# Dithiatopazine[1] and Related Systems. Synthesis, Chemistry, X-ray Crystallographic Analysis and Calculations

K. C. Nicolaou,*[,†] S. A. DeFrees,[†] C.-K. Hwang,[†] N. Stylianides,[†] P. J. Carroll,[†] and J. P. Snyder*[,‡]

*Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Drug Design Section, G. D. Searle and Company, Skokie, Illinois 60077.* *Received June 29, 1989*

**Abstract:** The synthesis and chemistry of dithiatopazine (**11**), a stable 1,2-dithietane system, are described. Theoretical studies with this novel system are also included. The synthesis of **11** was achieved via controlled photoirradiation of dithionolactone **10**. Photolytic or thermal decomposition of **11** led to olefin **12**, a conversion that could also be carried out by a variety of reagents. Triphenylphosphine treatment of **11** led to the loss of one sulfur and the formation of the rearranged products **18** and **19**. Treatment of **11** with $PhS^-$ resulted in the formation of **25**, whereas brief exposure to $NaBH_4$ followed by trapping with MeI led to the novel episulfides **31a** and **31b**. Exposure of **11** to $AgBF_4$–$Et_3SiH$ resulted in a novel skeletal rearrangement leading to compound **36**. Dithiatopazine (**11**), served as a sulfur-transfer reagent converting, under thermal conditions, diene **41** to cyclic sulfides **42** and **43** and acetylene **44** to the novel systems **45** and **46**. Kinetic studies on the thermal decomposition of **11** revealed an activation energy for this process of 26.3 kcal/mol. Several X-ray crystallographic analyses, including that on dithiatopazine (**11**) are included in this study. MM2 parameterization for dithietanes and subsequent molecular mechanics evaluation permits the conclusion that dithiatopazine is a remarkably rigid structure experiencing little conformational mobility. Quantum mechanical (PRDDO) calculations for various dithietane systems suggest the singular stability of dithiatopazine to arise from a combination of thermodynamic factors and internal energy redistribution. Finally, MM2 parameters for episulfides were derived to allow for a comparison between dithiatopazine and its episulfides and bis(methylthio) analogues.

1,2-Dithietanes (A, Chart I) and their derivatives are of fundamental theoretical, physical, chemical, and biological interest.[2,3] Until recently such structures were considered only as theoretical curiosities or transient intermediates. Thus, systems **1–3** (Chart II) have been postulated as unstable intermediates enroute to the corresponding olefins and sulfur by Schmidt (**1**),[4] Cava (**2**),[5] and Steliou (**3**).[6] The relative instability of these systems has been attributed to the expected destabilizing repulsion between lone pairs of electrons on adjacent sulfur atoms[7] and to thermochemical factors.[6] It is worth noting, however, that several isolable 1,2-dioxetanes[8] and a 1,2-oxathietane[9] have been reported.

Substitution of the lone pairs on one of the sulfurs with oxygen atoms gave the first isolable 1,1-dioxide derivative (B, Chart I) of a 1,2-dithietane as reported by Block.[10] Several aromatic systems of type C (Chart I) with $6\pi$ electrons have also been reported as stable compounds. These include compounds **4**,[11] **5**,[12] **6**,[13] **7**,[14] **8**,[14] and **9**[14] (Chart III).[15,16]

During our synthetic studies in the area of marine natural products, we had the opportunity to prepare and study the chemistry of a number of dithionolactones of type D (Scheme I).[17] A conceivable pathway to 1,2-dithietanes of type F (Scheme I) was considered, via the radical species E (Scheme I), or its equivalent, which may be generated from D by photolytic methods. The special molecular environment of the 1,2-dithietane moiety in structure F was explored for its potential to provide extra stabilization needed for successful isolation of such structures. Happily, these investigations led to the isolation of the first stable 1,2-dithietane compound, dithiatopazine (**11**, Scheme II), which we recently reported in a preliminary communication.[18] In this article, we describe the isolation of further 1,2-dithietane systems and detail the chemistry and properties of dithiatopazine, including its X-ray crystallographic analysis. In addition, we report a series of calculations on the conformational surface of **11** and its analogues. The question of stability is addressed from a thermodynamic viewpoint.

Chart I

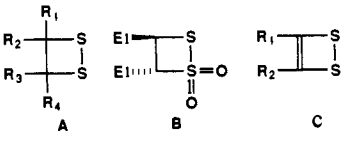


Chart II

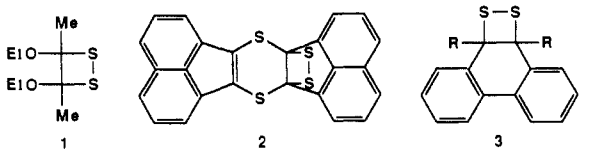
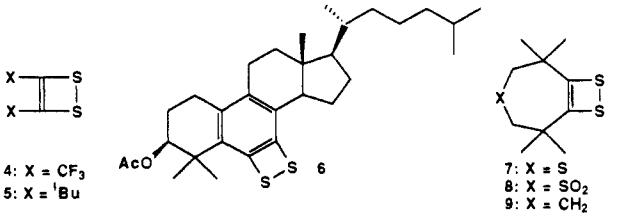
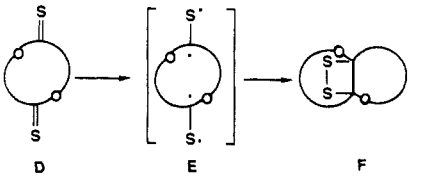


Chart III



Scheme I



## Synthesis of Dithiatopazine

As mentioned above, the opportunity for the synthesis of 1,2-dithietanes arose when dithionolactones such as **10** (Scheme II) became available.[19] Thus, when **10** was irradiated in toluene solution (0.05 M, Hanovia UV lamp, ambient temperature) for

* Address correspondence to this author at: Department of Chemistry, Research Institute of Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA 92037 and Department of Chemistry, University of California, San Diego, La Jolla, CA 92093-0301.

† University of Pennsylvania.

‡ Inquiries regarding the computational aspects of this work should be addressed to this author at G. D. Searle and Co.

(1) The name dithiatopazine was coined for compound **11** for its beautifully yellow-orange topazlike crystalline form. The preferred name according to the IUPAC rules for this compound is (4a*R*,5a*S*,7a*r*,11a*S*,12a*S*,14a*S*)-dodecahydro-6*H*,13*H*-12a-epidithiopyrano[3,2-*b*]pyrano[2′,3′:6,7]oxepino-[2,3-*f*]oxepin.

(2) For some intriguing properties of the disulfide linkage, see: Guttenberger, H. G.; Bestmann, H. J.; Dickert, F. L.; Jorgensen, F. S.; Snyder, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 159.

0002-7863/90/1512-3029$02.50/0 

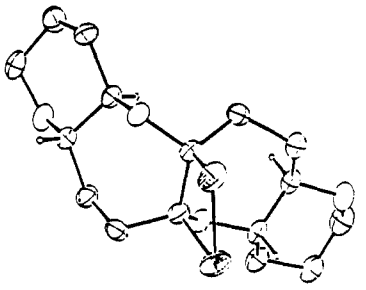
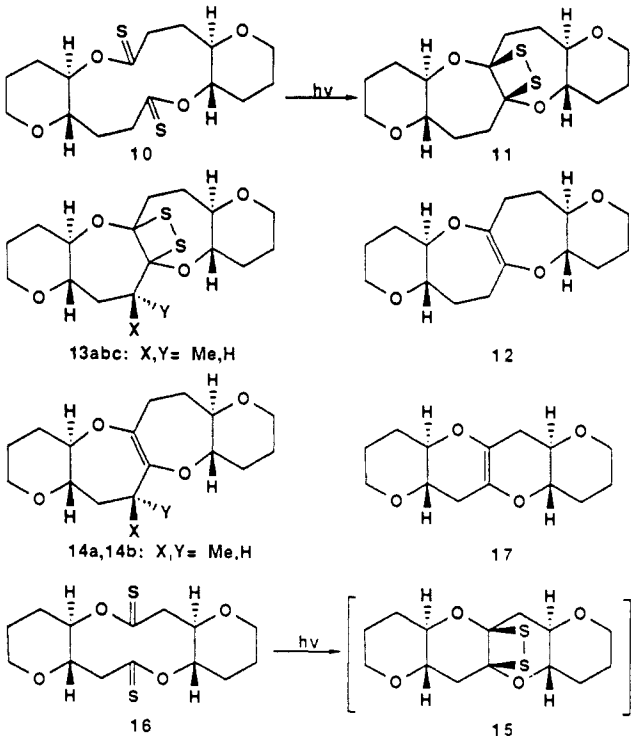


**Figure 1.** ORTEP drawing of **11**. Bond distances (Å): C5a–C12a = 1.571 (6); C12a–S15 = 1.844 (4); S15–S16 = 2.084 (2); S16–C5a = 1.881 (4). Bond angles (deg): C5a–C12a–S15 = 97.4 (3); C12a–S15–S16 = 82.2 (1); S15–S16–C5a = 80.7 (1); S16–C5a–C12a = 96.8 (3). Dihedral angle between planes: C12a–S15–S16 and C5a–S16–S15 = 11.0 (4).

**Scheme II**




0.5 h, a mixture of starting material (**10**), 1,2-dithietane **11**, and olefin **12** was obtained (Scheme II). Chromatographic separation gave, in order of elution, **10** (10%), **11** (65%), and **12** (12%). Compound **11** crystallized in beautiful yellow-orange, topazlike crystals (Figure 1, ORTEP drawing of **11**, vide infra; see also Table IV, supplementary material for X-ray crystallographic data), mp 134–135 °C (from hexane), and was, therefore, given the trivial name dithiatopazine.[1] Longer irradiation times resulted in the complete consumption of **10** and **11** and the exclusive formation of olefin **12** (1 h, 85% yield). The structure of dithiatopazine (**11**) was based on its spectroscopic data (see Table I, supplementary material) and was confirmed by X-ray crystallographic analysis (vide infra). Three related 1,2-dithietanes (**13a–c**, three diastereomers; Scheme II) were obtained by the same photolytic procedure from the corresponding dithionolactones,[19] together with the corresponding olefins **14a** and **14b** (unassigned stereochemistry). However, attempts to prepare the 1,2-dithietane **15** (Scheme II) from the 10-membered ring dithionolactone **16** failed. Under these conditions the olefin **17** was the only observable product. In connection with this result it is interesting to note that X-ray crystallographic studies on dithionolactones **10** and

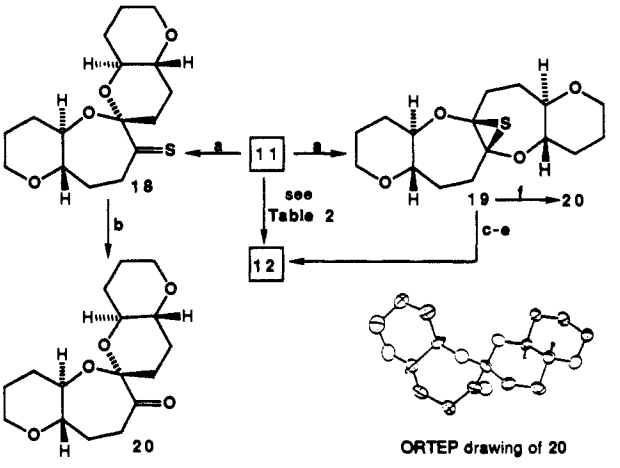
**Table II.** Reagents and Conditions for the Desulfurization of **11** to Olefin **12**

| entry | reagent | solvent | temp, °C | time, h | yield, % |
|---|---|---|---|---|---|
| 1 | Δ | xylene | 140 | 0.75 | 95 |
| 2 | Δ | neat | 140 | 0.75 | 95 |
| 3 | *hν* | toluene | 25 | 1 | 90 |
| 4 | $n$Bu$_3$SnH–AIBN | toluene | 110 | 0.25 | 97 |
| 5 | Raney Ni | EtOH | 25 | 0.5 | 95 |
| 6 | *m*CPBA | $CH_2Cl_2$ | 0 | 0.1 | 94 |
| 7 | $Fe_2(CO)_9$ | $CHCl_3$ | 25 | 2 | 88 |
| 8 | $Mo(CO)_6$ | THF | 25 | 48 | 90 |

**Table III.** Rate Constants and Half-Lives ($t_{1/2}$) for the Thermal Decomposition of Dithiatopazine (**11**) at Various Temperatures

| kinetic run | temp, °C | rate const. $k$, h$^{-1}$ | $t_{1/2}$, h |
|---|---|---|---|
| 1 | 80 | 0.02 | 34.28 |
| 2 | 90 | 0.07 | 10.10 |
| 3 | 100 | 0.190 | 3.32 |
| 4 | 110 | 0.463 | 1.10 |

**Scheme III**[a]




[a] Reaction of dithiatopazine (**11**) with $Ph_3P$. Reagents and conditions: (a) 1.2 equiv of $Ph_3P$, $CH_2Cl_2$, 30 min, 25 °C, **18** (46%), **19** (45%); (b) ozone, $CH_2Cl_2$, −78 °C, then 10 equiv of $Me_2S$, −78 → +25 °C, 1 h, 85%; (c) xylene, sealed tube, 160 °C 2 h, 88%; (d) 2 equiv of $n$Bu$_3$SnH, AIBN (catalytic) toluene, 110 °C, 1 h, 93%; (e) 10 equiv of $(EtO)_3P$, toluene, 1 h, 110 °C, 94%; (f) 2 equiv of *m*CPBA, 10 equiv of $H_2O$, $CH_2Cl_2$, 25 °C, 2 h, 55%.

