these conditions.[23] It is noteworthy that the tetraamine ligand was intact during the oxidation of chelated α-amino acids.[24] This suggests that the carboxylate group of amino acids enhances the susceptibility of α-amino group of amino acids to oxidation.

Nucleophilic addition of hydride (as BH_4^-) to the imine carbon center of the $NH{=}C(CH_3)CO_2$ chelate complex has been reported.[9] Since the complexes employed here have a chiral metal center, it will provide a new synthetic pathway to chiral α-amino acids.[25] It indicates a possibility of a kind of asymmetric transformation[13] of DL-amino acids to chiral amino acids via iminocarboxylates wtih chiral (tetraamine)cobalt(III) complexes. The study in this line is in progress.

(23) It has been reported that some attempts to achieve amine oxidation of Co(III) complexes failed.[2a,19]

(24) With [Co(oxalato)(2,3,2-tet)]ClO_4 complex, no reaction was observed under the same conditions.

(25) Preliminary results of the reduction of the 2-iminocarboxylato complexes with $NaBH_4$ showed stereoselectivity on hydride addition. The *R*/*S* values of the reduced product for **3** was 75/25.

(*E*,*Z*)-Ajoene: A Potent Antithrombotic Agent from Garlic[1]

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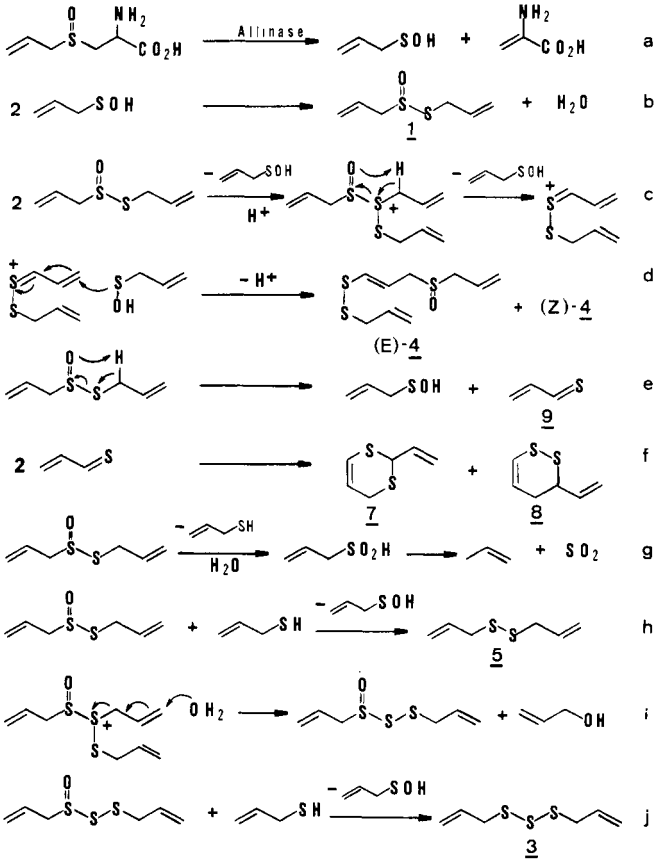
Garlic (*Allium sativum*) is reputed to offer protection against stroke, coronary thrombosis, and atherosclerosis.[2,3a] These beneficial effects of garlic have been attributed to its ability to inhibit platelet aggregation.[3b] This effect, in turn, has been ascribed to allicin ($CH_2{=}CHCH_2S(O)SCH_2CH{=}CH_2$, *S*-allyl 2-propenethiosulfinate (**1**)), allyl methyl trisulfide (**2**), and diallyl trisulfide (**3**), all of which are found in garlic extracts.[3c] Recently

Scheme I



Apitz-Castro et al.[4a] reported that 2-vinyl-4*H*-1,3-dithiin (**7**) and an unknown compound, now named ajoene,[4b] are potent antithrombotic agents derived from garlic extract. Unlike several other inhibitors of platelet aggregation, these components have been found to inhibit aggregation induced by all known inductors.[4a] We report herein the structural characterization and a simple synthesis of (*E*,*Z*)-ajoene (**4**) as well as **7** from allicin (**1**).

