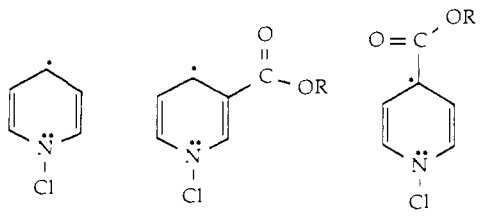

12 13 14

bilization).[15,16] Such stabilization should make these radicals relatively selective.

We are pursuing the questions of the chemical selectivity and spectroscopy of these novel radical species. However, even at this stage the selectivities observed and the ready availablility of pyridine derivatives suggest that they will prove to be the templates of choice for directed radical relay reactions.

Acknowledgment. Support of this work by the NSF, and by an NIH Postdoctoral Fellowship to A. Adams, is gratefully acknowledged.

(15) Simple HMO calculations predict this stability sequence, but higher level calculations are in progress. For a relevant calculation, see: Yonezawa, T.; Nakatsuji, H.; Kawamura, T.; Kato, H. *Mol. Phys.* **1967**, *13*, 589–590.
(16) For a related radical, see: Kosower, E. M.; Poziomek, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 5528–5533 and later publications.

Dithiatopazine:[1] The First Stable 1,2-Dithietane

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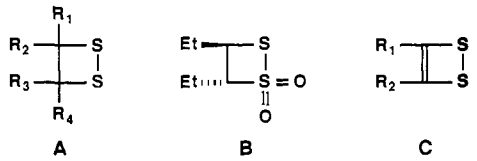
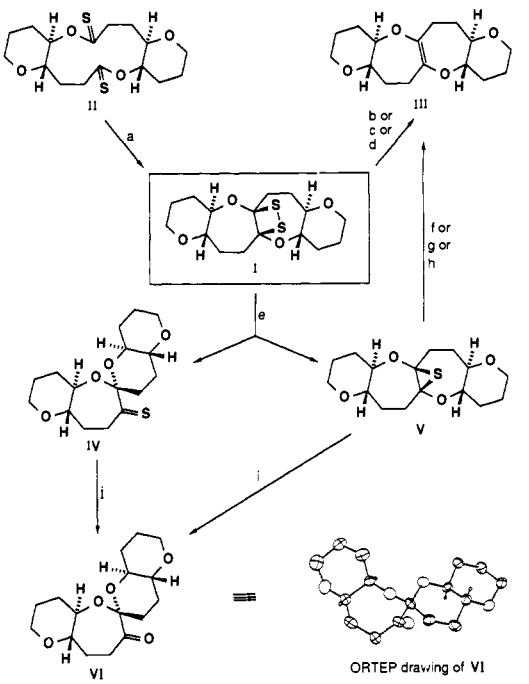
1,2-Dithietanes (A) are of fundamental theoretical, chemical, and biological interest.[2–4] Although postulated as transient in-



A B C

termediates,[5] to the best of our knowledge, no representative of this class of compounds has yet been isolated. Their hypothesized unstable nature has been attributed largely to the expected destabilizing repulsion between the lone pairs of electrons on the adjacent sulfur atoms imposed by the geometrical constraints of the 4-membered ring.[6] Replacement of the lone pairs in one of the sulfurs with oxygen atoms removed this destabilizing effect and resulted in the first isolable example of the 1,2-dithietane 1,1-dioxide B as recently reported by Block.[7] Aromatic systems with 6π electrons of type C (1,2-dithietenes) have also been reported as stable compounds.[8] We now report the synthesis, some physical and chemical properties, and the X-ray crystallographic analysis of the first stable 1,2-dithietane system, dithiatopazine[1] (I, Scheme I).