(3) (a) For a monograph on sulfur chemistry, see: Block, E. In *Reactions of Organosulfur Compounds*; Blomquist, A. T., Wasserman, H. H., Eds.: Academic Press: New York, 1978. (b) Cyclic disulfides have been associated with biological activity; for some non-peptide examples, see glyotoxin and α-lipoic acid: *Merck Index*, 10th ed.; Merck & Co., Inc.: Rahway, NJ, 1983; entries 4301 and 9166, respectively, and references cited therein.

(4) Jahn, R.; Schmidt, V. *Chem. Ber.* **1975**, *108*, 630.

(5) Orahovatz, A.; Levinson, M. I.; Carroll, P. J.; Lakshmikanthan, M. V.; Cava, M. P. *J. Org. Chem.* **1985**, *50*, 1550.

(6) Steliou, K.; Salama, P.; Brodeur, D.; Gareau, Y. *J. Am. Chem. Soc.* **1987**, *109*, 926.

(7) Vasil'eva, T. P.; Lin'kova, M. G.; Kil'disheva, O. V. *Russ. Chem. Res. (Engl. Transl.)* **1976**, *45*, 639–659. Cf. footnote 21 in ref 10.

(8) See: Bartlett, P. D.; Landis, M. E. *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979.

(9) Lown, J. W.; Koganty, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 3811.

(10) Block, E.; Bazzi, A. A.; Revelle, L. K. *J. Am. Chem. Soc.* **1980**, *102*, 2490.

(11) Krespau, C. F. *J. Am. Chem. Soc.* **1961**, *83*, 3434.

(12) Kopke, B.; Voss, J. *J. Chem. Res., Synop.* **1982**, *11*, 314.

(13) Boar, R. B.; Hawkins, D. W.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 515.

(14) Krebs, A.; Golberg, H.; Hopfner, V.; Kinling, J.; Odenthal, J. *Heterocycles* **1979**, *12*, 1153.

(15) See also: Bock, H.; Rittmeyer, P.; Krebs, A.; Schultz, K.; Voss, J.; Kopke, B. *Phosphorus Sulfur* **1984**, *19*, 131, and references cited therein.

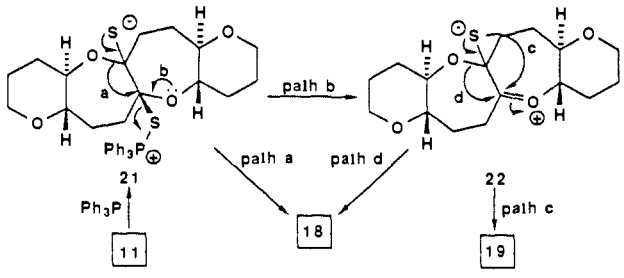
(16) See also: (a) de Mayo, P.; Weedon, A. C.; Wong, G. S. U. *J. Org. Chem.* **1979**, *44*, 1977. (b) Ishibe, N.; Odano, M.; Teramura, K. *J. Chem. Soc. Chem. Commun.* **1970**, 371. (c) Reference 7.

(17) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 6800.

(18) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Carroll, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 3801.

(19) Nicolaou, K. C.; Hwang, C.-K.; DeFrees, S.; Marron, B. E.; Abe, Y.; Snyder, J. P. *J. Am. Chem. Soc.*, following article in this issue.

**Scheme IV**[a]




[a] Presumed mechanism for the formation of **18** and **19** from **11** and $Ph_3P$.

**16**, revealed in both cases an anti relationship for the two sulfur groups.[19] MM2 and PRDDO calculations on the strain energies of systems **11** and **15** relative to the corresponding olefins (**12** and **17**) suggest an explanation for the successful isolation of **11** and the failure to isolate **15** (vide infra).

### Chemistry of Dithiatopazine

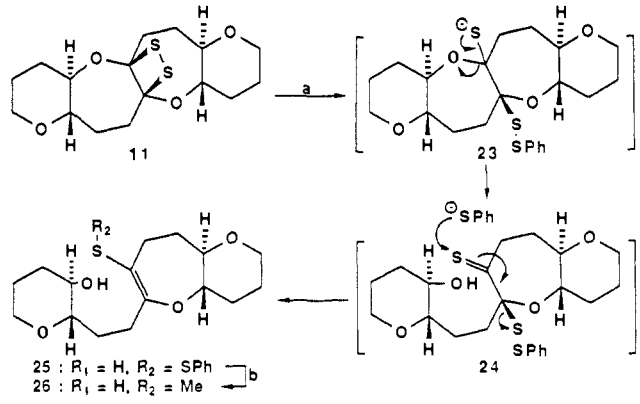
The unusual molecular structure of dithiatopazine (**11**) suggested interesting reactivity and prompted us to investigate its chemistry.[18,20] The first conversion we studied was the one already observed during the photolytic generation of dithiatopazine (**11**), namely, the loss of sulfur leading to olefin **12** (Scheme II). Table II summarizes some reagents and conditions that induce, rather cleanly, this transformation. Thus, besides the photolysis (entry 3), thermal conditions (entries 1 and 2) were found to be quite effective in forming olefin **12** from **11**. Exposure of **11** to radical conditions ($n$Bu$_3$SnH–AIBN, entry 4, or Raney Ni, entry 5) or to oxidative conditions ($m$CPBA, entry 6) also produced olefin **12** in high yield. The thiophilic properties of iron and molybdenum prompted us to study the reaction of dithiatopazine **11** with $Fe_2(CO)_9$ and $Mo(CO)_6$ (entries 7 and 8). In both instances the sulfur atoms were removed, leading to **12** in high yield. Apparently the "pull" from the metal coupled with the "push" from the ring oxygens and the lower energy well for **12** relative to **11** results in this facile transformation, rather than the formation of a stable metal complex of **11**.

We then investigated the reaction of $Ph_3P$ with dithiatopazine (**11**), which led to the isolation of the two new and fascinating compounds **18** (46%) and **19** (45%) by abstraction of one of the sulfur atoms (Scheme III). The structures of these products were determined on the basis of their spectral data and their chemistry. Thus, compound **18** (pale purple color) exhibited the expected characteristic signals in the $^{13}C$ NMR spectrum (125 MHz, benzene-$d_6$) for the C=S ($\delta$ 262.56) and the O—C—O groups ($\delta$ 106.32). Furthermore, **18** was converted by ozonolysis to ketone–spiro ketal **20**, whose X-ray crystallographic analysis (see ORTEP drawing, Scheme III) firmly established both its structure and the structure of its pregenitor **18**. The surprisingly stable episulfide **19** exhibited in its $^{13}C$ NMR spectrum (125 MHz, $CDCl_3$) signals at $\delta$ 93.28 and 86.91 for the two O—C—S groups. Episulfide **19** suffered loss of sulfur and high-yield transformation to olefin **12** by thermolysis (160 °C, 88%), $n$Bu$_3$SnH–AIBN (110 °C, 93%), or exposure to $(EtO)_3P$ (110 °C, 94%). Treatment of **19** with $m$CPBA in wet $CH_2Cl_2$ at room temperature furnished the ketone–spiral ketal **20** in 55% yield (Scheme III).

A plausible mechanism for the formation of products **18** and **19** from dithiatopazine (**11**) is shown in Scheme IV. Thus, initial attack on **11** by $Ph_3P$ may, in principle, result in two isomeric species **21**, depending on the regiochemistry of the attack. These stereochemically distinct species (if both formed) may prefer different reaction pathways, depending on stereoelectronic effects, and may lead to **18** (path a) or oxonium species **22** (path b). Oxonium species **22** may then collapse to episulfide **19** (path c) or rearrange to thioketone **18** (path d).

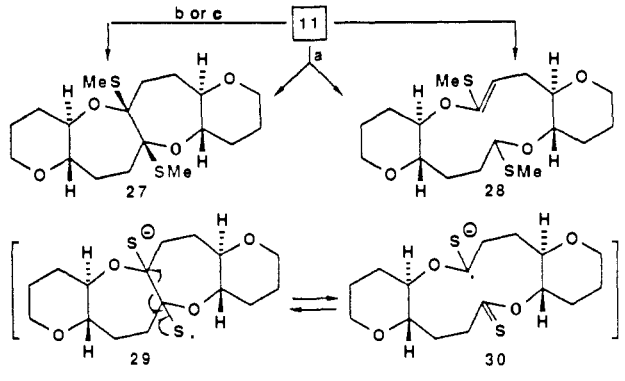
(20) For a preliminary communication on some chemistry of dithiatopazine, see: Nicolaou, K. C.; Hwang, C. K.; DeFrees, S.; Stylianides, N. *J. Am. Chem. Soc.* **1988**, *110*, 4868.

**Scheme V**[a]




[a] Reaction of dithiatopazine (**11**) with thiophenoxide ion. Reagents and conditions: (a) 3.0 equiv of PhSH, 2.0 equiv of NaH, THF, 0 °C, 24 h, 60%; (b) 1.5 equiv of L-Selectride, THF, −78 °C, 15 min, then 15.0 equiv of MeI −78 → +25 °C, 30 min, 65%.

**Scheme VI**[a]



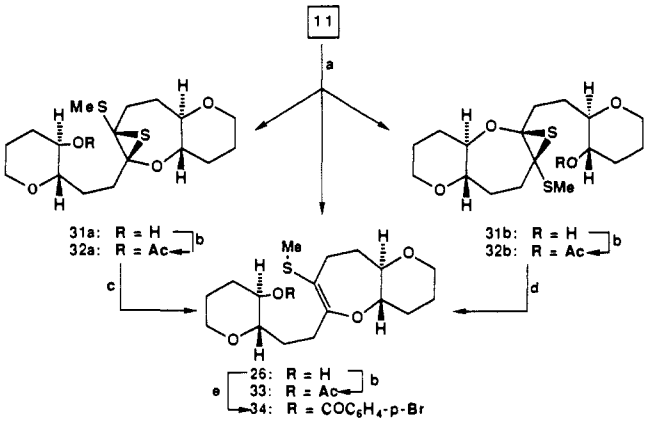

[a] Reagents and conditions. (a) 3.0 equiv of sodium naphthalide, THF, −78 °C, 0.5 h, then 15.0 equiv of MeI −78 → 25 °C, 0.5 h, **27**, (70%), **28**, (29%); (b) 2.2 equiv of L-Selectride, THF, −78 °C, 15 min, then 15.0 equiv of MeI −78 → +25 °C, 0.5 h, 70%; (c) 2.0 equiv of $NaBH_4$, EtOH, 0 °C, 20 s, then 15.0 equiv of MeI, 0 → 25 °C, 0.5 h, 93%.

Scheme V shows an interesting reaction of dithiatopazine (**11**) with thiophenoxide ion leading to the tricyclic system **25** via the presumed intermediates **23** and **24** as outlined. The structure of **25** was based on its spectral data and chemistry. Particularly revealing was the $^{13}C$ NMR spectrum (125 MHz, benzene-$d_6$) of **25** exhibiting signals at $\delta$ 164.20 and 117.19 for the enolic carbons. Rupture of the disulfide linkage in **25** with L-Selectride followed by quenching with MeI led to the methylthio ether **26**, a compound encountered in another reaction of dithiatopazine (Scheme VII, vide infra).

The reduction of dithiatopazine (**11**) with sodium naphthalide, L-Selectride, and $NaBH_4$ was then investigated (Scheme VI). Sodium naphthalide reacted rapidly with **11** at −78 °C producing, upon quenching with MeI and warming to room temperature, the bis(methylthio) ethers **27** (70%) and **28** (29%). These previously prepared compounds[17] were presumed to arise from the initially formed radical anion **29** (Scheme VI). Thus, **29** may accept a second electron to give the dianion corresponding to **27** or it may rearrange by rupturing the central C–C bond leading to radical anion **30**, which can easily be imagined to give rise to both **27** and **28**.[19]

A novel series of compounds was obtained when dithiatopazine (**11**) was reduced with $NaBH_4$. Scheme VII depicts the transformations taking place when **11** was exposed to $NaBH_4$ in EtOH at 25 °C for 10 min, followed by quenching with excess MeI. The three products **31a**, **31b**, and **26** were isolated in 35, 28 and 12% yields, respectively, by preparative thin-layer chromatography [$R_f$ values (silica, 30% EtOAc in benzene): **31a**, 0.27; **31b**, 0.23; **26**, 0.20]. The structures of these compounds were based on spec-

Scheme VII[a]




[a] Reagents and conditions. (a) 2.0 equiv of $NaBH_4$, EtOH, 0 °C, 10 min, then 15.0 equiv of MeI, 0.5 h, **31a** (35%), **31b** (28%), **26** (12%); (b) 2.0 equiv of $Ac_2O$, 2.0 equiv of $Et_3N$, 0.1 equiv of DMAP, $CH_2Cl_2$, 0 °C, 1 h; **32a** (85%), **32b** (80%), **33** (81%); (c) 4.0 equiv of $Ph_3P$, benzene, 50 °C, 48 h, from **32a** (87%); (d) 4.0 equiv of $Ph_3P$, benzene 50 °C, 48 h, from **32b** (80%); (e) 1.0 equiv of *p*-$BrC_6H_4COCl$, 2.0 equiv of $Et_3N$, 0.1 equiv of DMAP, $CH_2Cl_2$, 0 °C, 24 h, 77%.

