Photochemistry of Thiarubrine A and Other 1,2-Dithiins: Formation of 2,6-Dithiabicyclo[3.1.0]hex-3-enes

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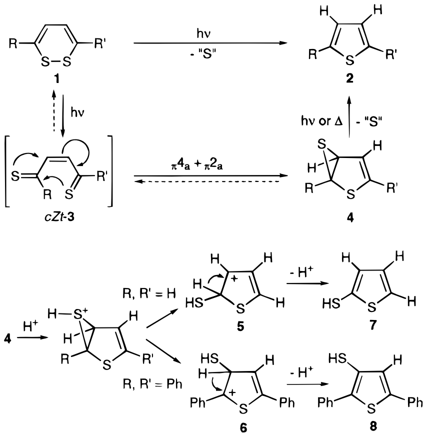
Thiarubrine A (**1a**) and related wine-red antibiotic pigments from species in the *Asteraceae*[2] are unique among natural products in containing an eight π-electron (1,2-dithiin) ring.[3] A notable property of 1,2-dithiins (**1**)[2,4] is their light sensitivity, with brief exposure to visible or ultraviolet light giving the corresponding thiophenes **2** (Scheme 1).[2b] Hitherto, little was known about the mechanism of this desulfurization process. The quantum yield for conversion of 3,6-diphenyl-1,2-dithiin (**1c**) to 2,5-diphenylthiophene (**2c**) is 0.91[4d] ring opening of **1** to (*Z*)-butenedithione derivatives (**3**) has been postulated,[2ab,6a] and involvement of various valence isomers of **3** in the desulfurization process has been suggested.[6b−d] As well, direct extrusion of singlet sulfur from **1b** is calculated to be disfavored by ca. 80 kcal mol^{-1}.[6a] Exposure of **1a** to visible light, leading to desulfurization, results in enhanced biological activity.[5] The recent observation that irradiation of **1a** results in a colorless solution which upon standing regains some of its red color has led us to speculate on the presence of an intermediate between 1,2-dithiins and thiophenes.

We have examined the photochemistry of **1a** and synthetic 1,2-dithiins **1b**−**d** in solution and under matrix isolation conditions. We report the direct observation of novel sulfur compounds whose formation provides an explanation for the light-induced conversion of 1,2-dithiins to thiophenes. In particular we find that brief irradiation of **1** with visible light at −60 to −75 °C affords in excellent yields 2,6-dithiabicyclo-[3.1.0]hex-3-enes (**4**), a previously unknown class of compounds.[7] Matrix isolation and flash photolysis techniques have been used to identify and determine the lifetime in solution of *s-cis-s-trans*-(*Z*)-2-butenedithial (*cZt*-**3b**), a presumed intermediate in the formation of **4**, and to define alternative low-temperature photochemical pathways available to *cZt*-**3b**. On warming or further exposure to light, **4** affords thiophenes **2** and sulfur, while with catalytic acid **4b** and **4c** rearrange to 2- and 3-mercaptothiophenes (**7** and **8**), respectively.

Scheme 1



R, R'

a R = MeC≡C-, R' = CH_2=CHC≡CC≡C- (thiarubrine A);
b H; **c** Ph; **d** CH_2OH

Samples of **1a**−**d**[2bd,4,8a] in deuterated solvents in NMR tubes were cooled to −60 to −75 °C and exposed to visible light until the original color faded,[8b] at which point low-temperature ^1H and ^{13}C NMR spectra (see Table 1) were recorded for photoproducts **4a**−**d** and the corresponding thiophenes **2a**−**d**.[9] On addition of catalytic CF_3CO_2H, **4b** and **4c** rearranged to mercaptothiophenes **7**[10a] and **8**,[10b,c] respectively. Analysis of irradiated samples of **1a** and **1c** by reversed-phase LC with photodiode array (PDA) detection showed in each case the presence of two compounds, different from **1a** and **1c** and lacking in long wavelength UV absorption.[11] The longer retention time (less polar) components were identified as thiophenes **2a** and **2c**. Repetitive injection of the irradiated solutions showed that the shorter retention time (more polar) components **4a** and **4c** were thermally unstable and disappeared after 1 h at 25 °C, being replaced by **2a** and **2c** and lower concentrations of dithiins **1a** and **1c**, respectively. Immediate analysis of the irradiated solution from **1a** by LC−APCI-MS showed **4a** to have the same molecular weight as that of **1a**.

