The Organosulfur Chemistry of the Genus *Allium* – Implications for the Organic Chemistry of Sulfur

By Eric Block*

A Cook's tour is presented of the organosulfur chemistry of the genus *Allium*, as represented, inter alia, by garlic (*Allium sativum* L.) and onion (*Allium cepa* L.). We report on the biosynthesis of the *S*-alk(en)yl-L-cysteine *S*-oxides (aroma and flavor precursors) in intact plants and on how upon cutting or crushing the plants these precursors are cleaved by allinase enzymes, giving sulfenic acids—highly reactive organosulfur intermediates. In garlic, 2-propenesulfenic acid gives allicin, a thiosulfinate with antibiotic properties, while in onion 1-propenesulfenic acid rearranges to the sulfine (*Z*)-propanethial *S*-oxide, the lachrymatory factor (LF) of onion. Highlights of onion chemistry include the assignment of stereochemistry to the LF and determination of the mechanism of its dimerization; the isolation, characterization, and synthesis of thiosulfinates which most closely duplicate the taste and aroma of the freshly cut bulb, and additional unusual compounds such as zwiebelanes (dithiabicyclo[2.1.1]hexanes), a bissulfine (a 1,4-butanedithial *S,S'*-dioxide), antithrombotic and antiasthmatic cepaenes (α-sulfinyl disulfides), and *vic*-disulfoxides. Especially noteworthy in the chemistry of garlic are the discovery of ajoene, a potent antithrombotic agent from garlic, and the elucidation of the unique sequence of reactions that occur when diallyl disulfide, which is present in steam-distilled garlic oil, is heated. Reaction mechanisms under discussion include [3,3]- and [2,3]-sigmatropic rearrangements involving sulfur (e.g. sulfoxide-accelerated thio- and dithio-Claisen rearrangements) and cycloadditions involving thiocarbonyl systems. In view of the culinary importance of alliaceous plants as well as the unique history of their use in folk medicine, this survey concludes with a discussion of the physiological activity of the components of these plants: cancer prevention, antimicrobial activity, insect and animal attractive/repulsive activity, olfactory–gustatory–lachrymatory properties, effect on lipid metabolism, platelet aggregation inhibitory activity and properties associated with ajoene. And naturally, comments about onion and garlic induced bad breath and heartburn may not be overlooked.

1. Introduction

We remember the fish which we did eat in Egypt, the cucumbers, melons, leeks, onions and garlic!
Num. 11:4–6

What is more familiar and pleasant to the senses than freshly chopped or sauted garlic, sliced or boiled onions, steaming leeks, finely diced chives, crisp raw scallions, or the delicate shallot? The scents of these commonplace plants brings back memories of mother's kitchen, a favorite restaurant or even a walk through a meadow rich with the aroma of wild onions. The adjectives applied to these plants, zesty, lusty, assertive, piquant, and distinctive, and even the botanical name *Allium*, derived from the Celtic word "all", which means pungent, betray the presence of a host of remarkable flavorants and odorants all having in common one element, sulfur. Many of these flavorful sulfur compounds contain the allyl group, which in turn gets its name from *Allium*. It is the presence of these organosulfur compounds, more than any other attribute, that defines the character of this extraordinary genus. The great American poet Carl Sanburg said: *"Life itself is like an onion; it has a bewildering number of layers. You peel them off, one by one, and sometimes you cry."* The "bewildering number of layers" of the onion has its counterpart in the complex chemistry of this and other alliaceous plants, representing a microcosm of the field of organosulfur chemistry. More specifically, *Allium* chemistry presents us with examples of sulfur compounds with striking physiological activity as well as culinary appeal, reactive organosulfur intermediates with unusual bonding, challenging analytical problems, compounds with chirality at sulfur and other stereochemical features related to the presence of sulfur, novel organosulfur heterocycles with notable spectroscopic properties, redox reactions involving sulfur, as well as processes involving sulfur radicals, sulfur stabilized carbocations, pericyclic reactions, noteworthy rearrangements, and reactions of utility in synthetic organic chemistry.[1]

For twenty-five years I have been exploring the organosulfur chemistry of the genus *Allium*, as represented by garlic (*Allium sativum* L.), onion (*Allium cepa* L.), leek (*Allium ampeloprasum* L. var. porrum), scallion (*Allium fistulosum*), shallot (*Allium ascalonicum* auct.), great-headed ("elephant") garlic (*Allium ampeloprasum* L. var. holmense), wild garlic (*Allium ursinum*), chive (*Allium schoenoprasum* L.), and Chinese chive (*Allium tuberosum* L.) (Fig. 1). When I began this study, much outstanding research had already been done in this area, e.g. as summarized in a review article by Nobel Laureate Arturi Virtanen.[2] As my research proceeded it became clear that there were still significant puzzles remaining to be solved, that these most common plants could teach us much about sulfur chemistry, and that the compounds and mixtures produced when these plants are cut display an even broader range of biological activities than

[*] Professor E. Block
Department of Chemistry
State University of New York at Albany
Albany, NY 12222 (USA)

  0570-0833/92/0909-1135 $ 3.50+.25/0

earlier suspected. While extracts and potions of garlic and onion have been used for millennia in folk medicine, commercial products derived from these plants are now enjoying growing popular use in many countries. Furthermore, responding to epidemiological evidence that lower cancer risks are associated with increased consumption of alliaceous plants, health organizations have recently targeted garlic and onion as prime candidates for "designer foods" programs, programs to develop new foods that will help prevent cells from becoming cancerous. For all of these reasons a detailed exploration of the organosulfur chemistry of the genus *Allium* seemed justified as well as timely. This review summarizes progress in this field both in my own and other laboratories.[3]

2. Organosulfur Compounds of Intact Plants

Well loved he garleek, oynons, and eek lekes,
and for to drynken strong wyn, reed as blood.

"Canterbury Tales"
Geoffrey Chaucer (1342–1400)

The earliest reports concerning the isolation of organic compounds from garlic (1844, 1892) and onion by Wertheim (1844) and Semmler (1892) in Germany identified diallyl sulfide[4] (corrected in 1892 to the disulfide[5]) and a propenyl propyl disulfide[5] as the principal components of the distilled oils ("ätherische Öle") of garlic and onion, respectively. In the 1940s it became apparent that these and other volatile sulfur compounds were secondary compounds formed by enzymatic action on precursors in the intact bulb. Thus, in 1945, Cavallito et al. in Rennselaer, New York, reported that when garlic cloves were frozen in dry ice, pulverized, and extracted with acetone, "the acetone extracts upon evaporation yielded only minute quantities of residue and no sulfides, indicating the absence of free sulfides in the plant. The [white] garlic powder had practically no odor, but upon addition of small quantities of water, the typical odor was detected and the antibacterial principle (**1**) could be extracted and isolated. This demonstrates that neither **1** nor the allyl sulfides found in "Essential Oil of Garlic" are present as such in whole garlic. When the powder was heated to reflux for thirty minutes with a small volume of 95% ethanol, no activity could be demonstrated by addition of water to the insoluble residue. When, however, a small quantity (1 $mg\,mL^{-1}$) of fresh garlic powder was added to the alcohol insoluble fraction in water (20 $mg\,mL^{-1}$), the activity of the treated sample was shown to be equal to that of the original untreated powder. The 95% ethanol treatment has inactivated the enzyme required for cleavage of the precursor and addition of a small quantity of fresh enzyme brought about the usual cleavage.[6]

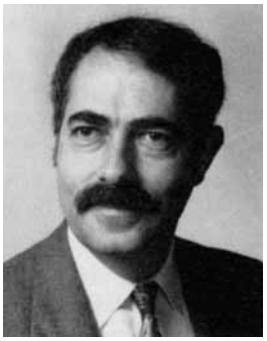
Since a strict definition of "essential oil" is "a volatile substance contained in certain aromatic plants that imparts distinctive odor to the plant" and since the volatile substances of the *Allium* spp. are not found in the plant but result from disrupting the plant cells, it is preferable to describe the process leading to a particular *Allium*-derived product, e.g. "steam volatile components" or "head space volatiles".[7]

2.1. Sulfur Amino Acids Secondary Metabolites in *Allium* spp.

Let onion atoms lurk within the bowl
and, scarce suspected, animate the whole.