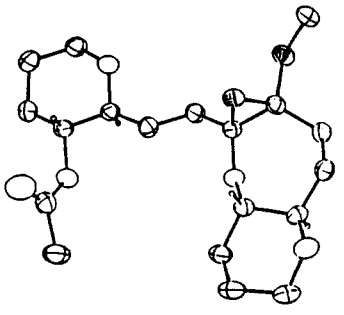
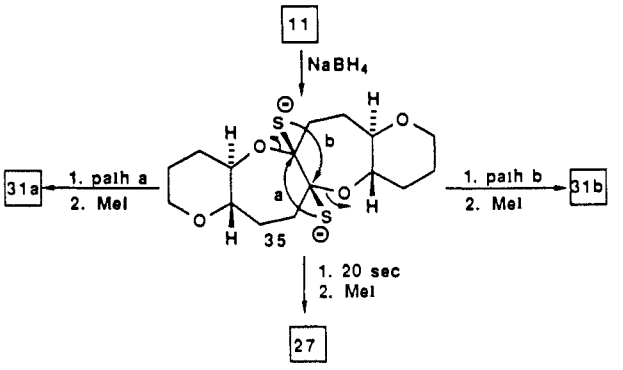


**Figure 2.** ORTEP drawing of **32a**. Bond distances (Å): S1–C8 = 1.849 (4); S1–C9 = 1.850 (4); S2–C9 = 1.792 (4); S2–C19 = 1.784 (5); C8–C9 = 1.483 (5). Bond angles (deg): C8–S1–C9 = 47.3 (2); C9–S2–C19 = 100.7 (2); S1–C8–C9 = 66.4 (2); S1–C9–C8 = 66.3 (2).

troscopic and chemical data. Thus, all three compounds yielded, upon acetylation with excess acetic anhydride, acetates **32a** (85%), **32b** (80%), and **33** (81%), respectively. Furthermore, exposure of either acetate **32a** or **32b** to excess $Ph_3P$ at 50 °C led to the unsaturated compound **33** via desulfurization, suggesting the presence of the episulfide moiety and the diastereomeric relationship of these two episulfides. The $^{13}C$ NMR spectra of compounds **32a** and **32b** also supported these structures by exhibiting the expected signal for the episulfide carbons (125 MHz, benzene-$d_6$) **32a**: $\delta$ 97.58 (SCO), 82.45 (SCS); **32b**: $\delta$ 94.07 (SCO), 81.98 (SCS). The $^{13}C$ NMR spectrum of compound **33** exhibited signals at $\delta$ 118.29 and 161.77, suggesting a double bond of the type shown in this structure. The *p*-bromobenzoate **34**, obtained from **26** by standard methods, failed as yet to form suitable crystals for X-ray crystallographic analysis. Compound **32a** formed monoclinic colorless crystals from hexane, mp 119–120.5 °C. An X-ray crystallographic analysis of this compound confirmed the proposed structure and provided further support for the assigned structures of **31a** and **31b**. Figure 2 shows an ORTEP drawing of **32a** (see Table IV, supplementary material, for X-ray data).

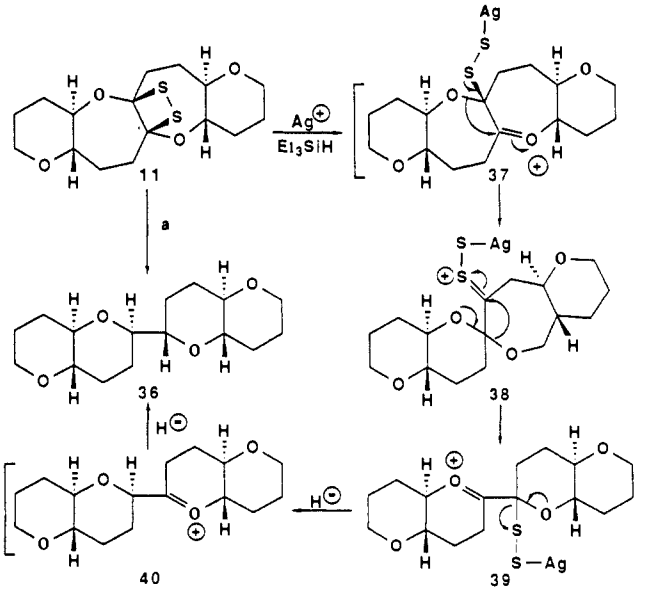
Mechanistically, **31a** and **31b** may arise from **11** as outlined in Scheme VIII. Thus, initial reductive cleavage of the S–S bond leads to the dianion **35**, which may suffer rearrangement via path a, leading to compound **31a**, or path b, leading to the diastereomeric compound **31b**. The intermediacy of **35** was confirmed by its interception with MeI after a 20-s exposure to $NaBH_4$, leading to the bis(methyl sulfide) ether **27** (93% yield). Episulfides **31a** and **31b** carrying an additional sulfur and an oxygen atom in this particular arrangement are, to the best of our knowledge, the first examples of their class.[21]

Scheme VIII[a]




[a] A plausible mechanism for the formation of episulfides **31a** and **31b**.

Scheme IX[a]




[a] Reagents and conditions. (a) 2.0 equiv of $AgBF_4$, 15.0 equiv of $Et_3SiH$, $CH_2Cl_2$, 25 °C, 2 h, 92%.

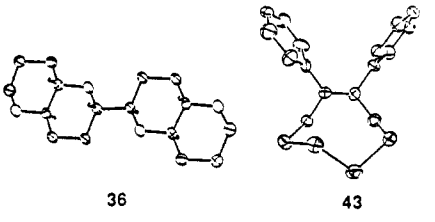
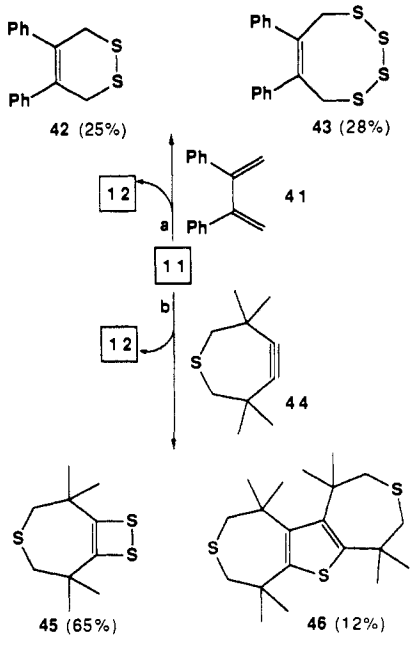



**Figure 3.** ORTEP drawings of **36** and **43**.

A most remarkable and stereospecific rearrangement took place when dithiatopazine (**11**) was reacted with excess $Et_3SiH$ in the presence of $AgBF_4$ in $CH_2Cl_2$ (Scheme IX). The spectral data of the single product obtained in 92% yield indicated a symmetrical structure (eight $^{13}C$ NMR signals), but failed to distinguish between the 6,6,6,6 structure **36** and the initially suspected isomeric 6,7,7,6 structure corresponding to the dithiatopazine skeleton. Fortunately, the product of this reaction crystallized in colorless needles from ether–hexane, mp 155–156 °C. An X-ray crystallographic analysis revealed structure **36** for the product (see ORTEP drawing, Figure 3), proving that a skeletal rearrangement

(21) To the best of our knowledge these oxygen- and sulfur-substituted episulfides are the first examples of this type. Some related examples are mentioned in: (a) Dittmer, C. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 7, p 131. (b) Fokin, A. V.; Kolomiets, A. F. *Russ. Chem. Rev. (Engl. Transl.)* **1975**, *44*, 138.

**Scheme X**[a]




[a] Transfer of sulfur from dithiatopazine (**11**) to unsaturated substrates. Reagents and conditions: (a) toluene, 100 °C, 5 h, **42** (25%), **43** (28%), **12** (90%); (b) toluene, 100 °C, 5 h, **45** (65%), **46** (12%), **12** (95%).

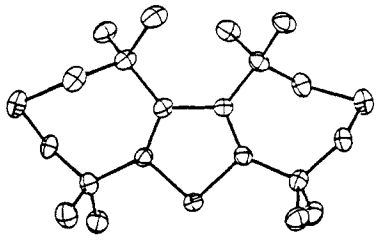


**Figure 4.** ORTEP drawing of **46**. Bond distances (Å): S1–C1 = 1.808 (8); S1–C12 = 1.777 (7); S2–C9 = 1.719 (7); S2–C10 = 1.726 (5); S3–C6 = 1.807 (6); S3–C7 = 1.767 (7); C4–C9 = 1.355 (7); C3–C4 = 1.518 (8); C3–C10 = 1.360 (9). Bond angles (deg): C1–S1–S12 = 100.6 (3); C9–S2–C10 = 92.8 (3); C6–S3–C7 = 100.3 (3); S2–C9–C4 = 112.3 (4); C3–C4–C9 = 111.0 (5); C4–C3–C10 = 110.6 (4); S2–C10–C3 = 112.2 (4).

had indeed taken place. A speculative mechanism for this rearrangement is depicted in Scheme IX. According to this proposal, the 1,2-dithietane moiety in **11** is ruptured by the silver ions, leading to oxonium species **37**. Two consecutive oxygen migrations–hydride additions then lead to the observed product (**36**) via intermediates **37**–**40**.

We then investigated the ability of dithiatopazine (**11**) to donate its sulfur atoms to appropriate acceptors as a potential route to novel polysulfides.[22] Scheme X summarizes some of the findings. Thus, diene **41**, when heated in toluene at 100 °C with dithiatopazine (**11**), led to disulfide **42**[22b,c] (25%) and tetrasulfide **43**[23] (28%). In this reaction, dithiatopazine (**11**) was converted to olefin **12**[17] in high yield (90%). The structure of tetrasulfide **43** was confirmed by an X-ray crystallographic analysis (see ORTEP structure, Figure 3). Under similar conditions, the highly strained acetylenic compound **44**[24] was converted to dithietene **45**[14] (65%)

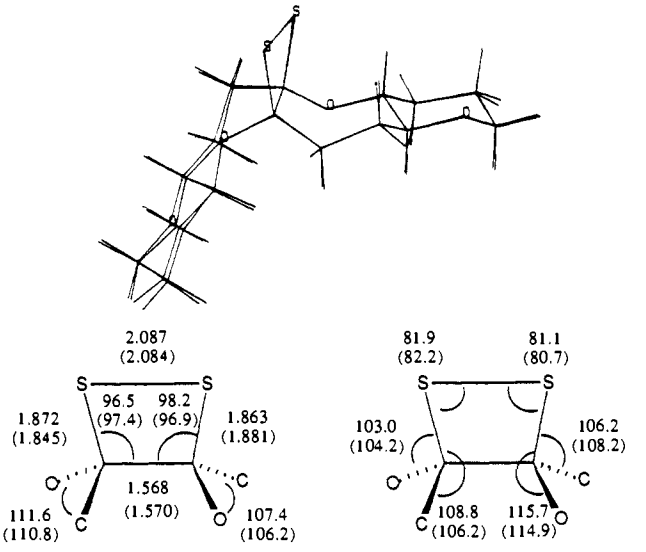
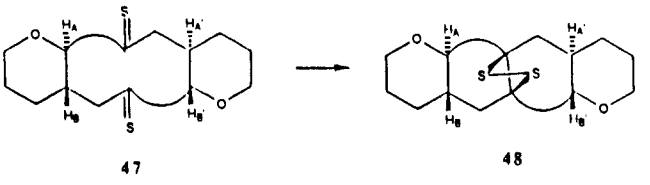



**Figure 8.** Superposition of the X-ray and MM2-optimized structures of dithiatopazine **11**; selected geometric variables. X-ray values are in parentheses.

**Scheme XI**




and the novel thiophene **46** (12%), mp 130.5–133 °C, resolidifing and then melting again at 160 °C (hexane), with olefin **12** again being formed in high yield (95%). The structure of thiophene **46** was confirmed by an X-ray crystallographic analysis (see ORTEP structure, Figure 4; see also Table IV, supplementary material, for X-ray crystallographic data).

