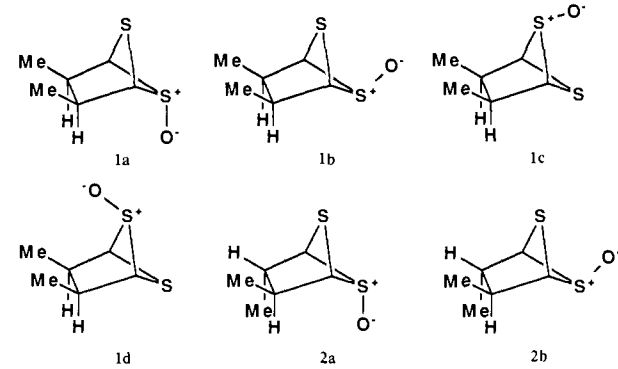
preparing the protein samples. This work was supported by USDA Competitive Grant 88-37262-3406 and National Institutes of Health Grant RR02301 from the Biomedical Research Technology Program, Division of Research Resources. This study made use of the National Magnetic Resonance Facility at Madison, which is supported in part by Grant RR023021. Additional equipment in the facility was purchased with funds from the University of Wisconsin, the NSF Biological Biomedical Research Technology Program (Grant DMB-8415048), NIH Shared Instrumentation Program (Grant RR02781), and the U.S. Department of Agriculture. B.H.O. is supported by a Peterson Fellowship from the University of Wisconsin—Madison.

Scheme I



Zwiebelanes: Novel Biologically Active 2,3-Dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-Oxides from Onion

Thomas Bayer[1a] and Hildebert Wagner*

Institute of Pharmaceutical Biology, University of Munich 8000 Munich 2, Federal Republic of Germany

Eric Block,* Serge Grisoni, and Shu Hai Zhao

Department of Chemistry State University of New York at Albany Albany, New York 12222

Andras Neszmelyi

Central Research Institute for Chemistry of the Hungarian Academy of Sciences H-1020 Budapest, Hungary

Received November 21, 1988

A variety of remarkable low molecular weight cyclic and acyclic organosulfur compounds has been isolated from extracts and essential oils of onion (*Allium cepa*) and garlic (*Allium sativum*) and have been shown to contain C_3, C_6, or C_9 units derived from the stable precursors *trans*-(+)-*S*-1- or (+)-*S*-2-propenyl L-cysteine sulfoxide, respectively.[1b-g] In connection with the search for antiasthmatic agents from onion[2] we have discovered two isomeric biologically active compounds of formula $C_6H_{10}OS_2$ which we name zwiebelane A and B (**1** and **2**, respectively).[3] We present evidence that **1** and **2** are, respectively, *cis*- and *trans*-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxides and that they originate from 1-propenesulfenic acid (**3**). We also report a mechanistically based, stereospecific one-step synthesis of **1** and **2**.