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[7] (a) 1,3,4,5-Tetrakis(trifluoromethyl)-2,6-dithiabicyclo[3.1.0]hex-3-ene is proposed as an intermediate in the addition of atomic sulfur to 2,3,4,5-tetrakis(trifluoromethyl)thiophene.[7b] (b) Verkoczy, B.; Sherwood, A. G.; Safarik, I.; Strausz, O. P. *Can. J. Chem.* **1983**, *61*, 2268−2279. (c) Formation of (*Z*)-2-butene-1,4-diones from 2,6-dioxabicyclo[3.1.0]hex-3-enes, oxygen analogs of **3** and **4**, respectively, has been described.[7d] (d) Adam, W.; Ahrweiler, M.; Sauter, M. *Chem. Ber.* **1994**, *127*, 941−946.

[8] (a) Thiarubrine A was isolated from roots of *Ambrosia chamissonis* as previously described.[2c] The sample in an NMR tube was deaerated by three freeze−pump−thaw cycles. (b) Samples in NMR tubes cooled with dry ice/acetone in Dewar flasks were irradiated using a Model LE60 Light Engine (General Electric Company; equipped with a 60 W metal halide lamp and a fiber optic bundle) or with focused light from a Sylvania 300 W lamp, both with output predominantly in the visible spectrum.

[9] Irradiation of unsymmetrical **1a** gives isomeric photoproducts **4a** and **4a′**, in a 97:3 ratio. For clarity only one isomer is shown in Scheme 1. Efforts are underway to determine which isomer predominates and provide an explanation for the surprising regioselectivity of the process.

[10] (a) Identified by comparison with a commercial sample. (b) Nakayama, J.; Shimomura, M.; Iwamoto, M.; Hoshino, M. *Heterocycles* **1985**, *23*, 1907−1910. (c) We thank Professor Nakayama for an authentic sample of **8** for comparison purposes.

[11] Reversed phase LC-PDA UV data: **1a** λ_{max} 238.5, 347.8, 491.2 nm; **2a** λ_{max} 338.2 nm; **4a** λ_{max} 276.4 nm; **1c** λ_{max} 233.8, 309.6, 462.1 nm; **2c** λ_{max} 323.9 nm; **4c** λ_{max} 252.7, 309.6 nm.

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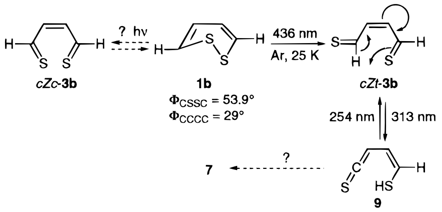
Table 1. 2,6-Dithiabicyclo[3.1.0]hex-3-enes **4a−d** from Irradiation of 1,2-Dithiins **1a−d**

compound	yield[d]	^{1}H NMR chemical shift (*J*)[a,b]	^{13}C NMR chemical shift
4a, [**4a′**][c,d]	91	2.04 (s), 5.88 (11.1, 2.1), 5.98 (17.6, 2.3), 6.08 (17.6, 11.1), 6.66/5.03 (2.6), [7.01/4.86 (2.8)[e]]	3.94 (CH_3), 53.88 (CH),[f] 58.65 (C),[f] 69.81, 71.34, 72.90, 76.47, 80.58, 95.21 115.83, 125.77, 129.41, 133.76[g]
4b	88	4.48 (2.4, 5.1), 5.17 (1.8, 5.1), 6.38 (2.1, 5.7), 6.51 (2, 5.6)	51.16, 52.63, 125.09, 129.41
4c	86	4.67 (2.7), 6.77 (2.7), 7.40−7.51 (m, 8H), 7.60 (1.5, 7.8, 2H)	58.21, 118.64, 126.14, 128−129, 132.37, 136.30, 146.90
4d[c]	96	3.83 (12.1), 4.09 (12.1), 4.20 (14.5, 1.6), 4.35 (17.4), 4.37 (s), 6.19 (s)	55.20, 60.18, 69.22, 73.16, 119.63, 150.64