Extraction and separation of the garlic-derived components was monitored with bioassay for inhibition of platelet aggregation.[4a] Chopped garlic pieces were soaked in methanol at 25 °C for 48 h; the concentrate was suspended in water and was extracted with diethyl ether. The extract was concentrated, and the residue was stored at 25 °C for 4 days as a 10% solution in methanol, filtered, and concentrated giving a yellow oil (1.6 g/5 kg of garlic bulbs). Chromatography (silica gel; hexane to benzene to chloroform) gave 18 components, of which three fractions inhibited platelet aggregation. Preparative TLC (silica gel) led to the isolation of pure samples of the nonpolar components. TLC fractions with R_f 0.5 and 0.25 in hexane were identified as diallyl trisulfide (**3**) and 2-vinyl-4*H*-1,3-dithiin (**7**),[4a,5] respectively. Allicin (**1**), allyl methyl trisulfide (**2**), diallyl disulfide (**5**), diallyl tetrasulfide (**6**), and 3-vinyl-4*H*-1,2-dithiin (**8**)[5,9] were also isolated and identified

† Fellow of the John Simon Guggenheim Memorial Foundation, 1984–1985.

(1) (a) The material covered in this communication is the subject of U.S. Patent Applications filed by the Research Foundation of the State University of New York. (b) Presented at the 1984 International Chemical Congress of Pacific Basin Societies, Honolulu, December 16, 1984. (c) The Chemistry of Alkyl Thiosulfinate Esters. 8. (d) Part 7: Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929–3944.

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(3) (a) Garlic also displays antibacterial, antifungal, and anticandidal activity, attributed to allicin (**1**): Cavallito, C. J.; Bailey, J. H. *J. Am. Chem. Soc.* **1944**, *66*, 1950–1951. Cavallito, C. J.; Buck, J. S.; Suter, C. M. *J. Am. Chem. Soc.* **1944**, *66*, 1952–1954. Barone, F. E. *Mycologia* **1977**, *69*, 793–825. (b) Bordia, A. *Atherosclerosis* (*Shannon, Irel.*) **1978**, *30*, 355–360. Samson, R. R. *Atherosclerosis* (*Shannon, Irel.*) **1982**, *44*, 119–120. (c) Augusti, K. T.; Mathew, P. T. *Experientia* **1974**, *30*, 468–470. Ariga, T.; Oshiba, S.; Tamada, T. *Lancet* **1981**, *1*, 150–151.

(4) (a) Apitz-Castro, R.; Cabrera, S.; Cruz, M. R.; Ledezma, E.; Jain, M. K. *Thromb. Res.* **1983**, *32*, 155–169 (**4** was misassigned here). (b) "Ajo" (pronounced "aho") is garlic in Spanish.

(5) Bock, H.; Mohmand, S.; Hirabayashi, T.; Semkow, A. *Chem. Ber.* **1982**, *115*, 1339–1348. Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445–1447.

(6) Structures such as $CH_2{=}CHCH_2SCH_2CH{=}CHS(O)SCH_2CH{=}CH_2$ possessing a –S(O)S– group instead of a C–S(O)–C group are ruled out by the IR spectrum since the former group shows strong absorption[1d] at 1100 cm^{-1}. Since allyl 1-alkenyl sulfoxides undergo facile thio-Claisen rearrangement at or below room temperature[7] the isomeric structure $CH_2{=}CHCH_2$-$S(O)CH{=}CHCH_2SSCH_2CH{=}CH_2$ can also be ruled out.

(7) (a) Ahmad, S.; Block, E., unpublished results. (b) Bell, R.; Cottam, P. D.; Davies, J.; Jones, D. N.; Meanwell, N. A. *Tetrahedron Lett.* **1980**, *21*, 4379–4382.

(8) It has been previously noted[3a] that allicin decomposes to a water-insoluble nondistillable liquid of undefined structure. Compound **4** can be purified by Kugelrohr distillation at 0.05 mm (air temperature 150–200 °C).