Allium cepa bulbs were peeled and chopped and, after ca. 30 min, squeezed to give onion juice, which was extracted with chloroform. The concentrated extract was then subjected (sequentially) to flash chromatography (C-18 silica gel, methanol; to remove triterpenes), chromatography on a Chromatotron (silica gel, chloroform), column chromatography (silica gel, 5:1 toluene–ethyl acetate), and finally HPLC (silica gel, 100:1 methylene chloride:acetone) affording **1**, **2**, and thiosulfinates (*E*,*Z*)-RS(O)SCH=CHCH$_3$ and RS(O)SR′ (R and R′ = Me or *n*-Pr), among other compounds.[2c,d] Compound **1** is a colorless oil of formula $C_6H_{10}OS_2$ (elemental analysis[4a] and CI- and EI-MS; prominent EI-MS fragment ions at *m*/*e* 99 and 113[4b]) with intense IR bands at 1065 and 1085 cm^{-1} (S=O) [UV λ_{max} 250 nm; ^{1}H NMR ($CDCl_3$)[4c] δ 4.12 (H_A, $J_{AA'}$ = 6.7, J_{AB} = 0.9 Hz, 2 H, CHS_2), 2.92 (H_B, J_{BC} = 6.8, $J_{BC'}$ = 0.3, $J_{BB'}$ = 5.8 Hz, 2 H, $CHCH_3$), 1.17 (H_C, 6 H, CH_3); ^{13}C NMR δ 79.5 (CH), 33.3 (CH), 12.6 (CH_3)]. Compound **2**, present in smaller amounts, also has formula $C_6H_{10}OS_2$ by MS [^{1}H NMR ($CDCl_3$)[4c] δ 4.25 (H_A, $J_{AA'}$ = 6.65, J_{AB} = 0.9 Hz, 1 H, CHS_2), 4.21 ($H_{A'}$, $J_{A'B'}$ = 1.1 Hz, 1 H, CHS_2), 2.85 (H_B, $J_{BB'}$ = 4.0, J_{BC} = 6.7 Hz, 1 H, $CHCH_3$), 2.33 ($H_{B'}$, $J_{B'C'}$ = 7.3 Hz, 1 H, $CHCH_3$), 1.45 ($H_{C'}$, d, 3 H, CH_3), 1.37 (H_C, d, 3 H, CH_3); ^{13}C NMR δ 79.4, 77.7, 48.0, 39.4 (CH), and 15.7, 14.2 (CH_3)]. On the basis of the above spectroscopic data we propose that **1** and **2** are, respectively, *cis*- and *trans*-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide. The mixture of **1** and **2** showed a 65–90% inhibition of thrombin-induced TXB_2 biosynthesis in human platelet rich plasma at a concentration of 0.1–1.0 mg/mL.[4d]

Four distinct isomers of **1** and *two* isomers of **2** are possible, namely **1a–d** and **2a,b** (see Scheme I)[5] although only one isomer each of **1** and **2** is observed in this work. On the basis of Eu(fod)$_3$ shift reagent and aromatic solvent induced shift studies[7] we propose that **1** and **2** have the respective structures (1α, 2α, 3α, 4α, 5β)- and (±)-(1α, 2α, 3β, 4α, 5β)-2,3-dimethyl-5,6-dithiabicyclo-[2.1.1]hexane 5-oxide (structures **1a** and **2a**, respectively). The 5,6-dithiabicyclo[2.1.1]hexane ring system, a bicyclic derivative of the well-studied 1,3-dithietane ring system,[6] has not been previously reported although the related, strained[8a] 5-thiabicyclo[2.1.1]hexane system[8b] is known.

(1) (a) Present address SUNY-Albany. (b) Block, E.; Penn, R. E.; Revelle, L. K. *J. Am. Chem. Soc.* **1979**, *101*, 2200. (c) Block, E.; Revelle, L. K.; Bazzi, A. A. *Tetrahedron Lett.* **1980**, *21*, 1277. (d) Block, E.; Bazzi, A. A.; Revelle, L. K. *J. Am. Chem. Soc.* **1980**, *102*, 2490. (e) Block, E.; Ahmad, S.; Jain, M. K.; Crecely, R. W.; Apitz-Castro, R.; Cruz, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 8295. (f) Block, E. *Sci. Am.* **1985**, *252*, 114. (g) Block, E.; Ahmad, S.; Catalfamo, J.; Jain, M. K.; Apitz-Castro, R. *J. Am. Chem. Soc.* **1986**, *108*, 7045. (h) Block, E.; Iyer, R.; Grisoni, S.; Saha, C.; Belman, S.; Lossing, F. P. *J. Am. Chem. Soc.* **1988**, *110*, 7813 and references therein.

(2) (a) Dorsch, W.; Ettl, M.; Hein, G.; Scheftner, P.; Weber, J.; Bayer, T.; Wagner, H. *Int. Arch. Allergy Appl. Immun.* **1987**, *82*, 535. (b) Dorsch, W.; Adelmann-Grill, B.; Bayer, T.; Ettl, M.; Hein, G.; Jaggy, H.; Ring, J.; Scheftner, P.; Wagner, H. *Allergologie* **1987**, *10*, 316. (c) Dorsch, W.; Wagner, H.; Bayer, T.; Fessler, B.; Hein, G.; Ring, J.; Scheftner, P.; Sieber, W.; Strasser, T.; Weiss, E. *Biochem. Pharmacol.*, in press. (d) Bayer, T. Ph.D. Dissertation, University of Munich, 1988. (e) Bayer, T.; Wagner, H.; Wray, V.; Dorsch, W. *Lancet* **1988**, 906. (f) Wagner, H.; Dorsch, W.; Bayer, T.; Breu, W.; Willer, F., submitted for publication. (g) Kawakishi, S.; Morimitsu, Y. *Lancet* **1988**, 330.