"Recipe for Salad",
Sydney Smith (1771–1845)

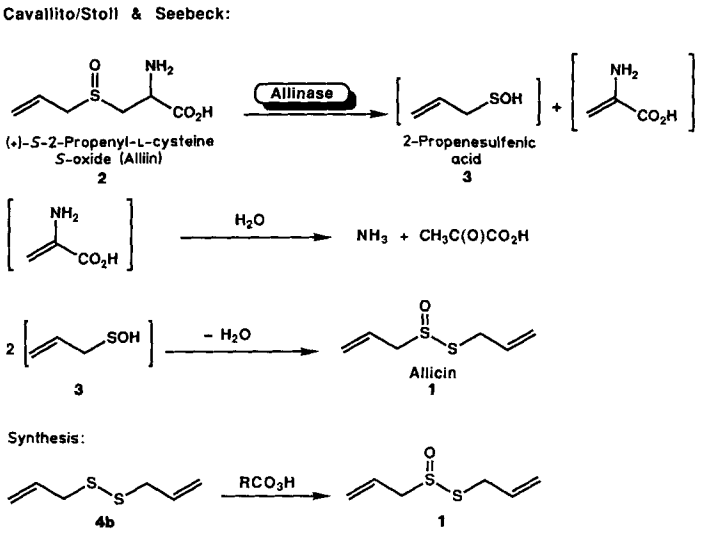
Garlic, onion and other members of the *Allium* spp. contain 1–5% dry weight of nonprotein sulfur amino acid secondary metabolites. Pioneering studies in the 1940s by Stoll and Seebeck in Basel demonstrated that the stable precursor of Cavallito's antibacterial principle of garlic **1** is (+)-*S*-2-propenyl-L-cysteine *S*-oxide (**2**, "alliin").[8] In the intact cell, **2** and related *S*-alk(en)yl-L-cysteine *S*-oxides (aroma and flavor precursors) are located in the cytoplasm and the C–S lyase enzyme allinase in the vacuole.[9] Disruption of the cell results in release of allinase and subsequent α,β-elimination of the *S*-oxides, ultimately affording volatile and odorous low molecular weight organosulfur compounds such as **1** (Scheme 1). Four sulfoxides occur in *Allium* spp.: *S*-2-propenyl-, *S*-(*E*)-1-propenyl-, *S*-methyl- and *S*-propyl-L-cysteine *S*-oxides (**2**, **5**–**7** respectively). Onions contain **5**–**7** while garlic contains **2**, **5**, and **6**.[10–13] The distinctive flavors of the various *Allium* spp. reflect the varying amounts of compounds **2**, **5**–**7**, particularly of **5** ("isoalliin"), which is



Eric Block, born in 1942 in New York City, studied chemistry at Queens College of the City University of New York. He received his Ph.D. degree from Harvard University, where in the laboratory of Professor E. J. Corey he first developed an interest in organosulfur chemistry, the chemistry of natural products, synthetic methods, and organic reaction mechanisms. In 1967 he joined the faculty at the University of Missouri-St. Louis where he was promoted to Professor. In 1981 he moved to the State University of New York at Albany, serving as Chairman of the Chemistry Department from 1985 to 1991. He has been the recipient of a number of awards and honors including a Guggenheim Fellowship and the ACS Award for Advancement and Application of Agricultural and Food Chemistry; he serves on several journal editorial boards, and has been a visiting professor at Harvard, and the Universities of Illinois-Urbana, Frankfurt, and Bologna. He is an avid photographer and traveler. In his overseas travels he enjoys visiting produce markets to see displays of local Allium species.

Fig. 1. Several plants of the genus *Allium*. a) C. C. Calwer, *Landwirtsch. Pflanzenf.*, Plate 26, Stuttgart, **1852**; b) L. Reichenbach, *Icones Florae Germanicae*, Plate 494, Leipzig, **1848**.

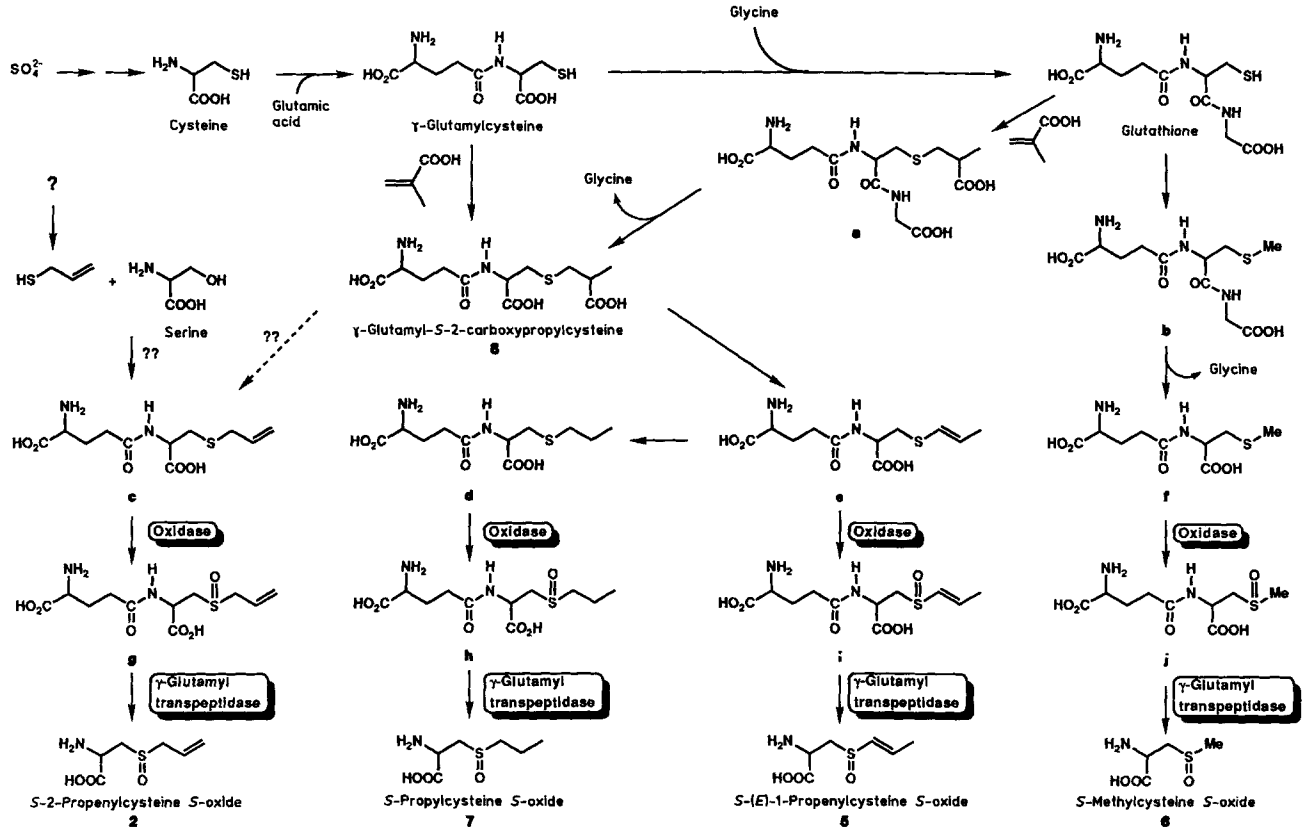
the precursor to the onion lachrymator, and of **2**, which is the precursor to the characteristic allylic compounds of garlic. Also present in *Allium* spp. are 24 γ-glutamyl peptides of sulfur amino acids. These are considered to function as storage compounds of nitrogen and sulfur (precursors to plant chemical defense agents?) and may have a role in the transport of amino acids across cell membranes.[14]



Scheme 1. Cavallito's pioneering discovery and synthesis of allicin **1**, the antibacterial principle of garlic (anticipating subsequent studies by Stoll and Seebeck on the precursor alliin **2**).