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in the nonpolar fractions.[11] Column chromatography (ethyl acetate) or HPLC (8:92 isopropyl alcohol:hexane) of the polar fraction afforded the most active component ajoene (**4**) as a colorless, odorless oil of formula $C_9H_{14}S_3O$ (elemental analysis[12] and CI-MS using methane and ammonia): IR 1050 (s, C—S(O)—C), 1650 cm^{-1} (s, C=C); UV λ_{max} 240 nm; ^1H NMR (250 MHz) δ 6.38 (dt, J = 14.8, 1 Hz, 1 H, =CHSS), 5.9 (m, 3 H, =$CHCH_2$), 5.4 (m, 2 H, CH_2=$CHCH_2S(O)$), 5.2 (m, 2 H, CH_2=$CHCH_2S$), 3.5 (m, 4 H, $CH_2S(O)CH_2$), 3.36 (d, J = 7.2 Hz, 2 H, $SSCH_2$); ^{13}C NMR δ 134.7, 132.6, 125.7, 123.7, 119.3, 116.9, 54.5, 53.1, 41.4. The spectroscopic data are consistent with the structure (*E*)-4,5,9-trithiadodeca-1,6,11-triene 9-oxide, (*E*)-CH_2=$CHCH_2S(O)CH_2CH$=$CHSSCH_2CH$=CH_2[6,8] (**4**-*E*). An isomeric compound with ^1H NMR (250 MHz) δ 6.56 (dt, J = 9.5, 1 Hz, 1 H, =CHSS), 5.8 (m, 3 H, =$CHCH_2$), 5.4 (m, 2 H, CH_2=$CHCH_2S(O)$), 5.2 (m, 2 H, CH_2=$CHCH_2S$), 3.5 (m, 4 H, $CH_2S(O)CH_2$), 3.38 (d, J = 7.2 Hz, 2 H, $SSCH_2$) and ^{13}C NMR δ 138.5, 132.7, 125.7, 123.8, 119.3, 118.2, 55.1, 49.7, 42.2 was identified as the *Z* isomer of **4**. The three compounds **3**, **4**, and **7** account for more than 75% of the platelet aggregation inhibitory activity of garlic extract.

We suggest (Scheme I) that compounds **3**–**8** are formed by decomposition of allicin (**1**), itself formed from a stable precursor by action of the allinase enzyme followed by dehydrative coupling of 2-propenesulfenic acid (steps a and b).[13] S-Thioallylation of **1** followed by Cope-type elimination and readdition of 2-propenesulfenic acid[14a] should give (*E*,*Z*)-ajoene (**4**) (steps c and d) while unimolecular decomposition of **1** (steps e and f) should afford thioacrolein (**9**) which would dimerize, following mechanisms previously advanced by one of us.[1d,14b] In accord with this proposal, (*E*,*Z*)-ajoene (**4**) could be obtained by refluxing a solution of **1**[15] (10% in 3:2 Me_2CO:H_2O)[16] for 4 h, centrifuging, and extracting (CH_2Cl_2) the upper layer, which had been diluted with methanol and repeatedly extracted with pentane to remove nonpolar materials. Flash chromatography of the methylene chloride concentrate (0.34 g from 1 g of **1**; ca. 34% yield of slightly impure **4**) gave **4** (4:1 *E*:*Z*) in 17% yield. Synthetic **4** was identical in all respects with the natural material. GC analysis of the pentane-soluble fraction (0.52 g from 1 g of **1**) including the methanol–water-washed centrifugate indicated a 21:17:50:12 mixture of **5**/**3**/**7**/**8**, respectively. This ratio changed to 4:4:75:17 when **1** was decomposed in the same solvent mixture at 37 °C for 2 days or 25 °C for 7 days, reflecting partial decomposition of some compounds at the higher temperature and/or different temperature dependence of the reactions of Scheme I. The near identity of the 4.4:1 ratio of **7** to **8** observed in the 37 or 25 °C decomposition of **1** and the 4.5:1 ratio of **7** to **8** found from dimerization at −180 °C of thioacrolein (**9**) from flash vacuum pyrolysis of diallyl sulfide[5] provides support for steps e and f.[17] Steps g and i are supported by formation of propene on refluxing **1** in water and occurrence[10] of sulfur dioxide and allyl alcohol in garlic extracts; steps h and j employ previously proposed mechanisms[1d,18] to rationalize formation of **3** and **5**. The mechanisms of Scheme I are also supported by studies on the decomposition of *S*-methyl 2-propenethiosulfinate.[19]