Scheme I[a]



[a] (a) *hν* (Hanovia UV lamp), toluene, ambient temperature, 15 min, I (65%), II (10%), III (13%); (b) as in (a), 1 h, 90%; (c) heat neat, 140 °C, 45 min, 95% or heat in xylene, 140 °C, 1 h, 95%; (d) 2 equiv of n-Bu_3SnH, AIBN catalyst, toluene, 110 °C, 15 min, 97%; (e) 1.2 equiv of PPh_3, CH_2Cl_2, 15 min, 25 °C, IV (46%), V (45%); (f) same as (c), 1 h, 93%; (g) 10 equiv of $(EtO)_3P$, toluene, 110 °C, 1 h, 94%; (h) heat in xylene, 160 °C, sealed vessel, 2 h, 88%; (i) 2 equiv of mCPBA, 10 equiv of H_2O, CH_2Cl_2, 25 °C, 2 h, 55%; (j) ozone, CH_2Cl_2, −78 °C then 10 equiv of Me_2S, −78 → 25 °C, 1 h, 85%.

Scheme I summarizes the synthesis and a number of selected reactions of the title compound (I). Irradiation of dithionolactone II[9,10] (toluene, Hanovia, UV lamp, ambient temperature) for 15 min resulted in a mixture of I (65%), II[10] (10%), and III[9,10] (13%) which were easily separated by flash column chromatography (silica, 15% EtOAc in benzene; R_fs, I, 0.42, II, 0.70, III, 0.32). Longer irradiation times resulted in the complete consumption of II and I and the exclusive formation of olefin III (1 h, 85% yield). Dithiatopazine (I) is a stable yellow-orange compound forming beautiful topazlike crystals from hexane, mp 134–135 °C.[11] Its structure was based on its spectroscopic and chemical

(1) The name dithiatopazine is suggested for compound I 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*-5a,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.* **1980**, *103*, 159.
(3) For a monograph on sulfur chemistry, see: Block, E. In *Reactions of Organosulfur Compounds*; Blomquist, A. T., Wasserman, H. H., Eds.; Academic: New York, 1978.
(4) Cyclic disulfides have been associated with biological activity; for some examples, see glyotoxin and α-lipoic acid: *Merck Index*, 10th ed.; 1983, entries 4301 and 9166, respectively, and references cited therein.
(5) See, for examples: (a) Steliou, K.; Salama, P.; Brodeur, D.; Gareau, Y. *J. Am. Chem. Soc.* **1987**, *109*, 926. (b) Orahovatz, A.; Levinson, M. I.; Carroll, P. J.; Lakshmikanthan, M. V.; Cava, M. P. *J. Org. Chem.* **1985**, *50*, 1550. (c) Jahn, R.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 630. (d) Ishibe, N.; Odani, M.; Teramura, K. *J. Chem. Soc., Chem. Commun.* **1970**, 371.
(6) 1,2-Dioxetanes, however, are isolable, see: Bartlett, P. D.; Landis, M. E. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979. Also, 3,3,4,4-tetramethyl-1,2-oxathietane has recently been reported: Lown, J. W.; Koganty, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 3811.
(7) Block, E.; Bazzi, A. A.; Revelle, L. K. *J. Am. Chem. Soc.* **1980**, *102*, 2490.
(8) See, for example: Boar, R. B.; Hawkins, D. W.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans.* **1977**, *1*, 515. de Mayo, P.; Weedon, A. C.; Wong, G. S. K. *J. Org. Chem.* **1979**, *44*, 1977. Krebs, A.; Colberg, A.; Hopfner, U.; Kimling, H.; Odenthal J. *Heterocycles* **1979**, *12*, 1153. For a review on four- and five-membered cyclic disulfides, see: Vasil'eva, T. P.; Lin'kova, M. G.; Kil'disheva, O. V. *Russ.* Chem. *Rev.* (*Engl. Transl.*) **1976**, *45*, 639.
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(10) Compounds II and III have C_i symmetry and are, therefore, meso, whereas compounds I and V are racemic.