Scheme 2 summarizes the proposed biosynthesis of the various *Allium* spp. peptides and aroma precursors based on the results of labeling experiments, in which $^{35}SO_4^{2-}$ was fed to onion plants[15]. By briefly boiling the bulb or homogenizing the plants with alcohol containing limited quantities of water the allinase enzymes can be deactivated, thus permitting analysis of the peptides by HPLC.[12, 16] The sulfate is reduced and assimilated into cysteine in the chloroplasts[17] and then enters the glutathione cycle.[18] Michael addition of γ-glutamylcysteine to methacrylic acid (from valine) can afford γ-glutamyl-*S*-2-carboxypropylcysteine (**8**) which in onion undergoes sequential decarboxylation to give γ-glutamyl-*S*-1-propenylcysteine **e**, oxidation to γ-glutamyl-*S*-1-propenylcysteine *S*-oxide **i**, and cleavage by γ-glutamyl transpeptidase [EC 2.3.2.1] to **5**.[19a] Labeling experiments have established that the precursor **8** is converted into **5** with loss of the 3-*pro-R* hydrogen atom and that the oxidative decarboxylation reaction proceeds with *anti* geometry, analogous to terminal alkene biosynthesis (Scheme 2).[19b] Parallel processes involve Michael addition of glutathione to methacrylic acid giving *S*-2-carboxypropylglutathione **a** followed by conversion of the latter into **8** and methylation of glutathione giving *S*-methylglutathione **b** followed by conversion of the latter into γ-glutamyl-*S*-methylcysteine **f**. The situation with garlic is less clear. γ-Glutamyl-*S*-2-propenylcysteine **c**, formed from **8**, or more likely, from serine and 2-propenethiol by a process not well understood,[20] is converted into γ-glutamyl-*S*-2-propenylcysteine *S*-oxide **g** by an oxidase and is then cleaved by γ-glutamyl transpeptidase to **2**.

It has recently been reported[11] that the concentration of γ-glutamyl-*S*-(*E*)-1-propenylcysteine **e** and γ-glutamyl-*S*-2-propenylcysteine **c**, the dominant γ-glutamyl peptides in homogenates of fresh garlic, decreases markedly when freshly



Scheme 2. An overview of biosynthesis from sulfate of the amino acid/peptide precursors to the flavorants and odorants of plants of the *Allium* spp. **a**, **b**, **c**, **e**, **f**, **g**, **i** see text. **d**: γ-glutamyl-*S*-propylcysteine; **h**: γ-glutamyl-*S*-propylcysteine *S*-oxide; **j**: γ-glutamyl-*S*-methylcysteine *S*-oxide.

picked garlic is stored, especially at 4 °C. The consequence of cold storage of garlic is increased production of **5** and therefore low molecular weight organosulfur compounds containing the 1-propenyl group (see Section 5.2.3). A second discovery, recently made in our laboratories is that garlic *grown* in colder climates contains far less **6** than garlic grown in more temperate climates, although levels of precursor compounds, such as γ-glutamyl-*S*-methylcysteine **f**, are normal.[21]

2.2. Allinase Enzymes

Allinases [EC 4.4.1.4] are pyridoxal 5′-phosphate dependent α,β-eliminating lyases which catalyze the decomposition of (+)-*S*-2-propenyl-L-cysteine *S*-oxide (**2**) and other (+)-*S*-alk(en)yl-L-cysteine *S*-oxides to ammonium pyruvate and allicin (**1**) and its homologs (Section 3). Synthetic **2** is racemic at the sulfur atom. The natural (+)-diastereomer (the first acyclic natural product with both an asymmetric carbon and an asymmetric heteroatom) is quantitatively and rapidly converted into **1** by garlic allinase, whereas the (−)-isomer of **2** decomposes much more slowly; derivatives of D-cysteine are completely inactive.[2] Conflicting results have been published in the case of garlic allinase. One group suggests that it is a dimer of molecular mass between 108000 and 111000 and subunit mass 53500 and requires a flavin-coenzyme in addition to pyridoxal 5′-phosphate,[22a] while a second group claims that it is a tetramer with a molecular mass of 180 kDa with subunits of mass 45 kDa.[23] Welsh onion (*Allium fistulosum* L.) allinase is a tetramer with a molecular mass of 220 kDa and subunit mass of 52 kDa and an optimum pH of 7.0.[24] Virtanen reported the purification of an onion allinase which showed maximal activity at pH 7.4.[3h, 8e, 25–27] Recent work suggests that there are *two* different allinase activities in garlic: one is specific for substrates **2** and **5**, has an optimum pH of 4.5, and cleaves 97% of **2**/**5** within 0.5 min at 23 °C; the second is specific for substrate **6**, has an optimum pH of 6.5, and cleaves 97% of **6** within 5 min at 23 °C. Both allinases are irreversibly deactivated at pH 1.5–3 (the pH of the stomach) and >9.[28]

2.3. A Question of Semantics

"What is a natural product?" This question can be raised with regard to all of the organic sulfur compounds that follow allinase-catalyzed release of the sulfenic acids, since none of the subsequently formed compounds occur in the bulb itself nor does their formation require enzyme involvement. On the other hand, volatile thiosulfinates are emitted in the field by *Allium* spp. such as the leek and are the most attractive compounds for predatory insects, e.g. the leek moth, *Acrolepiopsis assectella*.[29] Thus, in a broad sense, thiosulfinates and related secondary products such as disulfides and thiosulfonates can be classified as "natural products".

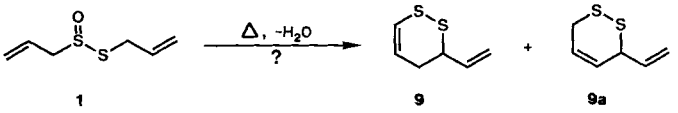
3. Organosulfur Compounds from Cut *Allium* spp.: Pre-1972 Results

If your Majesties is remembered of it, the Welshmen did good service in a garden where leeks did grow, wearing leeks in their Monmouth caps, which your Majesty know to this hour is an honourable badge of the service. And I do believe your Majesty takes no scorn to wear the leek upon Saint Davy's day.

"Henry V", IV. vii. 100
William Shakespeare (1564–1616)

For the purposes of this review I have chosen to first summarize research on the organosulfur compounds of cut *Allium* spp. prior to 1972, when my contributions first appeared, allowing me to subsequently describe my own work, and recent work of others, in the proper historical perspective. In 1944 a series of notable reports by Cavallito et al.[30] appeared describing the isolation and characterization of allicin (2-propenyl-2-propenethiosulfinate) (**1**),[31] an odoriferous, unstable antibacterial substance ("considerably more bacteriostatic than bactericidal"; "exceptionally sensitive and polymerizes easily ...must be stored at a low temperature"[30]) isolated from cut garlic cloves by extraction with ethanol at room temperature. Decomposition of allicin was said to afford diallyl disulfide as a major breakdown product. Cavallito found that reversal of this decomposition process, e.g. oxidation of diallyl disulfide (**4b**)[32] with peracetic acid, represents the most direct method of synthesizing allicin (Scheme 1).[33, 34] Attempts by Brodnitz et al. in 1971 to determine allicin **1** by GC-MS provided evidence for another more unusual mode of decomposition. A 2.4:1 mixture of two compounds claimed (incorrectly as we shall see below) to be 3-vinyl-3,4-dihydro-1,2-dithiin (**9**) and 3-vinyl-3,6-dihydro-1,2-dithiin (**9a**) were found by GC (Scheme 3).

Brodnitz:



1 **9** **9a**

Scheme 3. Decomposition of allicin **1** in a gas chromatograph according to Brodnitz.

It was suggested that "upon gas chromatography diallyl thiosulfinate undergoes dehydration" affording **9** and **9a**.[35a] At room temperature neat **1** is said to rearrange, affording sulfur dioxide and diallyl mono-, di-, and trisulfide (**4a–c**)[35]. Analytical methods for quantitative allicin determination which rely on GC detection of "**9**" and "**9a**" are still employed[36] even though serious problems exist with this method and more accurate HPLC methods have been developed.

All-S-All **4a** All-S-S-All **4b** All-S-S-S-All **4c**

After the discovery of alliin in garlic, other *S*-alk(en)yl-L-cysteine *S*-oxides such as **5–7** were discovered in other *Allium* spp.[37] Upon cutting the plants, such *S*-oxides (type **a** and **b**) are cleaved by allinase to sulfenic acids, whose condensation could lead to four types of thiosulfinates. These thiosulfinates, and polysulfides derived therefrom, were assumed to be the principle sources of flavor and aroma in *Allium* spp., and were viewed as important taxonomic markers. Indirect methods were used to identify and quantify the various thiosulfinates.