(3) "Zwiebel" is German for onion.

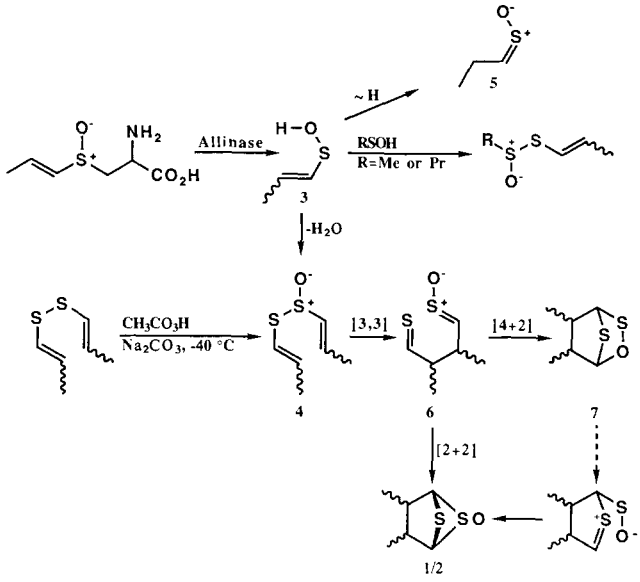
(4) (a) Anal. Calcd for $C_6H_{10}OS_2$: C, 44.4; H, 6.2; O, 9.9; S, 39.5. Found: C, 44.5; H, 6.1; O, 9.3; S, 38.2. (b) High resolution EI-MS: 113.0429 corresponding to C_6H_9S. (c) The ^{1}H NMR spectra of **1a** and **2a** are not first order and were therefore interpreted through LAOCOON III analysis of the 10 spin systems; full details will be given elsewhere. Coupling constants are in excellent agreement with those determined for isomers of 2-bromo-5-thiabicyclo[2.1.1]hexane and its 5-oxide: Naganathan, S.; Block, E., unpublished results. (d) Dorsch, W., Wagner, H., private communication.

(5) (a) According to the Cahn–Ingold–Prelog convention **1a–d**, **2a**, and **2b** are named (1α, 2α, 3α, 4α, 5β)-, (1α, 2α, 3α, 4α, 5α)-, (1α, 2β, 3β, 4α, 5α)-, (1α, 2β, 3β, 4α, 5β)-, (±)-(1α, 2α, 3β, 4α, 5α), and (±)-(1α, 2α, 3β, 4α, 5β)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide, respectively. (b) Oxygen assumes an equatorial position in 1,3-dithietane 1-oxide itself[6] which would correspond to the oxygen orientation in **2a**.

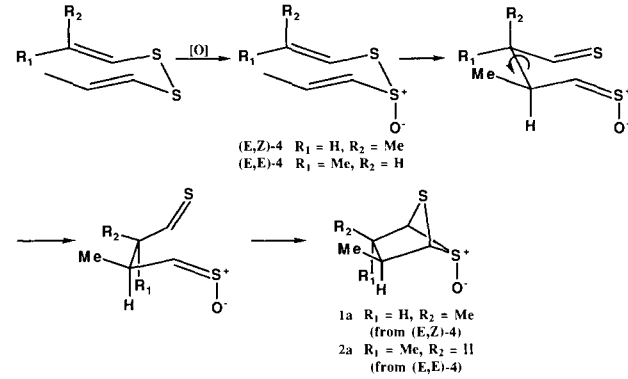
(6) Block, E.; Corey, E. R.; Penn, R. E.; Renken, T. L.; Sherwin, P. F.; Bock, H.; Hirabayshi, T.; Mohmand, S.; Solouki, B. *J. Am. Chem. Soc.* **1982**, *104*, 3119.