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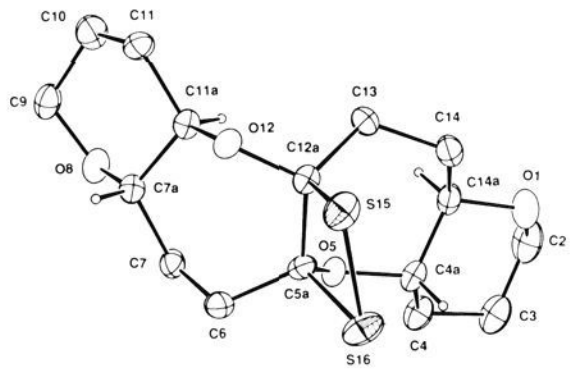


Figure 1. ORTEP drawing of dithiatopazine (I). Bond distances of 1,2-dithietane system (Å): C5a–C12a = 1.571 (6); C12a–S15 = 1.844 (4); S15–S16 = 2.084 (2); S16–C5a = 1.881 (4). Bond angles (deg): C5a–C12a–S15 = 97.4 (3); C12a–S15–S16 = 82.2 (1); S15–S16–C5a = 80.7 (1); S16–C5a–C12a = 96.8 (3). Dihedral angle (deg) between planes C12a–S 15–S16 and C5a–S16–S15 = 11.0 (4).

properties and was confirmed by an X-ray crystallographic analysis (vide infra). Thus, I exhibited the following spectra data: UV–vis (hexane) λ_{max} 213 (ϵ 4074), 426 nm (ϵ 102);[12] IR (CCl_4) ν_{max} 2940, 2840, 1450, 1275, 1160, 1094, 1052, 965 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 (m, 1 H, C*HO* closest and syn to S–S bridge), 3.90 (m, 1 H, CH_2O, equatorial), 3.82 (m, 1 H, CH_2O, equatorial), 3.35–3.12 (m, 5 H, C*HO*, CH_2O), 3.00 (m, 1 H, CH_2), 2.54 (m, 1 H, CH_2), 2.34 (m, 1 H, CH_2), 2.15 (m, 1 H, CH_2), 2.03–1.40 (m, 12 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.02, 102.18, 82.69, 80.71, 77.69, 76.17, 67.82, 67.14, 39.04, 34.43, 31.25, 30.86, 29.40, 28.99, 25.80, 25.42; HRMS (CI) calcd for $C_{16}H_{24}O_4S_2$ + H 345.1194, found 345.1233 (M + H).

The chemistry of I is quite intriguing and has already led to a number of novel systems as indicated in Scheme I. Thus, irradiation of I (toluene, Hanovia UV lamp, 1 h) at ambient temperature resulted in extrusion of sulfur and the clean formation of olefin III (90%). Extrusion of sulfur from I and generation of III (95%) was also observed upon thermolysis of I (neat, or in xylene solution, 140 °C). Reduction of I with *n*-Bu_3SnH–AIBN also produced III in high yield (97%). Treatment of dithiatopazine (I) with PPh_3 (CH_2Cl_2, 25 °C) led smoothly to the fascinating compounds IV (46%) and V[10] (45%) by abstraction of one of the sulfur atoms.[13] The structure of the spiro ketal–thioketone IV was based on its spectral data, particularly its ^{13}C NMR spectrum [125 MHz, benzene-d_6, δ 262.56 (C=S) and 106.32 (O–C–O)], and is smooth conversion to spiro ketal–ketone VI by ozonolysis (85%) (structure VI) and was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Scheme I). The structure of the surprisingly stable episulfide V was assigned on the basis of its spectral data, particularly its ^{13}C NMR spectrum [125 MHz, $CDCl_3$, δ 93.28 (O–C–S) and 86.91 (O–C–S)], and its chemistry. Thus, V suffered loss of sulfur and transformation to olefin III by any one of the following procedures: (i) *n*-Bu_3SnH–AIBN catalyst, toluene, 110 °C, 93%; (ii) $(EtO)_3P$, toluene, 110 °C, 94%; (iii) xylene, 160 °C, 88%. Furthermore, episulfide V was transformed to the spiro ketal–ketone VI upon exposure to mCPBA–H_2O in CH_2Cl_2 (55%).