$RS(O)CH_2CH(NH_2)COOH$ **a** $R'S(O)CH_2CH(NH_2)COOH$ **b**

RS(O)SR **c** RS(O)SR′ **d** R′S(O)SR **e** R′S(O)SR′ **f**

One method involved separation of the thiosulfinates by paper chromatography followed by treatment with cysteine to form *S*-alk(en)ylthiocysteines, which in turn were chro-

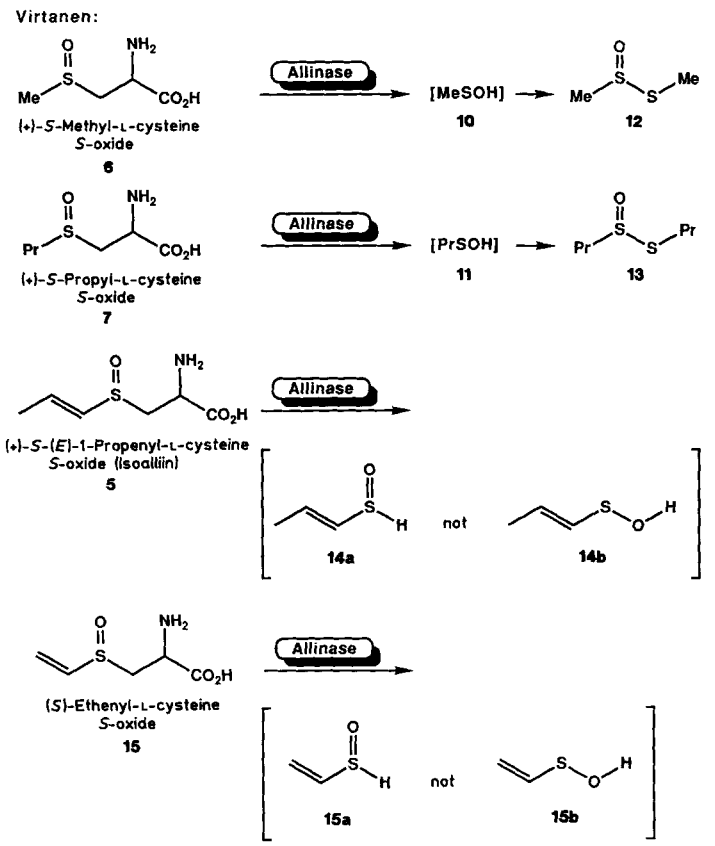
$RSSCH_2CH(NH_2)COOH/R'SSCH_2CH(NH_2)COOH$

matographed.[38] In this manner the following thiosulfinate profiles were determined (increasing amounts indicated as +, ++, +++): in garlic, MeS(O)SMe **12** (+), MeS(O)SAll **101** (++), MeS(O)SPr **29** (+), AllS(O)SAll **1** (+++), AllS(O)SPr (++), PrS(O)SPr **13** (+); in onion, **13** (++), **29** (+), **12** (+); in Chinese chive, **12** (+++), **101** and **1**.[38] This working group also allowed allinase to react with a mixture of **2** and **6**, and obtained **1**, **12**, and "MeS(O)SAll".[38]

A second method involved "headspace" GC analysis, where it was assumed that the proportion of different alk(en)yl groups in the stable, volatile polysulfide fraction paralleled the relative abundance of the same alk(en)yl groups in the thiosulfinates.[39] It was felt that even if the polysulfides revealed by GC are artifacts of analysis, they are [still] clearly related to *Allium* odors.[39] Although both methods of analysis give data which are generally in agreement with more recent composition profiles, significant errors are apparent (see Section 5.2).

With the development of mass spectrometry, gas chromatography (GC), and IR spectroscopy it was possible in 1956 to identify the following compounds as constituents of raw onion vapor:[40] 1-propanethiol, propanal, dipropyl disulfide, SO_2, H_2S, and a substance of *m/z* 90 (C_3H_6SO), showing loss of OH (*m/z* 73) as well as *m/z* 45. It was assumed, albeit on somewhat feeble grounds, that it could be 3-hydroxypropanethial. In 1961 Virtanen et al. showed[10a] that (+)-*S*-((*E*)-1-propenyl)-L-cysteine *S*-oxide (**5**), present to the extent of ca. 0.2% by weight in the onion, is the precursor of the lachrymatory factor (LF; the *E*-geometry of the 1-propenyl group was later established by NMR spectroscopy).[10a, 12, 41–43] Virtanen also demonstrated that onion allinase converts *S*-methyl- and *S*-propyl-L-cysteine *S*-oxides (**6** and **7**, respectively), present to the extent of ca. 0.005–0.02% by weight in the onion,[44, 45] and *S*-2-propenyl-L-cysteine *S*-oxide (**2**), found in garlic, into the corresponding thiosulfinates **12**, **13**, and **1** via sulfenic acids **10**, **11**, and **3**, respectively (Schemes 4 and 1).[2]

On the basis of the above results, Virtanen formulated the LF as the S–H tautomer (**14a**) of (*E*)-1-propenesulfenic acid rather than the S–OH tautomer **14b** (Scheme 4).[2] The assignment of structure **14a** to the LF was said to be consistent with deuteration studies involving crystallized precursor **5** and a purified onion enzyme preparation. Thus, when the

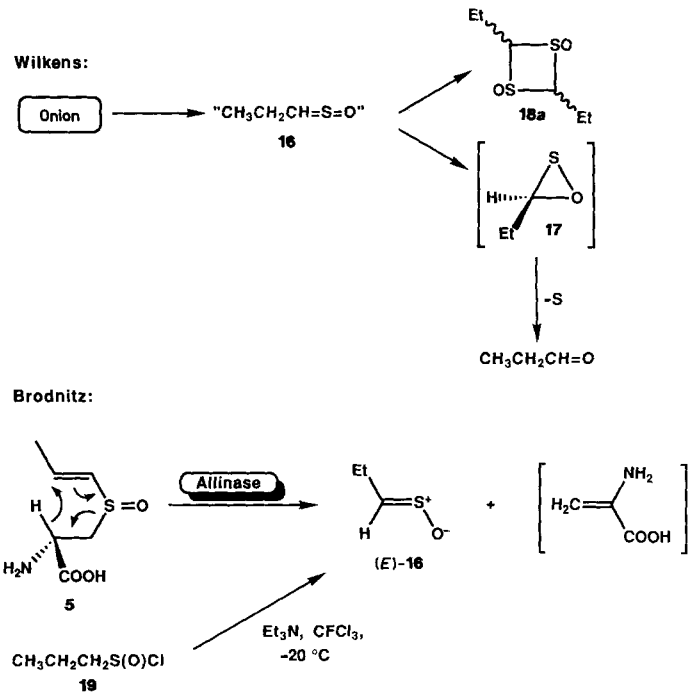


Scheme 4. Virtanen's view of the action of allinase on homologues of alliin **2**. In the case of **6**, **7**, **5**, and **15** they are L-cysteine derivative; **6**, **7**, and **5** are dextrorotatory.

LF is generated in D_2O, its mass spectrum shows a shift in the molecular peak from 90 to 91, indicating a single exchangeable proton. Fragmentation of the normal LF as well as the deuterated LF shows that in both cases an OH fragment is set free. The molecule therefore contains no OH group (the hydrogen of which would be replaced by deuterium in D_2O).[10b] Virtanen raises the perplexing question of why **14a** does not form 1-propenyl 1-propenethiosulfinate analogous to the ready formation of allicin from 2-propenesulfenic acid.[43] He hypothesizes that perhaps 2-propenesulfenic acid disproportionates immediately to 2-propenesulfinic acid and 2-propenethiol, which afford allicin by elimination of water, whereas in **14a** the position of the double bond is a possible stabilizing factor.[2] Virtanen suggests that (*E,Z*)-1-propenyl propyl (and methyl) disulfides, found in *Allium* volatiles and possessing "strong onion-like flavors", might arise from precursor **5** by splitting of a C–S bond, reduction, and coupling with some thiol present when the plants are crushed.[43] Virtanen and Däbritz synthesized the non-natural homolog of **5**, *S*-vinyl-L-cysteine *S*-oxide (**15**) and demonstrated that onion allinase converted it into a lachrymatory substance formulated as ethenesulfenic acid tautomer **15a**, paralleling the conversion of **5** into **14a**.[46]

In 1961, simultaneous with the work of Virtanen, Wilkens of Cornell University isolated by preparative GC the purified LF, which was depicted as propanethial *S*-oxide (**16**; Scheme 5; drawn by him with a linear ketene-like structure $CH_3CH_2CH{=}S{=}O$).[47] Evidence supporting structure **16** included: 1) the presence of strong IR absorption bands at 1113 and 1144 cm^{-1} (S=O region) together with the absence of bands attributable to S–H, O–H, or C=C; 2) ready decomposition of the LF to propanal (suggested to involve the intermediacy of 3-ethyloxathiirane (**17**)) and to a second compound possessing IR bands at 1140 and 1330 cm^{-1} formulated as condensation product 2,4-diethyl-1,3-dithietane 1,3-dioxide (**18a**).[47] Wilkens rationalized the inconsistency between the IR data for **18a**, which showed absorption bands typical of the sulfone stretching modes, and the postulated disulfoxide structure **18a** as due to the proximity of the antipodal sulfinyl groups in this strained-ring structure... postulated to induce a pseudosulfone infrared absorption, which would be of less intensity than that of a true sulfone.[47]