[a] Unless otherwise indicated solvent is $CDCl_3$ and each signal corresponds to 1H. [b] Coupling constants in Hz. [c] In $CD_3C(O)CD_3$. [d] Minor component in brackets; major isomer 88.8%, minor isomer 2.6%; only thiirane ring protons seen for minor isomer. [e] Ring protons. [f] Thiirane ring. [g] Major component signals only. [h] From NMR analysis; also formed 8.6% **2a** from **1a**, 12% **2b** from **1b**, 14% **2c** from **1c**, 4% **2d** from **1d**.

Scheme 2



We propose that photoproducts **4a−d**, identified spectroscopically as 2,6-dithiabicyclo[3.1.0]hex-3-enes,[12] are formed by a $_{\pi}4_a + _{\pi}2_a$ rearrangement of initally formed (*Z*)-2-butenedithials (**3**), a process analogous to that reported by Padwa for photolysis of 4-phenylisothiochromene (see below for evidence for *cZt*-**3b**).[13] At least in the cases of **4a** and **4c**, the process can be partially reversed under thermal conditions, regenerating dithiins **1a** and **1c**. Rearrangement of photoproducts **4b** and **4c** to mercaptothiophenes **7** and **8** presumably involves acid-catalyzed ring opening giving the most stable carbocation, **5** and **6**, respectively. In common with photochemical and thermal loss of sulfur from related thiiranes,[10b,12c,13a] further irradiation of **4b** yields **2b**.

To obtain additional information on intermediates in 1,2-dithiin photochemistry, Ar matrix isolation spectroscopy at 25 K[14,15a] was performed with **1b**. Irradiation of the matrix with visible light (436 nm, 2 h) caused the complete disappearance of **1b** and the simultaneous production of *s-trans-Z-s-cis* 2-butenedithial (*cZt*-**3b**).[15] Irradiation of *cZt*-**3b** at shorter wavelengths (313 nm, 8 h) gave (*Z*)-4-mercapto-1,3-butadienethial (**9**) (Scheme 2).[15] Irradiation of **9** at 254 nm caused the reappearance of the bands of **3b** which grew until a photostationary state containing both species was reached (5 h). In this fashion, **3b** and **9** could be interconverted over several cycles by changes in irradiation wavelength.[16] The IR spectrum of **3b** exhibited strong bands in the 1100−1200 cm^{-1} region (C═S)[15,17b] and a weaker band at 1558 cm^{-1} (conjugated C═C). In addition to an intense UV band at 319 nm, an extremely weak absorption was observed in the visible region at 500−600 nm (CH═S nπ*).[15,17b] Compound **9** displays characteristic thioketene IR absorption at 1760 cm^{-1}.[15,17]

To confirm the structural assignments, ab initio calculations (HF, 6-31G*) were carried out of the vibrational spectra of **3b** and **9**.[15a] While *cZt*-**3b** was twisted ca. 40° out of plane, *tZt*-**3b** (not shown) was found to be planar; no energy minimum was found corresponding to *cZc*-**3b** in either planar or twisted geometries.[6a,15a] The frequencies and intensities calculated for the *cZt*-**3b** geometry fit the experiments nicely.[15a] An energy minimum was found for **9** in a slightly twisted s-cis geometry. The calculated vibrational spectrum for this conformer of **9** agrees well with experiment.[15a]