### Kinetic Study of the Thermal Decomposition of Dithiatopazine

As discussed above, dithiatopazine (**11**) undergoes thermal decomposition to olefin **12**, extruding its two sulfur atoms, which could be trapped with suitable acceptors. In order to obtain a better understanding of this potentially useful process, we carried out thermal reactions at 80, 90, 100, and 110 °C. The reactions were performed in a sealed NMR tube in toluene-$d_8$ (0.01 M concentration) and followed by recording the $^1$H NMR spectrum (500 MHz) at regular intervals. The intensities of the signals at $\delta$ 2.65 [for dithiatopazine (**11**)] and 2.80 (for olefin **12**) were used to determine the concentrations for the two compounds present in solution. The results (Table III) supported the expected first-order character of the decomposition **11** → **12** at each of the temperatures examined. Figure 5 (supplementary material) shows the initial stages of the kinetic run at 110 °C (concentrations of **11** and **12** versus time), revealing a half-life ($t_{1/2}$) of 1.1 h. Figure 6 (supplementary material) presents the linear relationship of ln (% of **11**) versus time (first-order kinetics) at 110 °C, whereas Figure 7 (supplementary material) depicts an Arrhenius plot showing the relationship of ln (rate) versus $1/T$ from which the activation energy for the thermal extrusion of diatomic sulfur from **11** was calculated to be $E_a$ = 26.3 kcal/mol.

### Molecular Mechanics Evaluation of Dithiatopazine

A number of intriguing questions are raised by the preparation of the shelf-stable dithiatopazine (**11**). Relative to transient **2** and **3**, why does it not spontaneously extrude diatomic sulfur? Similarly, what prevents the related formation of the polytetrahydropyran (THP) system **15**? What characterizes dithiatopazine's conformational profile? To address these and related

(22) For some recent references of the generation and trapping of diatomic sulfur, see: (a) Steliou, K.; Gareau, Y.; Harpp, D. N. *J. Am. Chem. Soc.* **1984**, *106*, 799. (b) Reference 7. (c) Schmidt, M.; Gorl, V. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 887. (d) Ando, W.; Sonobe, J.; Akasaka, T. *Tetrahedron Lett.* **1987**, *28*, 6653.

(23) Dodson, R. M.; Srinivasan, V.; Sharma, K. S.; Sauers, R. F. *J. Org. Chem.* **1972**, *37*, 3267.

(24) Krebs, A.; Kimling, H. *Justus Liebigs Ann. Chem.* **1974**, 2074. We thank Professor A. Krebs for a generous gift of compounds **44** and **45**.

**Table V.** MM2 Parameters for Dithietanes and Episulfides[a,b]

Bond Stretching and Dipole

| bond | $l_0$, Å | $k$, mdyn/Å$^2$ | D |
|---|---|---|---|
| S–S | 2.068 | 3.10 | 0.0 |
| $C_{sp3}$–S | 1.815[c] | 3.21 | 0.0 |
| $C_e$–$S_e$ | 1.840 | 3.21 | 1.20 |
| $C_e$–O | 1.383 | 5.36 | 0.44 |
| $C_e$–S | 1.776 | 3.21 | 1.20 |
| $C_e$–$C_e$ | 1.454 | 4.40 | 0.0 |
| $C_e$–H | 1.083 | 4.60 | 0.0 |

Angle Bending

| angle | $\theta_0$ | $k$, mdyn/rad$^2$ | angle | $\theta_0$ | $k$, mdyn/rad$^2$ |
|---|---|---|---|---|---|
| $C_{sp3}$–S–S | 93.80 | 0.97 | $C_{sp3}$–$C_e$–O | 109.57 | 0.45 |
| $C_{sp3}$–$C_{sp3}$–S | 109.49 | 0.45 | $C_{sp3}$–$C_e$–$C_{sp3}$ | 120.00[c] | 0.45 |
| O–$C_{sp3}$–S | 102.18 | 0.50 | $C_{sp3}$–$C_e$–S | 115.72 | 0.50 |
| $C_e$–$C_e$–$S_e$ | 66.40 | 0.50 | S–$C_e$–$S_e$ | 115.29 | 0.42 |
| $C_{sp3}$–$C_e$–$C_e$ | 120.00 | 0.60 | $C_{sp3}$–O–$C_e$ | 110.50 | 0.77 |
| O–$C_e$–$C_e$ | 115.40 | 0.60 | $C_e$–O–LP | 104.20 | 0.35 |
| S–$C_e$–$C_e$ | 119.09 | 0.55 | $C_{sp3}$–S–$C_e$ | 96.14 | 0.72 |
| $C_e$–$S_e$–$C_e$ | 47.20 | 0.50 | H–$C_e$–$S_e$ | 116.50 | 0.36 |
| O–$C_e$–$S_e$ | 108.50 | 0.45 | H–$C_e$–$C_e$ | 118.20 | 0.36 |
| $C_{sp3}$–$C_e$–$S_e$ | 116.33 | 0.45 | H–$C_e$–H | 115.80 | 0.32 |

Torsions[c,d]

| angle | $V_1$ | $V_2$ | $V_3$ |
|---|---|---|---|
| $C_{sp3}$–S–S–$C_{sp3}$ | 0.203 | −7.735 | −3.060 |
| $C_{sp3}$–$C_{sp3}$–S–S | 0.00 | 0.00 | 1.10 |
| $C_{sp3}$–O–$C_{sp3}$–S | 0.50 | −0.42 | 0.00 |
| S–$C_{sp3}$–$C_{sp3}$–S | −0.80 | 0.90 | 1.20 |
| O–$C_{sp3}$–S–S | 0.00 | 0.00 | 0.30 |
| $C_{sp3}$–S–$C_{sp3}$–O | −0.62 | 0.30 | 0.25 |
| $C_{sp3}$–$C_{sp3}$–O–$C_e$ | 0.00 | 0.00 | 0.40 |
| $C_{sp3}$–O–$C_e$–$S_e$ | 0.50 | −0.42 | 0.00 |
| $C_{sp3}$–$C_e$–$C_e$–O | 0.20 | 0.30 | 0.10 |
| $C_{sp3}$–$C_e$–$C_e$–$S_e$ | 0.20 | 0.30 | 0.10 |
| O–$C_e$–$C_e$–$S_e$ | 0.14 | 0.00 | 0.00 |
| $C_{sp3}$–$C_{sp3}$–$C_e$–$S_e$ | 0.14 | 0.00 | 0.00 |
| $C_{sp3}$–$C_{sp3}$–$C_e$–O | 0.00 | 0.00 | 0.00 |
| $C_{sp3}$–O–$C_e$–$C_{sp3}$ | 0.40 | 0.50 | 0.50 |
| $C_{sp3}$–O–$C_e$–$C_e$ | 0.30 | 0.00 | 0.50 |
| $C_{sp3}$–$C_e$–$S_e$–$C_e$ | 0.00 | 0.00 | 0.10 |
| O–$C_e$–$S_e$–$C_e$ | 0.00 | 0.00 | 0.10 |
| O–$C_e$–$C_e$–$C_e$ | 0.20 | 0.30 | 0.10 |
| $C_{sp3}$–$C_{sp3}$–$C_e$–S | 0.00 | 0.00 | 0.69 |
| $C_{sp3}$–S–$C_e$–$C_{sp3}$ | −0.62 | 0.30 | 0.25 |
| $C_{sp3}$–S–$C_e$–$C_e$ | −0.62 | 0.30 | 0.25 |
| $C_{sp3}$–$C_e$–$C_e$–S | 0.20 | 0.30 | 0.10 |
| S–$C_e$–$S_e$–$C_e$ | 0.00 | −0.90 | 0.30 |
| $C_{sp3}$–S–$C_e$–$S_e$ | 0.00 | −0.90 | 0.30 |
| O–$C_e$–$C_e$–S | −0.80 | 0.90 | −0.30 |
| O–$C_e$–$C_e$–O | 0.20 | 0.30 | 0.10 |
| S–$C_e$–$C_e$–$S_e$ | 0.20 | 0.30 | 0.10 |
| H–$C_{sp3}$–O–$C_e$ | 0.00 | 0.00 | 0.50 |
| H–$C_{sp3}$–S–$C_e$ | 0.00 | 0.00 | 0.54 |
| H–$C_{sp3}$–$C_e$–S | 0.00 | 0.00 | 0.69 |
| H–$C_{sp3}$–$S_e$–$C_e$ | 0.00 | 0.00 | 0.54 |
| H–$C_{sp3}$–$C_e$–$S_e$ | 0.00 | 0.00 | 0.30 |
| H–$C_{sp3}$–$C_e$–O | 0.00 | 0.00 | 0.70 |
| H–$C_e$–$S_e$–$C_e$ | 0.00 | 0.00 | 0.54 |
| H–$C_e$–$C_e$–$S_e$ | 0.00 | 0.00 | 0.33 |

[a] The force field equations are those found in ref 25. [b] $C_e$ and $S_e$ are episulfide carbon and sulfur, respectively. [c] A number of the parameters, particularly the force constants and the torsions, have been borrowed by analogy from the original MM2 set.[25] [d] For all LP-containing torsions $V_1 = V_2 = V_3 = 0.00$.

questions, the Allinger MM2 force field[25] was parameterized for the oxygen-substituted 1,2-dithietane system (Table V). Application of the enhanced force field to the X-ray conformation of **11** shows that the four-membered ring disulfide geometry is well described in this framework (Figure 8).

(25) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *No. 13*, 395.

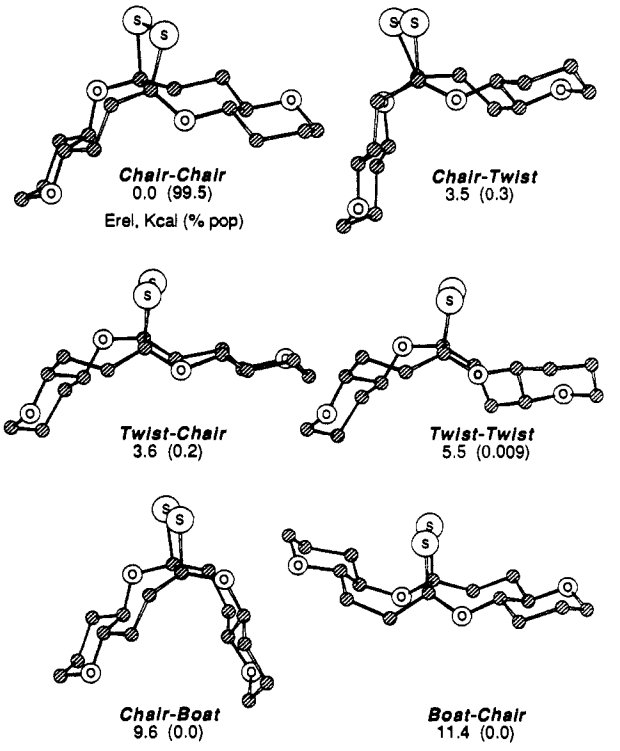
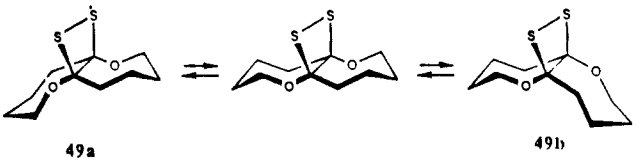



**Figure 9.** The six lowest energy dithiotopazine conformations and their relative energies (MM2; kilocalories). Percent populations were calculated as a Boltzmann distribution.

**Scheme XII**



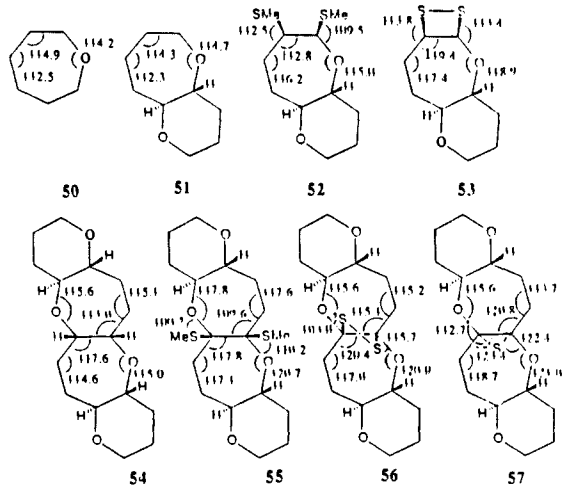

The present synthetic route to polycyclic 1,2-dithietanes **11** and **15** involves internal bridging of a medium-sized ring that is constrained by trans fusion to a pair of tetrahydropyrans. The bridgehead hydrogen atoms along each edge of representations **47** and **48**, $H_A/H_{A'}$ and $H_B/H_{B'}$, respectively, are syn to one another (Scheme XI). This particular topology, inspired by the similarly disposed central region of the natural marine substance brevetoxin,[17,26] leads to several consequences for the molecules under consideration in this work.