In 1963–1964 the first syntheses of *S*-oxides of thials and thiones (termed *sulfines*) were reported, involving dehydrochlorination of the corresponding sulfinyl chlorides (Scheme 5),[48,49] and evidence was presented for a bent C–S–O group[48,49] (e.g. the methyl groups in Me_2CSO are nonequivalent according to NMR).[48a] In 1971 Brodnitz



Scheme 5. Contributions by Wilkens and Brodnitz on proposed structure, "biosynthesis" and laboratory synthesis, and mechanisms for desulfurization and dimerization of onion lachrymatory factor (LF).

and Pascale[50] showed that propanethial *S*-oxide (arbitrarily depicted by them as (*E*)-**16**), from dehydrochlorination of propanesulfinyl chloride (**19**), was spectroscopically identical to the natural onion LF. These authors provided the

mechanism for the formation of the LF from its known precursor **5** shown in Scheme 5.[50]

4. Structures of Reactive Organosulfur Compounds Relevant to *Allium* Chemistry

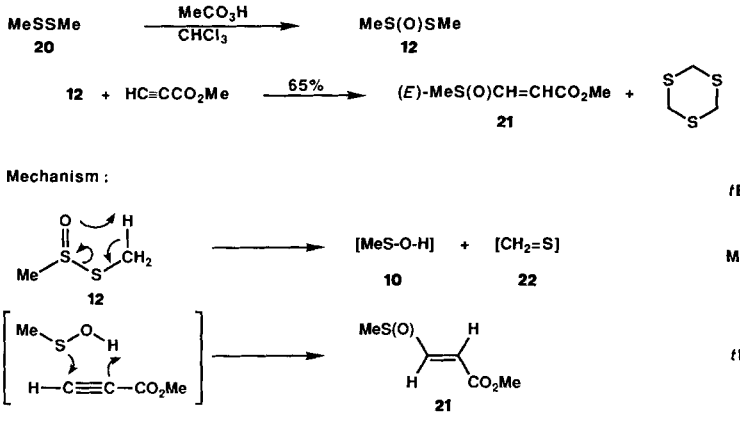
I counted two and seventy stenches,
All well defined, and several stinks.

"Cologne"
Samuel Taylor Coleridge (1772–1834)

4.1. Methyl Methanethiosulfinate, Higher Homologs and Derivatives

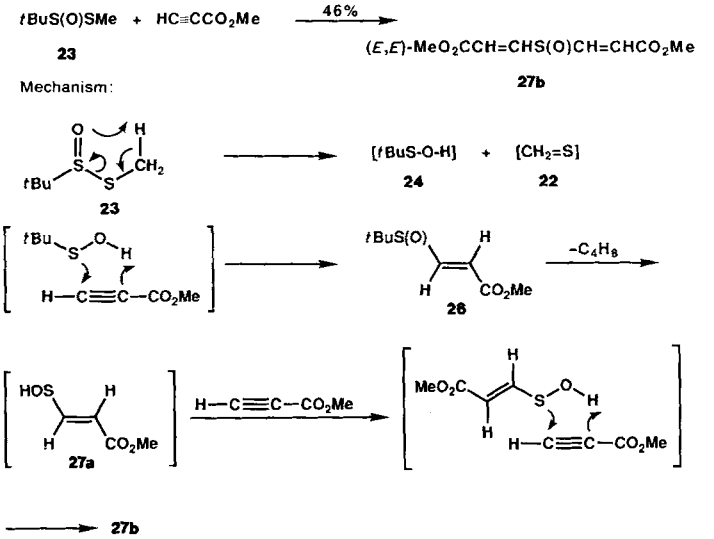
Despite the identification of the active agent of garlic as allyl 2-propenethiosulfinate (**1**, allicin), an alkyl alkanethiosulfinate, little systematic information existed in 1970 on the chemistry of this class of compounds, perhaps because of their reputation as malodorous, unstable substances.[51] Thus, in 1970 I undertook a study of the naturally occurring parent member of this family, methyl methanethiosulfinate (**12**).

True to its reputation, methyl methanethiosulfinate (**12**) prepared by careful oxidation of dimethyl disulfide (**20**) with peroxy acids or singlet oxygen,[52, 53] is an unpleasant smelling, reactive and unstable vesicant with the property of readily attaching itself to hair and clothing. Fortunately, **12** proved to have a rich chemistry.[54] Pyrolysis of **12** in the presence of methyl propiolate affords methyl (*E*)-β-(methylsulfinyl)acrylate (**21**) in good yield by a sequence involving cycloelimination to methanesulfenic acid (**10**) and thioformaldehyde (**22**), followed by regiospecific addition of the



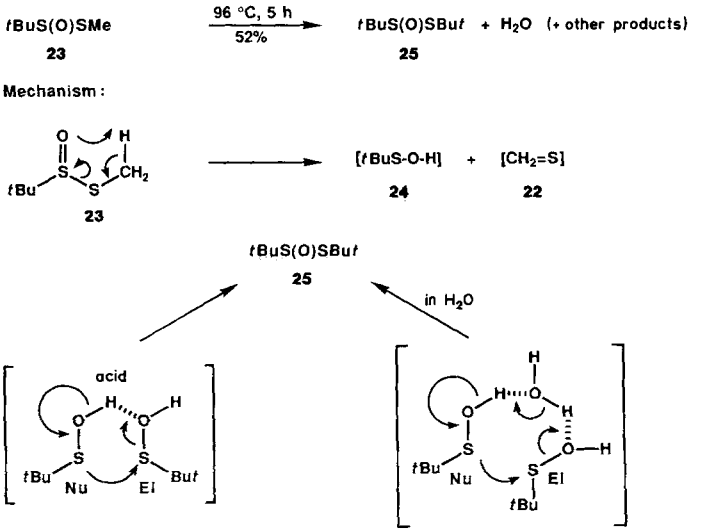
Scheme 6. Methyl methanethiosulfinate decomposes into thioformaldehyde **22** and methanesulfenic acid **10**. The latter can be trapped giving α,β-unsaturated sulfoxides such as **21** in a synthetically useful procedure.

former to the alkyne and trimerization of the latter (Scheme 6). This procedure represents a convenient synthesis of α,β-unsaturated sulfoxides.[54] Both **10** and **22** were subsequently identified by microwave spectroscopy; **10** was shown (see Section 4.3) to have the structure MeS–O–H rather than MeS(O)H.[55] When methyl 2-methyl-2-propanethiosulfinate (**23**) is heated with methyl propiolate, the major product is (*E,E*)-dimethyl-3,3′-sulfinyldiacrylate (**27b**; Scheme 7).[54] Compound **27b** is thought to be formed by a sequence involving generation of 2-methyl-2-propanesulfenic acid (**24**), addition of this to methyl propiolate giving methyl (*E*)-β-*tert*-butylsulfinylacrylate (**26**), elimination of isobutylene from **26** giving α,β-unsaturated sulfenic acid **27a**, and finally addition of **27a** to methyl propiolate. When



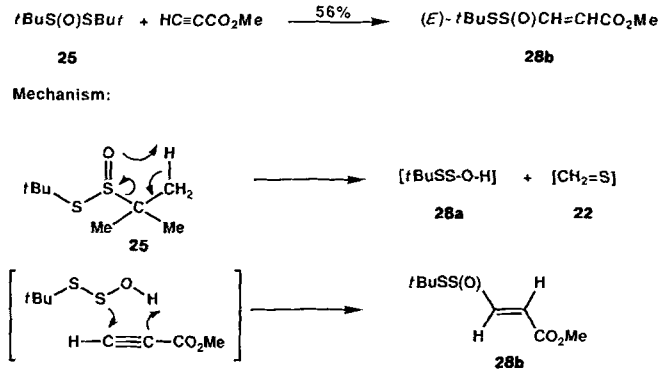
Scheme 7. Alkyl-2-methylpropanethiosulfinates like **23** react with alkynes to furnish adducts which lose isobutylene giving α,β-unsaturated sulfenic acids such as **27a**. These add to a second molecule of alkyne ultimately giving bis(1-alkenyl)sulfoxides such as **27b**.