0002-7863/89/1511-3085$01.50/0

Scheme II



Scheme III



A one-step synthesis of **1a** and **2a** in a ratio of ca. 2:3 in 20% yield can be achieved simply by peracetic acid[9a] oxidation at −40 °C of isomers of bis(1-propenyl) disulfide[9c] followed by warming to 8 °C and rapid workup. The synthesis is based on the assumption that **1a** and **2a** originate from 1-propenyl 1-propenethiosulfinate (**4**, $CH_3CH{=}CHS(O){-}SCH{=}CHCH_3$) by the process shown in Scheme II. By analogy with the formation of 2-propenyl 2-propenethiosulfinate (allicin, $CH_2{=}CHCH_2S(O)SCH_2CH{=}CH_2$) in garlic from 2-propenesulfenic acid ($CH_2{=}CHCH_2SOH$)[1g] it was anticipated that 1-propenesulfenic acid (**3**, $CH_3CH{=}CHSOH$) from onion would afford **4**. Although it has been previously sought in onion extracts,[9d] compound **4** remains unknown. A highly substituted homologue is reported to be stable.[10] While the facile rearrangement of **3** to the onion lacrymatory factor (*Z*)-propanethial *S*-oxide[1b,c] (**5**) might be thought to preclude formation of **4**, compound **3** and certain derivatives have been trapped with alkynes.[11] The above noted occurence of 1-propenyl alkanethiosulfinates in onion extracts also suggests that **3** can be trapped before it rearranges. We suggest that **4** is indeed formed along with **5** when onions are cut but immediately undergoes an unusually facile [3,3]-sigmatropic rearrangement to 2,3-dimethylbutanedithial 1-oxide (**6**). This reaction is analogous to the sulfoxide thio-Claisen rearrangement[12a] and rearrangement of di(1-alkenyl) disulfides[12b-e] but is even more facile due to the weak thiosulfinate S–S bond.[13] Compound **6** can then afford **1a** or **2a** through intramolecular head-to-tail 2 + 2 cycloaddition. Alternatively, compound **6** can undergo an intramolecular 1,3-dipolar cycloaddition reaction[14a] involving the thial *S*-oxide group as a 1,3-dipole[1d] and the thial group as a 1,3-dipolarophile[14b] affording 5,6-dimethyl-2,7-dithia-3-oxabicyclo-[2.2.1]heptane (**7**), a structure similar to the well-known 2,5-dimethylthiophene–singlet oxygen adduct.[15] Heterolytic or, less likely, homolytic rearrangement of **7** would then afford **1a** or **2a**.[17]

To examine the stereospecificity associated with the rearrangement of **4**, the (*E*,*Z*), (*E*,*E*), and (*Z*,*Z*) isomers were separated by preparative HPLC (C-18 column; CH_3CN–H_2O). To our delight oxidation of (*E*,*Z*)-**4** afforded exclusively **1a**, while oxidation of (*E*,*E*)- and (*Z*,*Z*)-**4** gave only **2a**. These observations are entirely consistent with the stereospecific [3,3]-process shown in Scheme III. Additional studies of the scope and stereochemistry of the remarkable sulfoxide-accelerated dithio-Claisen rearrangement intramolecular cyclization process described herein and of the chemistry of compounds **1a** and **2a** are in progress and will be reported in due course.

Acknowledgment. We gratefully acknowledge support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, the Société Nationale Elf Aquitaine, the National Science Foundation, the McCormick Company (E.B., T.B., S.G., and S.H.Z.) and NATO. We thank Joy Merritt of the Chemical Abstracts Service for advice on nomenclature.

(7) (a) In C_6D_6, **1** shows δ 3.15 (s, 2 H), 2.60 (m, 2 H), 0.65 (dm, J = 6.9 Hz, 6 H), while **2** shows δ 3.42, 3.34 (AB, J_{AB} = 6.9 Hz, 2 H), 2.55 (qdd, J = 6.8, 3.8, 1.2 Hz, 1 H), 1.74 (m, 1 H), 1.26 (d, J = 7.3 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H). In $CDCl_3$ with added $Eu(fod)_3$ the 2.95 ppm peak of **1** shows a much greater change than the 1.15 ppm CH_3 peak; similarly with **2**, the 1.45 ppm CH_3 doublet and the 2.85 ppm multiplet show significantly larger changes than the 1.37 ppm CH_3 doublet and the 2.33 ppm multiplet. (b) For related work: Juaristi, E.; Cruz-Sanchez, J. S.; Petsom, A.; Glass, R. S. *Tetrahedron* **1988**, *44*, 5653.