Consider the central tricyclic core of **11** unaccompanied by the terminally fused tetrahydropyran rings. The two seven-membered oxacycles under conditions of rapid exchange can be expected to exist as a mixture of degenerate chair–chair conformations **49a** and **49b** interconverting by way of *C*2-symmetric conformers (Scheme XII). The $^{13}C$ NMR spectrum of the simplified 7,4,7 ring system would then show only the five different carbons.

The trans-fused end rings in dithiatopazine (**11**) prevent this process completely since gauche carbon and oxygen atoms would be forced anti, an impossible situation in a six-membered ring. As a result, **11** shows the full complement of 16 different carbons in the $^{13}C$ NMR spectrum. Furthermore, the signals appear to belong to a single conformational isomer. The six lowest energy conformations were located (Figure 9) by employing an efficient ring search procedure[27] for **11**. The global minimum, the all-chair X-ray conformation, comprises 99.5% of the conformer mix based on a Boltzmann distribution of the MM2 relative energies. The next nearest conformations, the seven-membered-ring chair–twist

(26) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514.
(27) Smith, G. M. *QCPE* **1986**, *No. 6*, 510.

**Chart IV**[a]



[a]Selected bond angles around the central bridgehead ($C_b$–$C_b$) of several MM2-optimized structures. Structures **54–57** correspond to the seven-ring chair–chair conformations.

and twist–chair species, are predicted to be 3.5 and 3.6 kcal/mol higher in energy, respectively. Because of these results, we suggest that the chemistry and spectroscopy of dithiatopazine (**11**) can be understood entirely by considering the chair–chair X-ray form.

In spite of the all-chair disposition of rings in **11**, there are a number of unusually large bond angles contributing to the overall molecular strain. In particular, the C–C–$C_b$, C–$C_b$–$C_b$, and C–O–$C_b$ angles in one of the two *exo*-cycloheptane chairs range from 117 to 122°. Comparison of the structures in Chart IV makes it clear that addition of the dithietane ring to the fused six- and seven-membered-ring systems (**51** → **52** → **53**) is sufficient to induce the enlarged bond angles (117–120°). Further elaboration to the pentacyclic system of dithiatopazine (**53** → **56**) produces only minor changes. In contrast, the process of angle deformation for dithioether **55**[19] occurs upon the hypothetical sulfuration of the bridgehead carbons of **54** (**52** → **54** → **55**). Bridgehead quaternization and/or closure to a small ring thereby transmits angle strain throughout the tetracyclic structure **54**.

A possible dynamic feature for **11** is the dithietane ring inversion taking the $\phi$(C–S–S–C) dihedral angle from its MM2 equilibrium position of −10° to a corresponding positive value. While we have no evidence for such motion, the literature of disulfide conformational analysis makes it clear that the structure corresponding to $\phi$(C–S–S–C) = 0° is a transition state between lower energy forms.[28] In the present case the disulfide bond was constrained to 0 and +10° with full geometric optimization of the remainder of the molecular structure. The MM2 energy rises to 0.6 and 2.1 kcal/mol, respectively, relative to the −10° minimum. The $\phi$(C–S–S–C) = +10° structure, when reoptimized without constraints, returns spontaneously to the −10° region.

The basis for a single minimum on one side of the $\phi$(C–S–S–C) = 0° torsional energy surface for dithiatopazine (**11**) is found as the subtle interplay of two factors. On the one hand, the energetics for S–S passage from −10 → 0 → +10° for either $H_2S_2$ or a simple cyclic disulfide system is undemanding; only a small energy price being exacted at the 0° barrier (1–2 kcal/mol). Second, the structural asymmetry introduced by the nonequivalent seven-membered-ring chairs flanking the dithietane ring (Figure 9 and Chart IV) results in a preference for small negative values of $\phi$(C–S–S–C). This is highlighted by MM2 optimization of S–S rotational isomers of the analogue of **11** with O → $CH_2$ for the oxygens attached to the four-membered ring. The $\phi$(C–S–S–C) energy surface from −10° to +10° is nearly flat (0°, 0.1 kcal/mol).

In summary, dithiatopazine (**11**) exists essentially as a single chair–chair conformation with respect to the four oxygen-containing rings at ambient temperature. The molecule undoubtedly

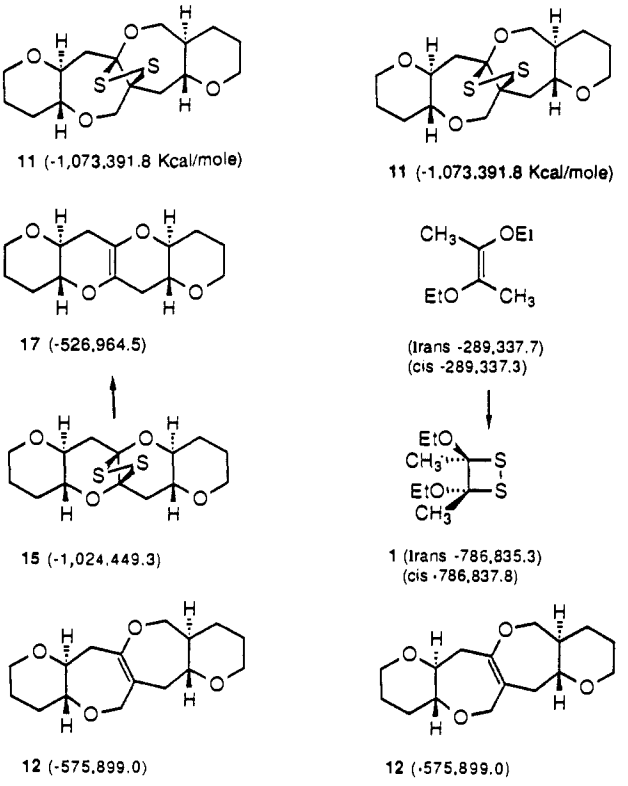
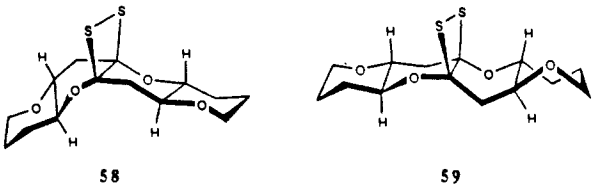



**Figure 10.** Two isodesmic reactions comparing the relative stability of dithiotopazine to loss of $S_2$. The hypothetical reaction on the left predicts **11** to be thermally stable by comparison to **12**[$E$(**15** + **12**) − (**11** + **17**) = 8.0 kcal/mol]. The isodesmic expression on the right posits **11** to be more susceptible to $S_2$ extrusion than either isomer of **1**[$E$(**1** + **12**) − (**11** + trans/cis) = −4.8 and −7.7 kcal/mol, respectively]. Energies (kilocalories) were obtained by fixed-point PRDDO calculation for the MM2 global minimum of each structure.

**Chart V**



experiences a mobile dithietane breathing motion for small values of $\phi$(C–S–S–C). The otherwise rigid molecule does not represent a case of conformationally enforced CS–SC chirality sought in other systems.[2] Whether the facile ring vibration contributes in a fundamentally important manner to the transition state for $S_2$ extrusion cannot be decided. The low-energy torsional freedom has the potential, however, for assisting either single C–S bond homolysis or a concerted [2 + 2] retrocycloaddition.

### Instability of 1,2-Dithietanes 1 and 15

Failure to prepare the all-tetrahydropyran (THP) pentacycle **15** under photochemical conditions identical with that used for dithiatopazine (**11**) is readily understood as a consequence of the ring-fusion stereochemistry depicted by **47** and **48**. Radiation-induced cyclization of the dithiono ester **16** to dithietane **15** can be accomplished only by forcing one of the four six-membered rings into a boat conformation. In addition, the two lowest energy forms obtained by stochastic ring search[29] place the boats adjacent to the dithietane ring (**58** and **59**, Chart V).

Obviously the strain energy of dithietane **58** is raised considerably relative to its enol ether **17** by comparison with dithiatopazine **11** relative to **12**. An estimate of the difference is given by an isodesmic reaction in which the MM2-optimized structures

(28) Snyder, J. P.; Jorgensen, F. *Tetrahedron* **1979**, *35*, 1399.

(29) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

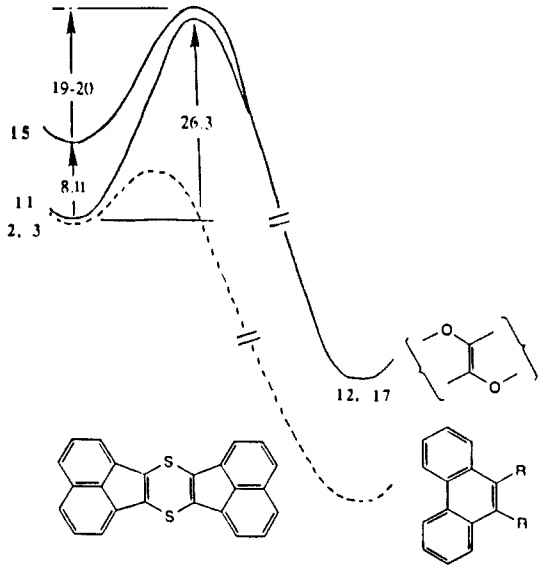



**Figure 11.** Energetics of singlet $S_2$ extrusion from dithietanes; activation barrier for **11** (26.3 kcal/mol) and **15** (ca. 19–20 kcal/mol, estimated). Barriers for **2** and **3** are reduced by aromatic product stabilization (dotted line).

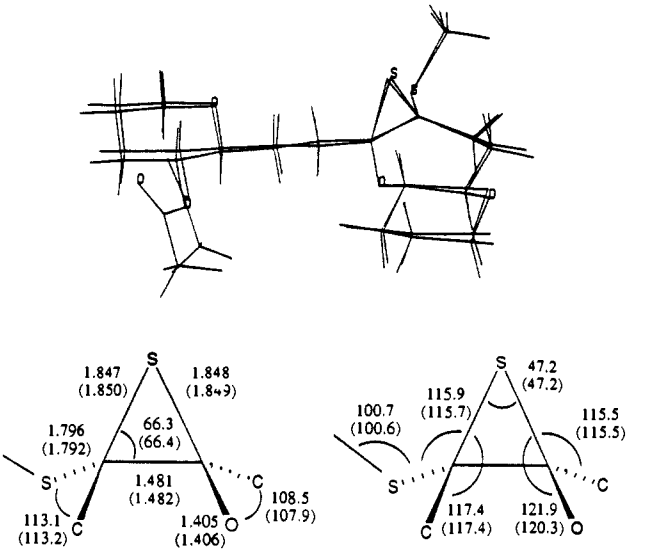



**Figure 12.** Superposition of the X-ray and MM2-optimized structures of episulfide **32a**; selected geometric variables. X-ray values are in parentheses.

were submitted to fixed-point energy evaluations by PRDDO[30] (Figure 10).

Dithietane **15** is predicted to be 8.0 kcal more exothermic to extrusion of $S_2$ than dithietane **11**. Since the latter expels sulfur with an activation energy of 26.3 kcal/mol, Hammond's postulate suggests that the barrier for $S_2$ loss in **15** may well be 6–7 kcal lower. The relationship is depicted in Figure 11. In this case, disulfide **15** would not survive the ambient photolytic closure of dithiono ester **16**. It might, however, be observable at lower temperatures.

Similar considerations apply to compounds **2** and **3** (Chart II) experiencing an energy-lowering resonance stabilization in the product hydrocarbons. Dithietane **3** (R = Ph), for example, is predicted to extrude $S_2$ with $\Delta H = -37.1$ kcal/mol.[6] This is, however, not the case for the simple dithietane **1**. Strain and resonance effects can be expected to play a reduced role in the energy requirements for thermal decomposition. For evaluation, the cis and trans isomers of **1** and the corresponding enol ethers were geometry optimized with MM2. Again fixed-point PRDDO calculations were performed on the resulting structures. Isodesmic comparison suggests unfused **1** to be 5–8 kcal/mol more stable than dithiatopazine (**11**) relative to the corresponding olefins (Figure 10).

The principle distinction between **1** and **11** is undoubtedly the ability of the latter to distribute its internal vibrational energy to regions of the molecule uncoupled to the thermally labile C–S bonds;[31] namely, throughout the network of bonds in the oxepane and tetrahydropyran rings. The simple system **1** possesses no such resources. The percentage of internal thermal energy focused in the C–S vibrations is therefore much higher than for the same bonds in **11**. Thus, even though the barrier to $S_2$ extrusion for **1** may be somewhat higher than for **11**, the probability for traversing it is likewise higher. Thermal stability is thereby diminished. The addition of large hydrocarbon substituents to otherwise thermally labile small molecules is a device used by numerous researchers to obtain stable members of interesting compound classes. Recent examples that undoubtedly take advantage of this mechanism are heavily alkylated derivatives of tetrahydropyran,[32] cyclopropanones,[33] benzvalene, and prismane.[34]

In light of these considerations it appears less likely that lone-pair–lone-pair repulsion on adjacent sulfurs[7] is responsible for thermal instability in highly substituted systems such as **2**, **3**, and **15**. For these cases, thermodynamic and thermochemical factors appear to dominate the fragmentation process. Given the isolation of simple dioxetanes[8] and a 1,2-oxathietane[9] accompanied by short bond lengths between the lone-pair-bearing atoms relative to dithietanes, similar conclusions can tentatively be drawn for **1** and its analogues. Further theoretical work will be necessary to deconvolute the energetic components in a more rigorous manner.