23 is heated neat at 96 °C for 5 hours, the major product is *tert*-butyl 2-methyl-2-propanethiosulfinate (**25**). Sulfenic acid **24** is suggested to be an intermediate in this reaction, condensing with itself via an acid-catalyzed S_N2-like process or, orbital geometry-permitting, via a five-membered or seven-membered hydrogen bonded transition state (Scheme 8). In these condensation reactions the sulfenic acid functions as both a nucleophile and electrophile. Compound **25** was also



Scheme 8. Upon heating, unsymmetrical alkyl alkanethiosulfinates such as **23** give symmetrical thiosulfinates such as **25** by a mechanism involving sulfenic acids.

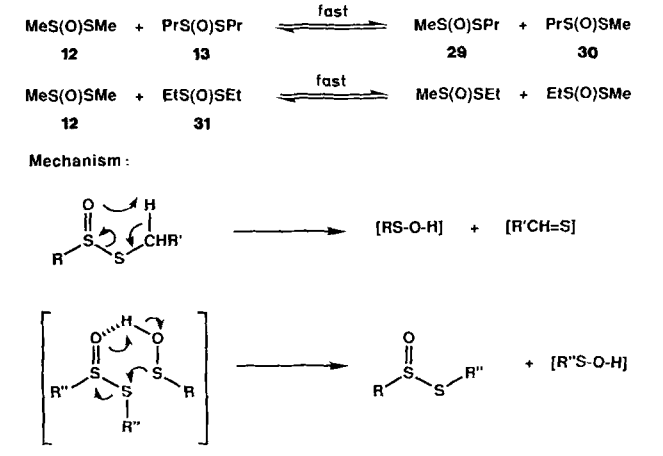
found to decompose thermally. When heated in the presence of methyl propiolate it gave the α,β-unsaturated adduct **28b** by way of 2-methyl-2-propanethiosulfoxylic acid (**28a**), a member of a previously unknown class of sulfur acids (Scheme 9).[54b]



Scheme 9. Formation and trapping of the thiosulfoxylic acid ester **28a**.

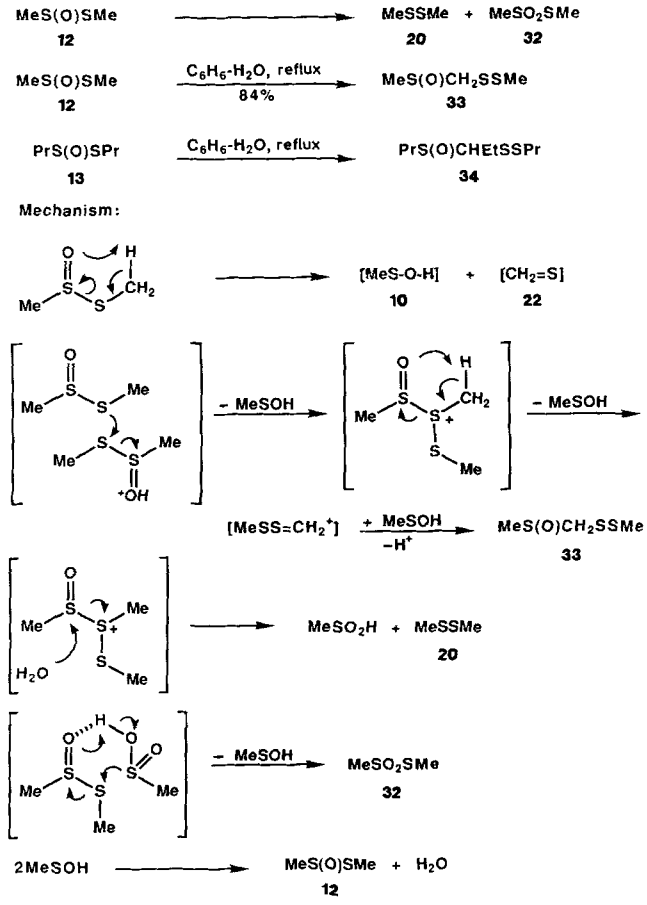
The unimolecular decomposition of **12** (cf. Scheme 6) is favored by the weak S–S bond, determined by appearance potential measurements to have a bond energy of 46 ± 4.6 kcal mol^{-1}, comparable to the S–S bond dissociation energy in dimethyl trisulfide, but considerably smaller than that in dimethyl disulfide (75 kcal mol^{-1}).[54f] For comparison the S–S bond energies in phenyl benzenethiosulfinate and diphenyl disulfide are ca. 35 and 65 kcal mol^{-1}, respectively.[56] The thiosulfinate oxygen actively participates in hydrogen bonding, although not quite as strongly as the oxygen in sulfoxides. Using the hydrogen bond strength method,[57] whereby the phenol OH stretching vibration band frequency shift is determined in the presence of oxygen donors, it was demonstrated that **12**, ethyl ethanethiosulfinate (**31**) and dimethyl sulfoxide caused frequency shifts of 278, 308 and 360 cm^{-1}, respectively.[54] Thiosulfinates can be distinguished from sulfoxides by a shift in the position of the S=O stretch in the infrared from 1075–1090 cm^{-1} for the former to 1030–1065 cm^{-1} for the latter.

When **12** and its higher homologs **13** or **31** were mixed, rapid equilibria were established at 25 °C affording in each case statistical mixtures of four thiosulfinates, even after substantial dilution (Scheme 10). The scrambling reaction is catalyzed by acid, inhibited by base or methyl acrylate, and the ESR spectrum shows no evidence of free radical formation. A rapid sulfenic acid–thiosulfinate exchange is postulated. In this reaction the sulfenic acid functions as a nucleophile and as a proton donor. Gas chromatography (GC) using short packed columns (2 m × 3 mm internal diameter) and injection port and column temperatures below 100 °C nicely separates the various thiosulfinates shown in Scheme 10; unique GC-MS data can be obtained for each regioisomer.[54e] As we shall see in Section 5.2.1, the processes of Scheme 10 and methods of isomer separation play an important role in *Allium* chemistry.



Scheme 10. The exchange reaction of the thiosulfinate pairs **12**/**13** and **12**/**31** involves attack of sulfenic acids on thiosulfinates.

While **12** undergoes ready disproportionation to dimethyl disulfide (**20**) and methyl methanethiosulfonate (**32**, Scheme 11), when **12** is refluxed in benzene with an equivalent of water, 2,3,5-trithiahexane 5-oxide (**33**) is formed in 84% yield. In a similar manner **13** affords 6-ethyl-4,5,7-



Scheme 11. Rearrangement of the Pummerer-type for the conversion of alkyl alkanethiosulfinates such as **12** and **13** into α-sulfinyl disulfides such as **33** and **34**, respectively. Reaction of sulfinic acids with thiosulfinates leading to alkyl alkanethiosulfonates, e.g. **32**.

trithiadecane 7-oxide (**34**). We had anticipated as long ago as 1973 that the unique combination of functional groups in α-sulfinyl and α-sulfonyl disulfides ought to lead to unusual physiological properties,[54d] a prediction recently borne out with the discovery of structurally analogous antithrombotic and lipoxygenase inhibitory cepaenes in onions (Sec-

tion 5.2.6). In order to account for the formation of **33** from **12**, we postulated the intermediacy of an α-alkyldithiocarbocation in a Pummerer-like reaction (Scheme 11). Solvolysis studies revealed that acyclic α-alkyldithiocarbocations are far less stable than α-alkylthiocarbocations (for example $MeSCH_2Cl$ hydrolyzes 6800 times faster than $MeSSCH_2Cl$.[58] We have suggested that the near 90° C–S–S–C dihedral angle adopted by acyclic disulfides is also favored by acyclic α-alkyldithiocarbocations and that this conformation precludes charge delocalization by the second (distant) sulfur, while at the same time diminishing by inductive effects the electron availability on the first (nearest) sulfur (see Fig. 2).[58] The above solvolysis study is relevant to

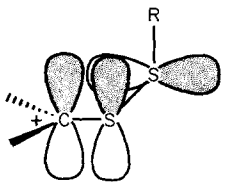
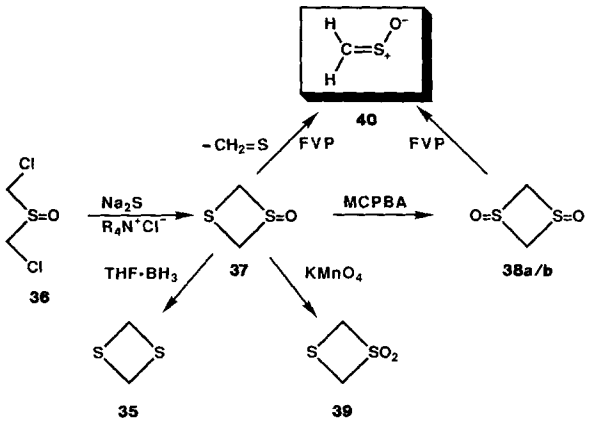


Fig. 2. Postulated conformation of acyclic carbocations containing the S–S–C$^+$ group.

the observation that in the mass spectrum of $MeSCH_2SSMe$, fragmentation to $MeSCH_2^+$/MeSS$^\cdot$ is greatly favored over fragmentation to $MeSSCH_2^+$/MeS$^\cdot$. This observation also proves useful in establishing the structures of "deoxycepaenes" (see Section 5.2.6).