Time-resolved irradiations of **1b** in solution were also carried out.[18] Laser flash photolysis of **1b** (Freon-113, 308 nm, 25 °C) produced a transient absorption with $\lambda_{max} = 329$ nm. The transient was fairly long lived, decaying by apparent first-order kinetics with a lifetime of 62 μs. The similarity of this absorption to that obtained in the low-temperature matrix isolation experiments suggests that the transient corresponds to *cZt*-**3b**. Flash vacuum pyrolysis of **1b** at 500 °C also affords thiophene **7**. This result could be explained either in terms of formation of **4b** followed by surface-catalyzed rearrangement or by conversion of *cZt*-**3b** to **9** which can give **4b** by an intramolecular thiol addition.[19] Microwave spectroscopy reveals that **1b** is nonplanar with a 53.9° CSSC dihedral angle (Scheme 2).[20] Electrocyclic ring opening followed by limited rotation about the C1−C2 bond could lead directly to *cZt*-**3b**. Rotation in the opposite direction would afford *cZc*-**3b**, disfavored relative to *cZt*-**3b**.[2b,6a] Compound *cZt*-**3b** can then undergo either a 1,5-sigmatropic shift[13a,21] giving **9** or a $_{\pi}4_a + _{\pi}2_a$ rearrangement giving **4b**. Formation of **9** is apparently favored at 25 K in the Ar matrix.

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Supporting Information Available: Text describing matrix isolation conditions, UV−vis spectra of Ar matrix dithiin before and after irradiation, matrix IR spectra of **1b**, **3b**, and **9**, ab initio calculation methods, calculated geometries, and IR spectra (tabular and graphical) for *cZt*-**3** and **9**, and NMR spectra of **4b**,**c** (12 pages). Ordering information is given on any current masthead page.

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(12) (a) The NMR assignments for **4** are supported by comparison with NMR data for 2-cyano-5-thiabicyclo[2.1.0]pent-2-ene[12b] and 2,3-dihydrothiophene.[12c] (b) Barltrop, J. A.; Day, A. C.; Irving, E. *J. Chem. Soc. Chem. Commun.* **1979**, 966−967. (c) Sauer, N. N.; Angelici, R. J.; Huang, Y. C. J.; Trahanovsky, W. S. *J. Org. Chem.* **1986**, *51*, 113−114.

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(15) (a) See the supporting information for details. (b) *cZt*-**3b**: IR 3024 (w), 2990 (w), 2953 (vw), 2948 (vw), 1558 (w), 1425 (s), 1422 (s), 1366 (m), 1357 (w), 1163 (s), 1151 (vs), 1076 (m), 1074 (m), 1033 (m), 998 (m), 871 (w), 786 (w), 691 (w) cm^{-1}; UV λ_{max} ca. 218, 319 (both strong), 500−600 (very weak) nm. **9**: IR 1773 (s), 1763 (s), 1753 (s), 1742 (s), 3082 (vw), 3039 (vw), 3015 (vw), 1903 (w), 1593 (m), 1526 (m), 1387 (w), 1351 (m), 1348 (m), 1221 (w), 957 (vw), 934 (vw), 880 (vw) cm^{-1}; UV λ_{max} ca. 215, 274, 327 (sh) nm, tailing out to ca. 700 nm.

(16) Broad-band irradiation (>200 nm, 10 h) of the matrix converted **3b** and **9** to CS_2 together with unknown material. No **2b** or **7** was observed in the IR by comparison to authentic material. No discrete products could be identified upon warming a 2-methylpentane matrix containing **9**.

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(18) Laser flash photolysis experiments were carried out at Ohio State University in the laboratories of Professor M. S. Platz.

(19) However, *cZt*-**3b** → **9** is predicted by ab initio calculations (HF, 6-31G*) to be thermodynamically unfavorable by ca. 10 kcal/mol.

(20) Gillies, J. Z.; Gillies, C. W.; Cotter, E. A.; Block, E.; DeOrazio, R. Submitted for publication in *J. Mol. Spectrosc.*

(21) Matrix isolation photochemical conversion of thioacrolein to methylthioketene via 1,3-H shift: Korolev, V. A.; Baskir, E. G. *Izv. Akad. Nauk., Ser. Khim.* **1995**, 464−470.