In conclusion, the successful isolation of dithiatopazine (**11**) and its thermal stability can be attributed to three factors. First is a stereochemical constitution (**48**) that permits low-energy conformations for each of its six- and seven-membered rings. Other ring-fusion topologies can promote a decisive lifting of the ground-state energy. For **11** a favorable energy gap from ground to transition state for $S_2$ extrusion is thereby created. Second, the enol ether product **12**, while stable, does not enjoy the additional stabilizing influence of an extended $\pi$-aromatic system, as do the products from $S_2$ loss of **2** and **3**. A highly exothermic (or exergonic) process can, in the spirit of Figure 11 (dotted line), lower the barrier to decomposition. Both **11** and **12** then cooperate to produce a "well-behaved" potential energy surface for fragmentation. Finally, the molecular bulk of **11** assists diffusion of internal thermal energy away from the C–S bonds. Externally applied energy is, therefore, required to raise the amplitude of C–S vibration sufficiently to cause bond rupture.

### Structure of Episulfide 19

Compound **19** shares with dithiatopazine (**11**) a conformational energy profile dictated by the shape of the six- and seven-membered rings. A set of MM2 episulfide parameters derived from the X-ray structure of **32a** (Table V and Figure 12; see Experimental Section) was applied to the polycyclic conformations given in Figure 9, but with the dithietane ring replaced by an episulfide moiety. The global minimum again proved to be the chair–chair conformation. Not surprisingly, the chair–twist and twist–chair forms are evaluated at 2.9 and 3.5 kcal/mol, respectively. The other conformers fall at relative energies between 4 and 14 kcal/mol.

(30) Marynik, D. S.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 1341.
(31) Lester, M. *Nature* **1988**, *331*, 12. Parmenter, C. S.; Stone, B. M. *J. Chem. Phys.* **1986**, *84*, 4710.
(32) Maier, G.; Pfreim, S.; Schafer, U.; Matusch, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *7*, 520.
(33) Pazos, J. F.; Greene, F. D. *J. Am. Chem. Soc.* **1967**, *89*, 1030. Sclove, C. B.; Pazos, J. F.; Camp, R. L.; Greene, F. E. *J. Am. Chem. Soc.* **1970**, *92*, 7488.
(34) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, *87*, 4004. Barlow, M. G.; Haszeldine, R. N.; Hubbard, R. *J. Chem. Soc. C* **1970**, 1232. Lemal, D. M.; Dunlap, L. H. *J. Am. Chem. Soc.* **1972**, *94*, 6562.

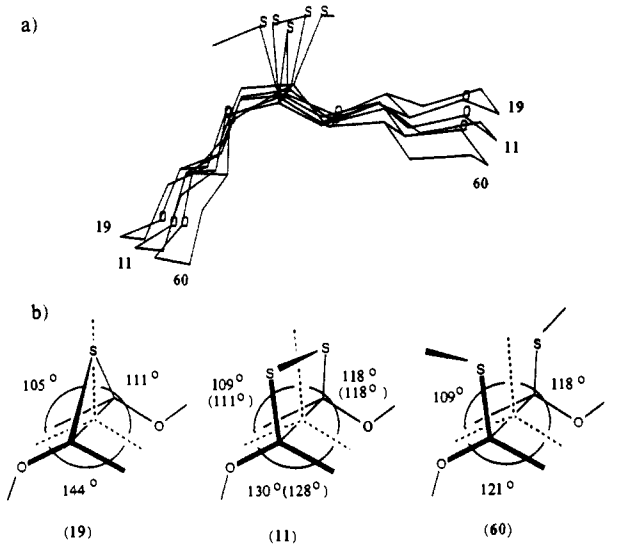



**Figure 13.** (a) Splaying of the "underside" of MM2-optimized dithiatopazine (**11**), episulfide **19**, and dithioether **60**; (b) angles between the best least-square planes around the bridgehead carbons. X-ray values for **11** are in parentheses.

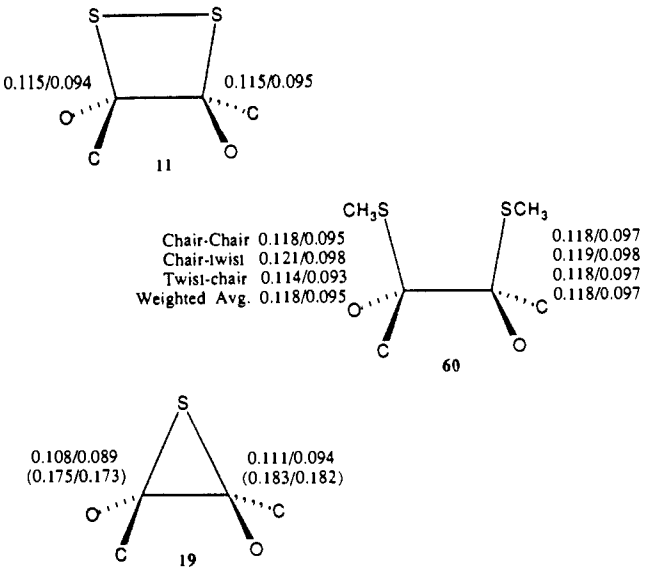



**Figure 14.** PRDDO atomic charges for chair–chair **11**, chair–chair **19**, and conformations of **60** (Mulliken/APS). For **19** the values in parentheses correspond to d orbitals on sulfur.

As in the case of dithiatopazine (**11**), the chemistry and spectroscopy of episulfide **19** originates exclusively from the chair–chair form. A comparison is given in Figure 13. Substitution of the three-membered ring (episulfide) for the four-membered ring (dithietane) causes splaying of the exocyclic bond angles of the former, which is clearly evident at the molecular extremities. Most affected is the plane–plane angle on the concave face of the structure anti to sulfur. Dithiatopazine (**11**) also behaves in a similar manner and spreads on its concave side when compared to the corresponding all-chair dithioether **60** (Figure 13).

An interesting difference between **11** and **19** is found in the $^{13}C$ NMR. The spectra are nearly superimposable except for the O–C–S quaternary carbons. Dithiatopazine **11** displays values of $\delta$(C–C–S) at 104.6 and 102.9 ($C_6D_6$); episulfide **19**, at $\delta$ 93.6 and 87.4 ($C_6D_6$). The upfield shifts for the latter are consistent with $^{13}C$ shift movements for the related contraction of cyclobutanes to cyclopropanes and sulfur-containing analogues.[35]

A surprising feature of the $^{13}C$ NMR spectra is the rather large separation of bridgehead O–C–S signals for episulfide **19** ($\Delta\delta$ = 6.2[36]) as compared with dithietane **11** ($\Delta\delta$ = 1.7). Similarly, the tetracyclic dithioether **60** displays its O–C–S signals at $\delta$ 98.6 and 96.0 ($\Delta\delta$ = 2.6). A rationale can be found in the differential deformation of O–$C_b$–S and C–$C_b$–$C_b$ bond angles around the pair of sulfurated quaternary bridgehead carbons as the structure is altered from open dithioether **60**, through dithietane **11** to episulfide **19** (**55** → **56** → **57**, Chart IV). In the $^{13}C$ NMR the paramagnetic shielding term ($\delta_p$) accounts for deviations of the electron distribution from spherical symmetry around carbon. Accordingly, it includes contributions from the electron density.[37] To obtain a qualitative measure of the effect, we subjected the MM2-optimized geometries to single-point PRDDO evaluation without d orbitals.[30] Mulliken and APS[38] charge densities were calculated. For dithioether **60**, all three conformations contributing to the ambient equilibrium were considered, the quaternary bridgehead charges being weighted according to the MM2 Boltzmann populations (298 K, chair–chair 72%, chair–twist 15%, twist–chair 13%).[19] The results portrayed in Figure 14 show the bridgehead carbons in **60** and **11** to be nearly equally charged, which is consistent with the diminutive $^{13}C$ $\Delta\delta$'s. The rigid episulfide **19**, however, exhibits a $\Delta\rho$ = 0.03 (Mulliken)/0.05 (APS) that increases to 0.08/0.09 when d orbitals are included. In this case, the d orbitals can be regarded as polarization functions, which provide a more realistic bonding description in the strained three-membered-ring system of **19**.

It should not be expected that charge densities alone can furnish a rigorous account of $^{13}C$ chemical shifts, though a number of excellent correlations are known.[37] Qualitatively, however, the bond and torsion angle variations depicted by Figures 13 and Chart IV appear to satisfactorily accommodate the bridgehead carbon shifts.

## Conclusion

Dithiatopazine (**11**), the first member of the 1,2-dithietane class of compounds, was synthesized and its properties were extensively investigated. The molecule shows intriging chemistry including a number of novel skeletal rearrangements, S–S bond ruptures, and "$S_2$"-transfer reactions. Unlike the dithionolactone precursor **10** and the dithioether **60**,[19] **11** is a rigid molecule confined at ambient temperatures to a narrow potential energy well, the average structure of which is adequately represented by the X-ray crystallographic all-chair conformation (Figure9). As a four-membered-ring disulfide, **11** possesses the smallest known S–S dihedral angle. Though $\phi$(C–S–S–C) exists primarily in one chiral manifestation (−11°), room temperature is sufficient to cause very low energy population of its local mirror image form (+11°).

The molecule is currently unique in serving as the only stable member of the dithietane family. It appears that molecular size and a favorable thermal decomposition energy surface (Figure 11) are primarily responsible for the isolation of **11**. The importance of stereochemistry is illustrated by the inability to isolate the 6,6,6,6 dithietane system **15**. It can be predicted that alternative fusion schemes for the terminal tetrahydropyran rings related to **15** may confer shelf stability on this system as well. The same can be said for dithietanes in which the ring oxy substituents are replaced by nitrogen or carbon. Further synthetic studies are contemplated to test these proposals.

## Experimental Section

**Photolysis of Dithionolactone 10. Preparation of Dithiatopazine (11) and Olefin 12.** A solution of dithionolide **10**[17] (50 mg, 0.15 mmol) in dry toluene (2 mL) was irradiated (Hanovia, quartz lamp) for 30 min. The solvent was removed under vacuum and the residue was subjected to flash chromatography (silica, 10% ethyl acetate in benzene) to afford, in order of elution, starting material **10** (5.0 mg, 10%), disulfide **11** (33.5 mg, 65%), and olefin **12** (5.5 mg, 12%). When **11** was irradiated under the above conditions for 1 **h**, olefin **12** was the only product isolated (85%).

(35) Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; John Wiley and Sons: New York, 1980; p 59.
(36) In $CDCl_3$ $\Delta\delta$(**19**) = 6.4 ppm.
(37) Craik, D. J. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 1.
(38) Armstrong, D. R.; Perkins, R. G.; Stewart, J. J. P. *J. Chem. Soc., Dalton Trans. 1* **1973**, 838.

Compound **11**: yellow-orange topazlike crystals, mp 134–135 °C (hexane); $R_f$ = 0.42 (silica, 15% ethyl acetate in benzene); IR ($CH_2Cl_2$) $\nu_{max}$ 2958, 2937, 2860, 1468, 1453, 1357, 1284, 1174, 1092, 1065, 965, 875 $cm^{-1}$; Raman (solid; laser 514.5 nm, Ar radiation) $\nu_{max}$ 554 (C–S), 490 (S–S) $cm^{-1}$; UV (hexane) $\lambda_{max}$ ($\epsilon$) 213 (4074), 426 (102) nm; $^1H$ NMR (250 MHz, $C_6D_6$) $\delta$ 4.05–3.80 (m, 3 H, C*H*O), 3.39–3.10 (m, 5 H, C*H*O, $CH_2O$), 3.08–1.47 (m, 16 H, $CH_2$); $^{13}C$ NMR (50.2 MHz, $C_6D_6$, TMS) $\delta$ 104.60, 102.85, 83.00, 81.27, 78.11, 76.50, 67.56, 66.91, 39.63, 34.96, 31.68, 31.11, 30.05, 29.71, 26.12, 25.82; HRMS (CI) calcd for $C_{16}H_{25}O_4S_2$ (M + H) 345.1194, found 345.1233. Compound **12**: colorless solid, mp 163–165 °C (from ether–hexane); $R_f$ = 0.33 (silica, 50% ether in petroleum ether); IR ($CH_2Cl_2$) $\nu_{max}$ 2950, 2858, 1468, 1459, 1435, 1345, 1226, 1175, 1092, 1021, 958 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.90–3.75 (br d, $J$ = 12.0 Hz, 2 H, $CH_2O$), 3.38–3.05 (m, 6 H, $CH_2O$, C*H*O), 2.62–2.45 (br dd, $J$ = 12.0, 12.0 Hz, 2 H, $CH_2C{=}C$), 2.24–1.41 (m, 14 H, $CH_2$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$, TMS) $\delta$ 148.28, 82.54, 80.48, 67.55, 31.26, 31.26. 29.09, 26.01; HRMS (CI) calcd for $C_{16}H_{24}O_4$ (M) 280.1675, found 280.1661.