4.2. 1,3-Dithietane *S*-Oxides

The suggestion by Wilkens that the dimer of the onion LF is 2,4-diethyl-1,3-dithietane 1,3-dioxide **18a**[47] piqued our interest in this little studied class of heterocycles. Although derivatives of 1,3-dithietane have been known since 1872, the parent compound **35** was unknown prior to our work. We developed convenient syntheses of **35** and its *S*-oxides (Scheme 12).[59] Thus, treatment of bis(chloromethyl)

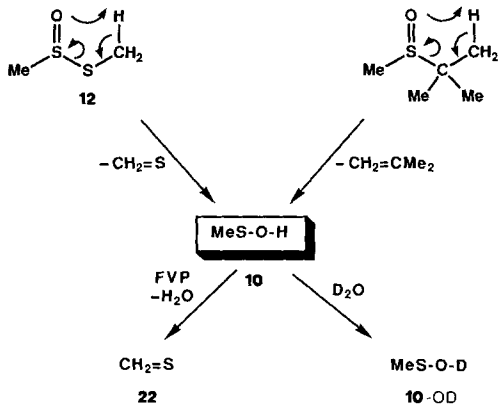


Scheme 12. Synthesis of 1,3-dithietane (**35**) (δ_C = 19), 1,3-dithietane 1-oxide (**37**) (δ_C = 53), 1,3-dithietane 1,3-dioxide (**38a/b**) (δ_C = 69), and 1,3-dithietane 1,1-dioxide (**39**) (δ_C = 68), and pyrolytic conversion of **37** and **38a/b** into sulfine (thioformaldehyde *S*-oxide) (**40**) (δ_C = 159, δ_H = 7.73, 7.84 (J = 5.5 Hz)). MCPBA = *m*-chloroperbenzoic acid.

sulfoxide (**36**) with sodium sulfide in the presence of a phase transfer catalyst gave 1,3-dithietane 1-oxide (**37**) in 36% yield as a colorless solid with a garlic like odor. Compound **37** could be reduced with THF · BH_3, giving the parent compound **35** in 70% yield, or oxidized with MCPBA or $KMnO_4$/acetone, giving *cis*/*trans*-1,3-dithietane 1,3-dioxide (**38a/b**) or 1,3-dithietane 1,1-dioxide (**39**), respectively, in excellent yields. While Wilkens[47] indicated that his LF dimer, formulated as **18a**, had sulfone type IR absorption at 1330 and 1140 cm^{-1}, we found compounds **37** and **38a/b** to have sulfoxide bands in the normal 1100–1035 cm^{-1} region,[1] with additional bands at 1132–1159 cm^{-1}, presumably associated with the four-membered ring. Sulfone **39** showed typical sulfonyl absorption bands[1] at 1393–1315 and 1200–1130 cm^{-1}. Compounds **38a/b** are stable solids melting above 200 °C, in contrast to **18a**, described by Wilkens[47] as an unstable liquid. Flash vacuum pyrolysis (FVP) of **37** and **38a/b** at 350–480 °C gave sulfine **40** (thioformaldehyde *S*-oxide).[59]

4.3. Sulfenic Acids

Sulfenic acids are key enzymatically formed intermediates in *Allium* chemistry. Prior to 1978 it was not known whether the structure of simple sulfenic acids was best represented by RS–O–H (**A**) or RS(O)H (**B**) or an equilibrium involving both forms.[51,60] Isolation proved difficult because of the high reactivity of sulfenic acids as *both* electrophiles and nucleophiles (cf. Scheme 8).[55] Using flash vacuum pyrolysis (FVP) we were able to demonstrate that above 250 °C at 0.1 torr both *tert*-butyl methyl sulfoxide and methyl methanethiosulfinate (**12**) decompose affording methanesulfenic acid (**10**) and isobutylene or thioformaldehyde (**22**), respectively (Scheme 13).



Scheme 13. Generation of methanesulfenic acid (**10**) by FVP methods.

Compound **10** showed a molecular ion at *m*/*z* 64 when examined using coupled FVP-mass spectrometric analysis. Through coupled FVP-microwave spectroscopic studies of a series of isotopically substituted forms of **10** (^{13}C, CD_3; ^{18}O, OD) its full structure was determined (Fig. 3). Compound **10** contains dicoordinate rather than tricoordinate sulfur (form

A rather than **B**) and a geometry similar to that of H_2S_2 (HSSH angle 90.6°).[61] The structural determination was aided by the finding that **10** readily exchanges with deuterium oxide in the waveguide giving **10**-OD. By means of a tandem pyrolysis experiment it was further demonstrated that **10** undergoes dehydration giving thioformaldehyde (Scheme 13). The half-life of **10** in the gas phase at 0.1 torr and 25 °C is ca. one minute. When condensed at −196 °C **10** could not be recovered on warming in vacuum. Analysis of the low-temperature condensate warmed to room temperature revealed the presence of **12**. In the gas-phase experiments we were unable to detect even minor amounts of the tautomer of type **B**. In agreement with our experimental observations, theoretical calculations confirm that CH_3S–O–H and its inorganic homologue H–S–O–H are significantly more stable than their respective isomers $CH_3S(O)H$[62] and $H_2S(O)$.[63] The preference for form **A** rather than **B** has also been found with stable, sterically hindered sulfenic acids.[64] In other relevant work, 1-anthraquinonesulfenic acid, another stable sulfenic acid, has been found to have a pK_a value of 7.51.[65]

calculated charge densities. The gas-phase lifetimes of **40** and **22** at room temperature and 30 μm are ca. 30 minutes and 20 seconds, respectively. Compound **40** could be generated at room temperature by fluorodesilylation of (trimethylsilyl)methanesulfinyl chloride (**41**; Scheme 14).[70] Cyclopentadiene was used as an *in situ* trap for **40**. The major cyclopentadiene Diels–Alder adduct of **40**, 2-thiabicyclo-[2.2.1]hept-5-ene *endo*-2-oxide (**42**; 10% of the *exo* isomer was also present) proved to be thermally unstable at room temperature, undergoing a [2,3]-sigmatropic rearrangement to 2-oxa-3-thiabicyclo[3.3.0]oct-7-ene (**43**), a rare example of an isolable sultene (a heterocycle containing an S–O single bond).