The ready availability of ajoene (**4**) permits study of the nature of its antithrombotic activity. Preliminary results indicate that when rabbits are fed 20 mg/kg of body weight of (*E*,*Z*)-**4** *100% inhibition of collagen-induced platelet aggregation is seen for a 24-h period after feeding.* In vitro tests provide other interesting information on inhibition by **4**: the effect of **4** increases with time of incubation with platelets; its effect cannot be reversed by washing platelets; aggregation induced by all known inductors is inhibited; rabbit granulocyte aggregation is also inhibited.[20] These physiological observations suggest that the age-old belief in the therapeutic effect of garlic on the circulatory system may indeed have some basis.

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Registry No. 4, 92285-01-3; (*E*)-**4**, 92284-99-6; (*Z*)-**4**, 92285-00-2; allicin, 539-86-6.

(9) Heterocycles **7** and **8** (incorrectly identified as 3-vinyl-6*H*-1,2-dithiin) were formed on preparative GC of **1** but were said not to be present in garlic extracts.[10]

(10) Brodnitz, M. H.; Pascale, J. V.; Van Derslice, L. *J. Agric. Food Chem.* **1971**, *19*, 273–275.

(11) HPLC analysis of commercial garlic oil or pearls showed that **4**, **7**, and **8** were absent; however, the latter three compounds would be unlikely to survive the steam distillation used to produce the commercial essential oil of garlic.

(12) Anal. Calcd for $C_9H_{14}S_3O$: C, 46.2; H, 5.98; S, 41.0. Found: C, 45.8; H, 5.90; S, 40.8.

(13) Stoll, A.; Seebeck, E. *Adv. Enzymol. Relat. Subj. Biochem.* **1951**, *11*, 377–400.

(14) (a) For a related process involving γ-chlorination of allylic sulfides, see: Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433–4436. (b) For thioaldehyde formation from thiosulfinates, see: Baldwin, J. E.; Lopez, R. G. *Tetrahedron* **1983**, *39*, 1487–1498.

(15) Prepared by oxidation of **5** (CH_3CO_3H).

(16) This solvent mixture was chosen because it maximizes the yield and *E*/*Z* ratio of **4** and gave an initially homogeneous solution with **1**. The *Z* isomer is the major product on decomposition of neat **1** or a solution of **1** in acetone or benzene/water.

(17) Direct observation of deep blue thioacrolein (**9**) could be achieved by distilling **1** into a liquid-nitrogen-cooled trap; 2-propenesulfenic acid could also be trapped with an alkyne as reported previously.[7b]

(18) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65–181.

(19) At 37 °C in acetone/water, $MeS(O)SCH_2CH$=CH_2 gives (*E*,*Z*)-$MeS(O)CH_2CH$=CH_2SSMe, (*E*,*Z*)-$MeS(O)CH_2CH$=$CHSSCH_2CH$=CH_2, $MeS(O)SMe$, **7**, and **8**.

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Asymmetric Total Synthesis of Levuglandin E_2[1]

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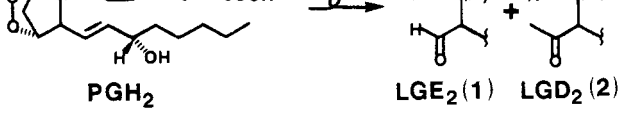
It is fascinating that the prostaglandin (PG) endoperoxide PGH_2 is extraordinarily unstable in the aqueous environment of its biosynthesis.[2] Recently we discovered that this solvent-induced decomposition yields (≃20%) two levulinaldehyde derivatives,[3] levuglandin E_2 (LGE_2) (**1**) and LGD_2 (**2**), in addition to the



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