**Preparation of Methyl Dithiatopazines 13a, 13b, and 13c and Olefins 14a and 14b.** The appropriate dithiono ester[19] (82 mg, 0.23 mmol) was irradiated by following the same procedure as described for **11**. Concentration and chromatography (silica, 10% ethyl acetate in benzene) gave the disulfides **13a** (10 mg, 12%), **13b** (10 mg, 12%), and **13c** (10 mg, 12%) as yellow oils and the enol ethers **14a** (15 mg, 22%) and **14b** (28 mg, 24%) as colorless oils. Compound **13a**: $R_f$ = 0.53 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 2940, 2860, 1180, 1150, 1100 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 4.61 (m, 1 H, C*H*O), 3.70 (m, 1 H, C*H*O), 3.64–3.58 (m, 3 H, C*H*O, $CH_2O$), 3.45 (m, 1 H, C*H*O), 3.13 (br t, $J$ = 8.1 Hz, 1 H, C*H*O), 3.03 (m, 1 H, C*H*O), 2.90 (br t, $J$ = 11.0 Hz, 2 H, $CH_2$), 2.56 (m, 1 H, C*H*), 2.23–2.10 (m, 2 H, $CH_2$), 2.90–1.95 (m, 1 H, C*H*), 1.83 (m, 2 H, $CH_2$), 1.63 (m, 1 H, C*H*), 1.41–1.07 (m, 6 H, $CH_2$), 1.17 (d, $J$ = 6.5 Hz, 3 H, $CH_3$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 110.15 (OCS), 102.29 (OCS), 81.16, 79.19, 79.08, 71.65, 67.44, 66.65, 38.25, 37.30, 37.16, 31.46, 31.03, 30.56, 25.75, 25.62, 20.01; HMRS (CI) calcd for $C_{17}H_{26}O_4$ (M – 2S) 294.183, found 294.183. Compound **13b**: $R_f$ = 0.51 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 2940, 2860, 1105, 1090, 1070, 1050, 965 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 3.98 (m, 1 H, C*H*O), 3.71 (dd, $J$ = 4.5, 11.0 Hz, I H, C*H*O), 3.62 (m, 1 H, C*H*O), 3.41 (t, $J$ = 12.8 Hz, 1 H, C*H*O), 3.23 (m, 1 H, C*H*O), 3.07 (m, 2 H, $CH_2O$), 2.97–2.77 (m, 3 H, C*H*O, $CH_2$), 2.23–2.18 (m, 2 H, $CH_2$), 2.09 (q, $J$ = 11.6 Hz, 1 H, C*H*), 1.93–1.88 (m, 1 H, C*H*), 1.82 (d, $J$ = 12.1 Hz, 1 H, C*H*), 1.68–1.60 (m, 2 H, $CH_2$), 1.41–1.11 (m, 6 H, $CH_2$), 0.98 (d, $J$ = 6.9 Hz, 3 H, $CH_3$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 110.17 (OCS), 102.66 (OCS), 82.38, 81.28, 77.87, 76.08, 67.70, 66.96, 40.27, 37.87, 34.70, 31.46, 31.00, 30.03, 26.11, 25.79, 17.65; HRMS (CI) calcd for $C_{17}H_{26}O_4$ (M – 2S) 294.183, found 294.183. Compound **13c**: $R_f$ = 0.47 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 2950, 2860, 1095, 1085, 1070, 965, 960 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 5.06 (m, 1 H, C*H*O), 3.72 (dd, $J$ = 4.6, 11.2 Hz, 1 H, C*H*O), 3.64 (br d, $J$ = 11.2 Hz, 1 H, C*H*O), 3.30–3.15 (m, 2 H, $CH_2O$), 3.06 (m, 2 H, $CH_2O$), 3.09–2.94 (m, 1 H, C*H*O), 2.77–2.73 (m, 2 H, $CH_2$), 2.17 (t, $J$ = 11.7 Hz, 2 H, $CH_2$), 2.04–1.95 (m, 2 H, $CH_2$), 1.81 (m, 1 H, C*H*), 1.67–1.56 (m, 3 H, $CH_2$), 1.41–1.15 (m, 5 H, $CH_2$), 1.01 (d, $J$ = 6.9 Hz, 3 H, $CH_2$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 108.47 (OCS), 104.70 (OCS), 82.57, 80.22, 78.09, 75.65, 67.57, 67.00, 39.02, 37.68, 24.70, 31.63, 30.46, 29.99, 26.06, 25.83, 18.26; HRMS (CI) calcd for $C_{17}H_{26}O_4$ (M – 2S) 294.183, found 294.184. Compound **14a**: $R_f$ = 0.31 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 2940, 2860, 1180, 1160, 1150, 1100, 1020, 960 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 3.67 (m, 2 H, $CH_2O$), 3.32 (m, 1 H, C*H*O), 3.20–3.11 (m, 2 H, C*H*O, $CH_2O$), 3.04 (m, 3 H, C*H*O, $CH_2O$), 2.66 (m, 1 H, C*H*), 2.26 (ddd, $J$ = 2.3, 7.6, 15.6 Hz, 1 H, C*H*), 2.02–1.83 (m, 6 H, $CH_2$), 1.69 (m, 1 H, C*H*), 1.45–1.33 (m, 6 H, $CH_2$), 1.23 (d, $J$ = 7.4 Hz, 3 H, $CH_2$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 148.10 (2 C), 82.92, 82.04, 81.19 (2 C), 79.15, 67.36 (2 C), 40.00, 35.41, 31.72, 31.55, 31.29, 29.26, 26.35, 18.12; HRMS (CI) calcd for $C_{17}H_{26}O_4$ (M) 294.1830, found 294.1811. Compound **14b**: $R_f$ = 0.28 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 2960, 2955, 2850, 1220, 1190, 1175, 1120, 1095, 960 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 3.66 (m, 2 H. $CH_2O$), 3.14–3.00 (m, 5 H, C*H*O, $CH_2O$), 2.93 (m, 1 H, C*H*O), 2.73 (m, 1 H, C*H*), 2.61 (m, 1 H, C*H*), 2.15 (ddd, $J$ = 2.2, 6.7. 15.5 Hz, 1 H, C*H*), 1.99–1.89 (m, 3 H, $CH_2$), 1.67–1.57 (m, 2 H, $CH_2$), 1.44–1.33 (m, 4 H, $CH_2$), 1.22 (m, 3 H, $CH_2$), 1.13 (d, $J$ = 7.3 Hz, 3 H, $CH_3$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 150.45, 149.39, 83.36, 83.89, 81.01, 80.55, 67.44, 67.34, 40.14, 31.70, 31.40, 30.87 (2 C), 28.75, 26.46, 26.31, 18.48; HRMS (CI) calcd for $C_{17}H_{26}O_4$ (M) 294.1830, found 294.1818.

**Photolysis of Dithionolactone 16. Preparation of Olefin 17.** The dithionolactone **16**[17] was irradiated by following the same procedure as described for **11**. Concentration and flash chromatography (silica, 15% ethyl acetate in benzene) gave a 12% yield of enol ether **17** as colorless solid: mp 169–171 °C (ether); $R_f$ = 0.5 (silica, 30% ethyl acetate in benzene); IR ($CH_2Cl_2$) $\nu_{max}$ 2940, 2960, 2845, 1175, 1148, 1090, 1076, 1026 $cm^{-1}$; $^1H$ NMR (250 MHz, $C_6D_6$) $\delta$ 3.85–3.68 (m, 2 H, $CH_2O$), 3.55–3.45 (m, 4 H, $CH_2O$), 3.25–3.15 (m, 2 H, C*H*O, $CH_2O$), 2.83–2.68 (m, 4 H, $CH_2$), 2.23–2.15 (m, 2 H, $CH_2$), 1.65–1.45 (m, 4 H, $CH_2$), 1.47–1.32 (m, 2 H, $CH_2$); $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 130.90, 130.90, 75.06, 75.06, 74.90, 74.90, 67.39, 67.39, 31.48, 31.48, 29.38, 29.38, 25.51, 25.51; HRMS (CI) calcd for $C_{14}H_{21}O_4$ (M + H) 253.1440, found 253.1434.

**Reaction of Dithiatopazine (11) with L-Selectride.** A solution of dithiatopazine (**11**; 25 mg, 0.072 mmol) in dry THF (1 mL) was cooled to –78 °C. L-Selectride (1 M solution in THF, 0.36 mL, 0.36 mmol) was then added. After 10 min, MeI (0.2 mL) was added and the mixture stirred for 20 min at 25 °C. Concentration and chromatography (silica, 0.5 mm × 20 cm × 20 cm, 1% triethylamine and 30% ether in petroleum ether) gave dithioether **27** (19 mg, 170%), which was chromatographically and spectroscopically identical with an authentic sample.[17]

**Reaction of Dithiatopazine (11) with Sodium Naphthalide.** To a solution of dithiatopazine (**11**; 16 mg, 0.046 mmol) in THF at –78 °C was added dropwise sodium naphthalide (0.2 M solution, 0.5 mL, 0.1 mmol) until the green color persisted. After the mixture was stirred for 1 h, excess MeI (2 mL) was added and the reaction mixture was stirred for 20 min at 25 °C. Concentration and chromatography (silica, 0.5 mm × 20 cm × 20 cm, 1% triethylamine and 30% ether in petroleum ether) gave the bridged product **27** (12 mg, 70%) and macrocycle **28** (5 mg, 29%) both spectroscopically identical with previously reported compounds.[19]

**Reaction of Dithiatopazine (11) with $Et_3SiH$–$AgBF_4$.** To a solution of dithiatopazine (**11**; 16 mg, 0.046 mmol) and $Et_3SiH$ (52 mg, 0.49 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 °C was added $AgBF_4$ (16 mg, 0.092 mmol). After 2 h, the reaction mixture was concentrated and chromatographed (silica, 0.5 mm × 20 cm × 20 cm, 30% ether in petroleum ether). Compound **36** (12 mg, 92%) was isolated as a white solid: mp 155–156 °C (hexane); $R_f$ = 0.35 (silica, 50% ether in petroleum ether); IR ($CH_2Cl_2$) $\nu_{max}$ 2950, 2938, 2860, 1457, 1442, 1218, 1095, 1028, 978, 875 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.84 (br d, $J$ = 11.5 Hz, 2 H, $CH_2O$), 3.45–2.88 (m, 8 H, C*H*O, $CH_2O$), 2.03–1.36 (m, 16 H, $CH_2$); $^{13}C$ NMR (50.2 MHz, $C_6D_6$), $\delta$ 80.23 (2 C), 79.10 (2 C), 78.75 (2 C), 67.80 (2 C), 30.26 (2 C), 29.94 (2 C), 28.31 (2 C), 26.21 (2 C); HRMS (CI) calcd for $C_{16}H_{26}O_4$ (M + H) 283.1909, found 283.1897.

**Reaction of Dithiatopazine (11) with $Ph_3P$.** To a solution of dithiatopazine (**11**; 34.4 mg, 0.1 mmol) in dry $CH_2Cl_2$ (3 mL) at 25 °C was added triphenylphosphine (31.5 mg, 0.12 mmol) in one portion. After stirring for 30 min, the solvent was removed under vacuo and the residue was subjected to flash column chromatography (silica, 30% ether in petroleum ether), giving pure episulfide **19** (14.1 mg, 45%) and the spiro ketal **18** (14.4 mg, 46%). Compound **18** was a faintly violet oil: $R_f$ = 0.36 (silica, 40% ether in petroleum ether); IR (neat) $\nu_{max}$ 2930, 2850, 1470, 1261, 1100, 735 $cm^{-1}$; $^1H$ NMR (250 MHz, $C_6D_6$) $\delta$ 4.20 (ddd, $J$ = 10.5, 10.5, 5.0 Hz, 1 H, C*H*O), 4.04–3.05 (m, 7 H, C*H*O, $CH_2O$), 2.36–1.28 (m, 16 H, $CH_2$); $^{13}C$ NMR (50.2 MHz, $C_6D_6$, TMS) $\delta$ 262.56, 106.32, 80.03, 77.20, 74.11, 72.63, 67.88, 67.21, 47.74, 35.85, 32.16, 32.07, 30.83, 25.92, 25.84, 24.72; HRMS (CI) calcd for $C_{16}H_{25}O_4S$ (M + H) 313.1474, found 313.1490. Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74; S, 10.26. Found: C, 61.79; H, 7.71; S, 9.98. Compound **19** was a colorless oil: $R_f$ = 0.33 (silica, 0.5 mm × 20 cm × 20 cm, 40% ether in petroleum ether); IR (neat) $\nu_{max}$ 2950, 2858, 1451, 1278, 1148, 961, 742 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$, TMS) $\delta$ 3.84 (m, 2 H, $CH_2O$), 3.49–3.22 (m, 4 H, $CH_2O$, C*H*O), 3.03 (m, 1 H, C*H*$_2$O), 2.75 (m, 2 H, C*H*O, $CH_2$), 2.60 (m, 1 H, $CH_2$), 2.35 (m, 2 H, $CH_2$), 2.05–1.47 (m, 12 H, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 93.28, 86.92, 82.13, 82.00, 77.25, 76.74, 67.42, 67.31, 37.86, 31.21, 30.90, 30.67, 30.55, 28.71, 25.98, 25.52; HRMS (CI) calcd for $C_{16}H_{24}O_4S$ (M) 312.1396, found 312.1382. Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74; S, 10.26. Found: C, 61.24; H, 7.97; S 9.99.