In order to confirm the 1,2-dithietane structure of compound I and to determine some of its molecular parameters, an X-ray crystallographic analysis was undertaken. Compound I crystallizes in the orthorhombic space group *Pbca* with a = 9.549 (3) Å, b = 12.024 (3) Å, c = 28.659 (7) Å, v = 3290.7 Å^3, and ρ(calcd) = 1.391 g cm^{-3} for z = 8. The structure was solved by direct methods and Fourier techniques and refined by full-matrix least squares to R_1 = 0.049 and R_2 = 0.057 using 1605 unique, observed ($I > 3\sigma$) reflections. Figure 1 shows an ORTEP representation of the molecule and includes a number of bond lengths and bond angles. Of special interest are the rather long S15–S16 [2.084 (2) Å] and C4a–C14a bond [1.571 (6) Å] as well as the remarkably small angles at sulfur [S16–S15–C12a = 82.2 (1)° and S15–S16–C5a = 80.7 (1)°]. The dihedral angle between planes S15–S16–C5a and S16–S15–C12a is notably small, 11.0 (4)°, and suggests considerable repulsive overlap of the lone pairs of electrons on the two sulfurs. Yet, the 1,2-dithietane moiety in this system is phenomenally stable.

Further exploration of the physical, chemical, and biological properties of dithiatopazine (I) and the design, synthesis, and study of other 1,2-dithietane systems are currently being pursued in these laboratories.[14]

Acknowledgment. We express thanks to Drs. George Furst and John Dykins of this Department for their superb NMR and mass spectroscopic assistance and useful commments. We also thank Professors E. R. Thornton, University of Pennsylvania, E. Block, University of New York, Albany, K. Steliou, University of Montreal, and Dr. J. P. Snyder, G. D. Searle, for stimulating discussions concerning this work. This work was financially supported by the National Institutes of Health, Merck Sharp and Dohme, Hoffmann-La Roche, and Smith Kline Beckman.

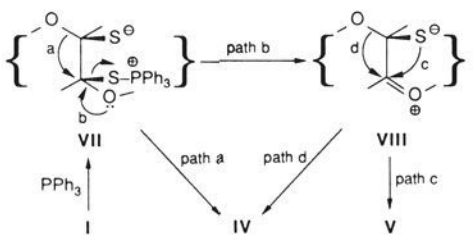
Supplementary Material Available: Spectroscopic and analytical data for compounds II–VI and tables of refined atomic positional and thermal parameters and bond distances and angles for compounds I and VI (7 pages). Ordering information is given on any current masthead page.

(11) TLC analysis of the melt revealed partial decomposition to olefin III, and presumably sulfur.

(12) Slow decomposition to olefin III, and presumably sulfur, was observed during the UV–vis measurements as indicated by decrease of absorbance with time. The reported ϵ values, therefore, must be minima.

(13) Scheme II shows possible mechanistic pathways for these interesting transformations. Thus initial attack by Ph_3P on I may in principle result in

Scheme II



two isomeric species VII depending on the regiochemistry of the attack. These stereochemically distinct species may prefer different reaction pathways depending on stereoelectronic effects and may lead to IV (path a) or oxonium species VIII (path b). Oxonium species VIII may then collapse to episulfide V (path c) or rearrange to thioketone IV (path d). Calculations, molecular modeling, and further experiments are expected to provide further mechanistic information.

(14) All new comounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Peptide Synthesis Catalyzed by Lipases in Anhydrous Organic Solvents

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One of the bottlenecks of the rapidly growing field of peptide research is the shortage of general methodologies for facile preparation of a wide range of diverse peptide structures.[1] Enzymatic, namely, protease-catalyzed, synthesis is emerging as a method of choice for the production of short peptides due to its mild reaction conditions, absence of racemization, minimal protection and activation requirements, and inherent regio- and stereoselectivities.[2] However, peptide bond formation catalyzed

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