M$^{-1}$ s$^{-1}$ in dichloromethane, and 9.5 M$^{-1}$ s$^{-1}$ in acetonitrile (at 23.2 °C).

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## Preparation and Study of a Low-Potential Flavin Analogue

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Flavins (7,8-dimethylisoalloxazines) serve as cofactors in numerous biochemical redox reactions. The basic flavin structure is present in certain enzymes in modified forms (substitution upon the methyl group at the 8-position, substitution at the 6-position, replacement of the 8-methyl group by hydroxyl or dimethylamino functional groups, replacement of the N$^5$ of the isoalloxazine ring by carbon, etc.).[1] The effect of these modifications may be to bind flavin to enzyme, to modify the potential, or to alter the chemistry to fit the catalytic role selected for the enzyme in question. Alteration in redox potentials of the 7,8-dimethylisoalloxazines is also brought about by the nature of the catalytic site of the apoprotein and by the preferential binding of the oxidized, reduced, and radical species. Notably absent among the known isoalloxazines are molecules with low reduction potentials comparable to that of the *N*-alkylnicotinamides. Our interest in low-potential flavin analogues is their possible great utility in the study of reaction mechanisms.

We report here preliminary results of our studies of 3,7,9,10-tetrahydro-3,7,10-trimethylpyrimido[5,4-*g*]pteridine-2,4,6,8-tetrone (PPT$_{ox}$)[2] and 1,3,5,7,9,10-hexahydro-3,7,10-trimethylpyrimido[5,4-g]pteridine-2,4,6,8-tetrone (PPTH$_2$)[3] as mimics of flavin and 1,5-dihydroflavin, respectively. The $E^{0\prime}$ for the two-electron reduction of $PPT_{ox} \rightarrow PPTH_2$ (25 °C, H$_2$O, carbon paste electrode) has been determined as −346 mV vs. the NHE. This

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(1) Walsh, C. *Acc. Chem. Res.* **1980**, 13, 148. Merrill, A. H., Jr.; Lambeth, J. D.; Edmondson, D. E.; McCormick, D. B. *Annu. Rev. Nutr.* **1981**, *1*, 281.

(2) Prepared by the condensation of *N*-methylalloxan with 3-methyl-5-amino-6-(methylamino)uracil in refluxing acetic acid;[1] NMR (TFA) $\delta$ 3.61 [s, 3 H, $N^{10}$-methyl], 3.20 [s, 6 H, $N^3$- and $N^7$-methyls]. Anal. Calcd. for $C_{11}H_{10}N_6O_4{\cdot}1.5H_2O$: C, 41.63; H, 4.12; N, 26.49. Found: C, 41.61; H, 4.16; N, 26.53.

(3) By photochemical reduction with EDTA.

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