**Reaction of Episulfide 19 with *m*CPBA.** To a solution of episulfide **19** (31.2 mg, 0.1 mmol), $H_2O$ (18 mg, 1.0 mmol), and $CH_2Cl_2$ (3 mL) was added *m*CPBA (34.5 mg, 0.2 mmol) at 25 °C. The reaction mixture was stirred for 2 h before $Me_2S$ (0.2 mL) was added. Dilution with ether (10 mL) followed by washing with aqueous $NaHCO_3$ solution (2 × 2 mL) and brine (2 mL) gave a clear solution, which was dried ($MgSO_4$) and concentrated. Flash chromatography (silica, 30% ether in petroleum ether) gave ketone **20** (16.3 mg, 55%). Compound **20**: Colorless crystals, mp 104–105 °C (from hexane); $R_f$ = 0.50 (silica, 60% ether in petroleum ether); IR ($CHCl_3$) $\nu_{max}$ 2930, 2856, 1728, 1450, 1262, 1090 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$, TMS), $\delta$ 3.78 (m, 3 H, C*H*O, $CH_2O$, equatorial), 3.57 (m, 1 H, $CHO_2$), 3.42–3.20 (m, 4 H, C*H*O, $CH_2O$), 2.93 (m, 1 H, $CH_2$), 2.29 (m, 1 H, $CH_2$), 2.25–1.36 (m, 14 H, $CH_2$); $^{13}C$ NMR (500 MHz, $C_6D_6$) $\delta$ 211.46, 100.75, 80.22, 78.14, 75.23, 73.90, 67.90, 67.17, 35.67, 32.06, 31.86, 31.15, 30.69, 26.18, 25.85, 25.82; MS

*m/e* (relative intensity) 297 (M + H) (51), 279 (78), 268 (84), 240 (100), 217 (12), 198 (100), 186 (12), 157 (100), 139 (100), 127 (16), 115 (14); HRMS calcd for $C_{16}H_{25}O_5$ (M + H) 297.1702, found 297.1701.

**Reaction of Thiono Ketone 18 with Ozone.** Ozone was passed through a solution of thio ketone **18** (31.2 mg, 0.2 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C until the solution turned blue (ca. ~20 min). Quenching of the reaction with $Me_2S$ (2 mL) followed by concentration and flash chromatography (silica, 30% ether in petroleum ether) gave 25.5 mg (85%) of spiro ketone **20**.

**Reaction of Dithiatopazine (11) with Thiophenol.** To a solution of thiophenol (20 μL, 0.2 mmol) in THF (0.5 mL) was added NaH (60% oil dispersion, 2.6 mg, 0.13 mmol) at 0 °C. After 15 min, a solution of dithiatopazine (**11**; 23 mg, 0.066 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred for 24 h at 0 °C. Concentration and chromatography (silica, 0.5 × 20 cm × 20 cm, 15% ethyl acetate in benzene) gave compound **25** as a clear colorless oil: 16.7 mg, 60%; $R_f$ = 0.1 (silica, 15% ethyl acetate in benzene); IR (neat) $\nu_{max}$ 3250 (br s, OH) $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) δ 7.56 (d, *J* = 7.1 Hz, 2 H, aromatic), 7.00 (t, *J* = 7.1 Hz, 2 H, aromatic), 6.91 (t, *J* = 7.1 Hz, 1 H, aromatic), 3.68 (dd, *J* = 4.6, 1.6 Hz, 1 H, C*H*O), 3.59 (dd, *J* = 4.6, 1.3 Hz, 1 H, C*H*O), 3.23 (m, 1 H, C*H*O), 3.07–2.74 (m, 7 H, C*H*O, $CH_2$ vinyl, O*H*), 2.64 (m, 2 H, C*H*O), 2.06 (m, 2 H, $CH_2$), 1.91 (m, 1 H, $CH_2$), 1.67 (m, 3 H, $CH_2$), 1.42–1.00 (m, 7 H, $CH_2$); $^{13}C$ NMR (125 MHz, $C_6D_6$) δ 164.20 (vinyl), 138.12 (aromatic), 130.07 (aromatic), 129.17 (aromatic), 127.99 (aromatic), 127.80 (aromatic), 127.42 (aromatic), 117.19 (vinyl), 82.38 (*C*O), 82.02 (*C*O), 80.81 (*C*O), 70.44 (*C*O), 67.44 (*C*O), 67.27 (*C*O), 33.43, 32.72, 31.02, 30.28, 30.01, 29.21, 26.12, 26.03; HRMS (CI) calcd for $C_{22}H_{30}O_4S_2$ (M + H) 423.1669, found 423.1594.

**Reaction of Disulfide 25 with L-Selectride.** To a stirred solution of disulfide **25** (11 mg, 0.026 mmol) in THF (2 mL) cooled to −78 °C was added excess L-Selectride (1 M THF solution, 0.2 mL). After 10 min, excess MeI (1 mL) was added and the resultant mixture stirred at 25 °C for 25 min. Concentration and chromatography (silica, 0.5 mm × 20 cm × 20 cm, 25% ethyl acetate in benzene) yielded monosulfide **26** (6 mg, 65%) as a clear colorless oil identical with a sample obtained as described below.

**Reaction of Episulfides 32a and 32b with $Ph_3P$. Preparation of Thioenol Ether 33.** Triphenylphosphine (40 mg, 0.15 mmol) was added to a solution of episulfide **32a** or **32b** (14 mg, 0.039 mmol) in benzene (1 mL) at 50 °C and this stirred for 48 h. Concentration and chromatography (silica, 0.25 mm × 20 cm × 20 cm, 15% ethyl acetate in benzene) gave the thioenol ether **33** (7 mg, 87% from **32a**, and 6.5 mg, 80% from **32b**) chromatographically and spectroscopically identical with **33** obtained above.

**Reaction of Dithiatopazine (11) with 2,3-Diphenyl-1,3-butadiene (41). Preparation of Compounds 42 and 43.** A solution containing dithiatopazine (**11**; 8.8 mg, 0.025 mmol) and 2,3-diphenyl-1,4-butadiene (**41**; 21.2 mg, 0.103 mmole) in toluene (0.1 mL) was heated in a sealed tube at 100 °C for 5 h. Concentration and chromatography (silica, 0.25 mm × 20 cm × 20 cm, 2% ether in petroleum ether) gave compounds **42** (1.7 mg, 25%), **43** (2.4 mg, 28%), and enol ether **12** (6.6 mg, 92%, identical with the sample described above). The spectroscopic data for compound **42** was identical with previously reported values.[22a] Compound **43** was isolated as a white solid: mp 137–139 °C, resolidifying at 150 °C and then slowly decomposing (hexane); $R_f$ = 0.34 (silica, 5% ether in petroleum ether); $^1H$ NMR (250 MHz, $CDCl_3$) δ 7.19–7.03 (m, 10 H, aromatic), 6.67 (s, 4 H, $CH_2S$); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 129.54 (6 C), 127.76 (5 C), 126.84 (3 C), 42.89 (2 C); HRMS (CI) calcd for $C_{16}H_{14}S_2$ (M − 2S) 270.0537, found 270.0530.

**Reaction of Dithiatopazine (11) with Krebs' Acetylene (44). Preparation of Compounds 45 and 46.** A solution of dithiatopazine (**11**; 29.2 mg, 0.085 mmol), and Krebs' acetylene[14] (**44**; 57 mg, 0.34 mmol) in toluene (0.5 mL) was heated at 100 °C for 5 h in a sealed tube. Concentration and chromatagraphy (silica, 0.5 mm × 20 cm × 20 cm, 20% benzene in petroleum ether) gave compounds **45** (10.9 mg, 65%), **46** (2.5 mg, 12%), and **12** (4.2 mg, 95%), identical with the sample described above. Compound **45** was chromatographically and spectroscopically identical with an authentic sample kindly provided by Professor Krebs.[14] Compound **46** was isolated as a white solid: mp 130.5–133 °C, then resolidifying and melting at 160 °C (heptane); $R_f$ = 0.22 (silica, 0.25 mm × 20 cm × 20 cm, 20% benzene in petroleum ether); IR ($CH_2Cl_2$) $\nu_{max}$ 2960, 2920, 2880, 1445, 1425, 1415, 1365, 1275, 1175, 1150, 1130, 1115 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 2.68 (br s, 4 H, $CH_2S$), 2.56 (br s, 4 H, $CH_2S$), 1.51 (s, 6 H, $CH_3$); $^{13}C$ NMR (125 MHz, $C_6D_6$) δ 145.60 (2 C, thiophene), 144.61 (2 C, thiophene), 47.61 (2 C) 42.31 (2 C), 41.52 (2 C), 40.48 (2 C), 30.40 (2 C), 28.94 (2 C); HRMS (CI) calcd for $C_{20}H_{32}S_3$ (M + H) 369.1742, found 369.1753.

**Kinetic Experiments of the Thermal Decomposition of Dithiatopazine (11) to Olefin 12.** Dithiatopazine (**11**) was dissolved in toluene-$d_8$ (0.01 M concentration) and sealed in an NMR tube under an argon atmosphere. The reaction was performed and monitored with a Bruker AM-500 spectrometer equipped with a variable-temperature probe at 80, 90, 100, and 110 °C. For each data point, 20 transients were collected over a sweep width of 5000 Hz, employing a pulse decay of 3 s and a pulse width of 8 μs. Data points were collected every 10 (110 °C), 15 (100 °C), 60 (90 °C), and 60 min (80 °C). The areas of the signals at δ 2.65 [for dithiatopazine (**11**)] and 2.80 (for olefin **12**) were determined by integration of the Fourier-transformed spectrum without line broadening and concentrations of **11** and **12** were calculated by assuming 100% conversion.

**Calculations on the Conformation and Molecular Structure. 1. MM2 Parameterization.** All force constants and bond moments were taken by analogy from previous parameters.[25] Length, angle, and S–S torsion parameters for oxygenated dithietanes (Table V) were derived by matching the X-ray structure of dithiatopazine (**11**) by use of an iterative simplex procedure coupled to the MM2 force field.[39] A comparison is given in Figure 8.

Similarly, the episulfide parameters (Table V) were obtained by performing an iterative simplex match on the X-ray structure of ring-opened episulfide **32a**. The $C_e$–H values were parameterized against the microwave structure of the parent episulfide.[40] Figure 12 provides a comparison between experiment and force field. For both parameters sets, the new torsional parameters were chosen by analogy with previous MM2 values.[25]

**2. Conformation Searching.** Two procedures were employed. On the one hand, Smith's program[27] was modified for convenient, interactve use and interfaced to the Searle modeling system.[41] Applied to the X-ray structure of **11**, a collection of conformations were optimized with the MM2 dithietane parameters to give the structures depicted in Figure 9. The episulfides were treated similarly.

In the case of the all-six-ring dithietane **15**, Saunder's stochastic search method[29] was applied with the new MM2 parameters leading to **58** and **59** as the lowest energy conformers. The current version of the program permits freezing of user-defined chiral centers, making it convenient to treat polycyclic systems such as **15** with several asymmetric centers.

**3. PRDDO Calculations.** All quantum mechanical computations were carried out with the second-row version of PRDDO[30] using MM2-optimized structures as input. Since the present version of the program allows only one second-row atom to carry d orbitals, only the episulfide was calculated with these additional functions.

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**Supplementary Material Available:** Kinetic studies for the decomposition of dithiatopazine (**11**) at 80, 90, 100, and 110 °C and X-ray crystallographic data for compounds **11**, **20**, **32a**, **36**, **43**, and **46** (31 pages). Ordering information is given on any current masthead page.

(39) Smith, G. M.; Snyder, J. P.; Krahn, J., unpublished results.
(40) Okiye, K.; Hirose, C.; Lister, D. G.; Sheridan, J. *Chem. Phys. Lett.* **1974**, *24*, 111.
(41) Pilipauskas, D.; Snyder, J. P., unpublished results.