(8) (a) The calculated strain energy for bicyclo[2.1.1]hexane is 38 kcal/mol;[8b] that for 5-thiabicyclo[2.1.1]hexane[8c] is 32 kcal/mol.[8d] It is likely that the strain energy for 5,6-dithiabicyclo[2.1.1]hexane is lower still. (b) Allinger, N. L., unpublished results personally communicated. (c) Tabushi, I.; Tamaru, Y.; Yoshida, Z. *Tetrahedron Lett.* **1970**, 2931. (d) Allinger, N. L.; Hickey, M. J. *J. Am. Chem. Soc.* **1975**, *97*, 5167.

(9) (a) The peracetic acid (FMC Corp.; 35%) must be freed from H_2SO_4 by treatment with NaOAc.[9b] A well-stirred 0.02 M CH_2Cl_2 solution of disulfide is treated at −78 °C under argon with CH_3CO_3H (1 equiv) in the presence of Na_2CO_3 (0.5 equiv).[9b] The mixture is placed in a −40 °C bath and warmed to 8 °C during 2 h with vigorous stirring, the suspension is washed with cold $NaHCO_3$ solution, and the organic phase is worked up in the usual manner. (b) Korach, M.; Nielsen, D. R.; Rideout, W. H. *J. Am. Chem. Soc.* **1960**, *82*, 4328. (c) Brandsma, L.; Schuijl, P. J. W. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 513. (d) Whitaker, J. R. In *Advances in Food Research*; Chichester, C. O., Mrak, E. M., Stewart, G. F., Eds.; Academic Press: New York, 1976; Vol. 22, p 73ff.

(10) (a) Bonini, B. F.; Foresti, E.; Leardini, R.; Maccagnani, G.; Mazzanti, G. *Tetrahedron Lett.* **1984**, *25*, 445. (b) We have prepared 2-methyl-1-propenyl 2-methyl-1-propenethiosulfinate (i) and 2-methyl-1-propenyl 2-methyl-1-propenethiosulfonate (ii) by careful oxidation of bis(2-methyl-1-propenyl) disulfide and find i to be moderately stable at room temperature. We assume that the rate of [3,3]-sigmatropic rearrangement of i is retarded relative to the rate for **4** by the *gem*-methyl groups.

(11) (a) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. (b) Shelton, J. R.; Davis, K. E. *J. Am. Chem. Soc.* **1967**, *89*, 718.

(12) (a) Block, E.; Ahmad, S. *J. Am. Chem. Soc.* **1985**, *107*, 6731. (b) Boelens, H.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 141. Campbell, M. M.; Evgenios, D. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2866. Larsson, F. C. V.; Brandsma, L.; Lawesson, S.-O. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 258. (c) Bis(1-propenyl) disulfide is completely rearranged at 80 °C in less than 3 h.[12d] We will report on this work elsewhere. (d) Zhao, S. H.; Block, E., unpublished results. (e) An analogous dihetero-Cope process occurs with 3,4-diphospha-1,5-hexadienes: Appel, R.; Winkhaus, V.; Knoch, F. *Chem. Ber.* **1987**, *120*, 125.

(13) The S–S bond energy in MeS(O)SMe is 46 kcal/mol: Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921.

(14) (a) For analogous intramolecular heterobicyclo[2.2.1]heptane-forming processes involving nitrones, see: Lumma, W. C., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2820. Hwu, J. R.; Robl, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 704. (b) Huisgen, R.; Rapp, J. *J. Am. Chem. Soc.* **1987**, *109*, 902.

(15) (a) Matturro, M. G.; Reynolds, R. P. *Tetrahedron Lett.* **1987**, *28*, 4981 and references therein. (b) Compound **7** can also be considered to be a bicyclic sultene.[16]

(16) Block, E.; Wall, A. *J. Org. Chem.* **1987**, *52*, 809.

(17) A difficulty with this second mechanism is that it requires cleavage of the stronger C–O bond rather than the weaker S–O bond.