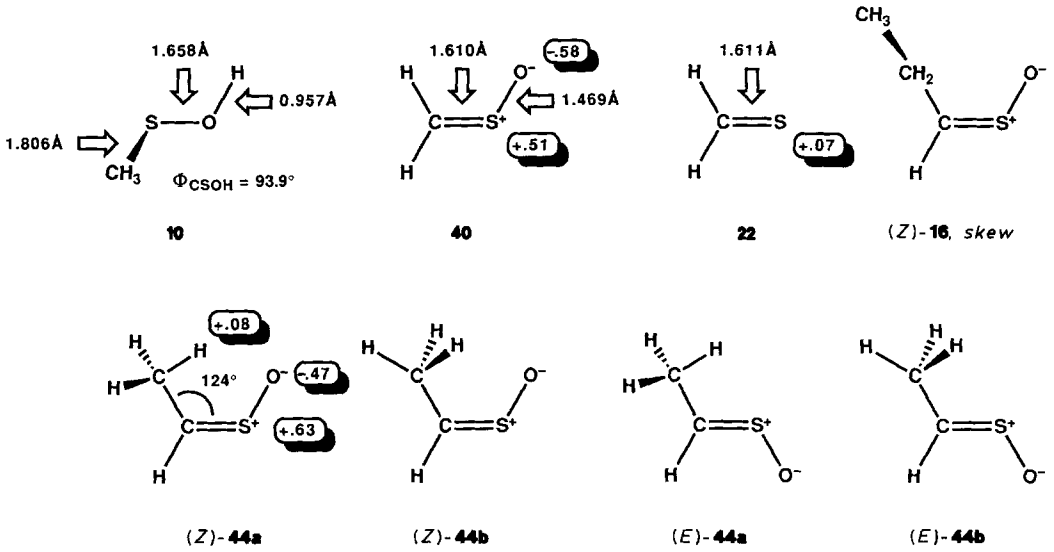
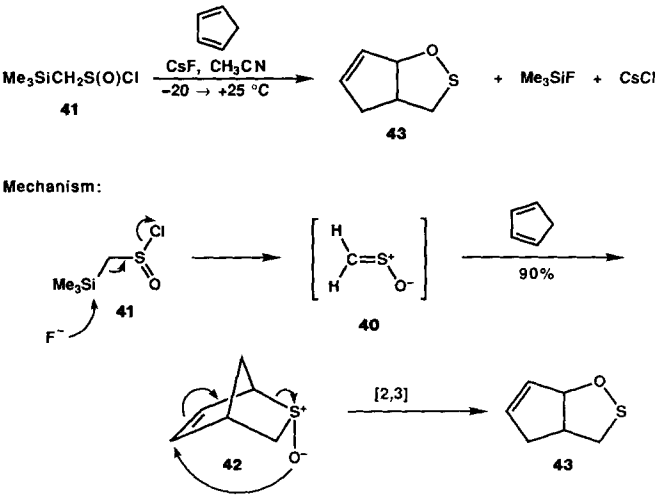


Fig. 3. Structures of methanesulfenic acid (**10**), thioformaldehyde *S*-oxide (**40**), thioformaldehyde (**22**), propanethial *S*-oxide (**16**), and the conformers of ethanethial *S*-oxide (**44**) determined by microwave spectroscopy.

4.4. Sulfine (Thioformaldehyde *S*-Oxide)

Like sulfenic acids, sulfines (thiocarbonyl *S*-oxides) are key compounds in *Allium* chemistry. We generated the previously unknown parent sulfine, thioformaldehyde *S*-oxide (**40**), by pyrolysis of 1,3-dithietane 1-oxide (**37**), 1,3-dithietane 1,3-dioxide (**38a/b**; cf. Scheme 12), or methanesulfinyl chloride. Compound **40** was fully characterized by mass spectrometry, microwave, photoelectron, IR and NMR spectroscopy.[66–69] The structures of **40** and, for comparison, thioformaldehyde (**22**) are shown in Figure 3 along with



Scheme 14. Generation and Diels–Alder trapping reaction of sulfine **40**, which was generated from **41** by fluorodesilylation. The rearrangement of the primary adduct **42** to led to the **43**.

5. Organosulfur Compounds from Cut *Allium* Spp.: Post-1972 Results

Come, follow me by the smell,
here are delicate onions to sell;
I promise to use you well.
They make the blood warmer,
You'll feed like a farmer;
For this is every cook's opinion,
no savoury dish without an onion;
But, lest your kissing should be spoiled,
Your onions must be thoroughly boiled:
Or else you may spare your mistress a share,
the secret will never be known:
She cannot discover the breath of her lover but think it as sweet as her own.

"Verses for Fruitwomen",
Jonathan Swift (1667–1745)

The work done prior to 1972 suggests that, when *Allium* spp. are cut, highly reactive sulfenic acids and/or sulfines are produced by enzymatic action on precursors in the intact bulb. The main fate of the short-lived sulfenic acids appears to be condensation to form thiosulfinates. The thiosulfinates can then participate in a variety of subsequent reactions which depend on conditions and which afford various types of organosulfur compounds. These compounds can be categorized as headspace volatiles (products formed above cut *Allium* or *Allium* homogenates at room temperature), products formed when the thiosulfinates stand in solution at room temperature, or compounds produced by more vigorous processes such as steam distillation (or decomposition in the injection port of a GC[71]!) (Scheme 15). The volatile, thermally stable compounds are best analyzed by GC or GC-MS while the thermally unstable compounds are preferably isolated/identified by milder chromatographic methods (e.g. HPLC, supercritical fluid chromatography (SFC), or GC under modified injection conditions). In our discussion we will first treat the unique low-temperature volatile onion lachrymatory factor and its dimer, then those thermally unstable constituents of *Allium* homogenates formed in solution, and finally those constituents of headspace volatiles and steam distillates identified primarily by gas chromatography.

5.1. Onion Lachrymatory Factor (LF) and its Dimer

Indeed the tears live in an onion that should water this sorrow.

"Antony and Cleopatra", I. ii. 173
William Shakespeare (1564–1616)

A number of points from the published work on the onion LF required clarification. Assuming that the LF is propanethial *S*-oxide (**16**) as postulated by Wilkens[47] and Brodnitz,[50] how can the exchange of a single proton (from Virtanen's deuteration studies[2]) be rationalized? Is the stereochemistry of the LF indeed *E* (anti)? Is it reasonable to assume that the same enzyme allinase could catalyze *both* the sulfenic acid eliminations of Schemes 1 and 4 as well as Brodnitz's retro-ene mechanism of Scheme 5? These questions will be addressed below.

Extraction of chopped onions at low temperatures with $CFCl_3$ followed by low-temperature vacuum distillation gave the onion lachrymatory factor (LF). The LF was purified by trap-to-trap distillation (−35 to −196 °C) at 0.001 torr. Authentic propanethial *S*-oxide (**16**) and its lower homolog ethanethial *S*-oxide (**44**) were prepared from the reactions of propanesulfinyl chloride (**19**) and ethanesulfinyl chloride (**45**), respectively, with triethylamine.

$$\underset{\mathbf{19}}{CH_3CH_2CH_2S(O)Cl} \longrightarrow \underset{\mathbf{16}}{CH_3CH_2CH{=}S^+{-}O^-}$$

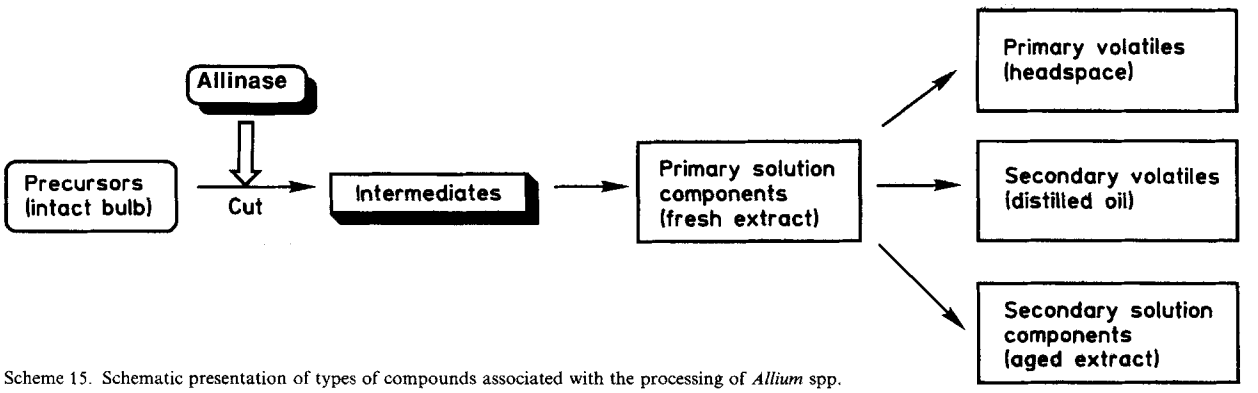
$$\underset{\mathbf{45}}{CH_3CH_2S(O)Cl} \longrightarrow \underset{\mathbf{44}}{CH_3CH{=}S^+{-}O^-}$$

5.1.1. Microwave and NMR Spectroscopic Analysis of Onion LF and Homologs

Mine eyes smell onions; I shall weep anon;
good Tom Drum, lend me a handkercher.

"All's Well That Ends Well", V. iii. 316
William Shakespeare (1564–1616)

Samples of the LF and **44**, prepared as described in Section 5.1, were evaporated at room temperature into a microwave guide. Only the normal isotopic species were used in the analysis of the microwave spectra of **16** and **44**. Structural conclusions for **44** are based upon the assumption that



Scheme 15. Schematic presentation of types of compounds associated with the processing of *Allium* spp.

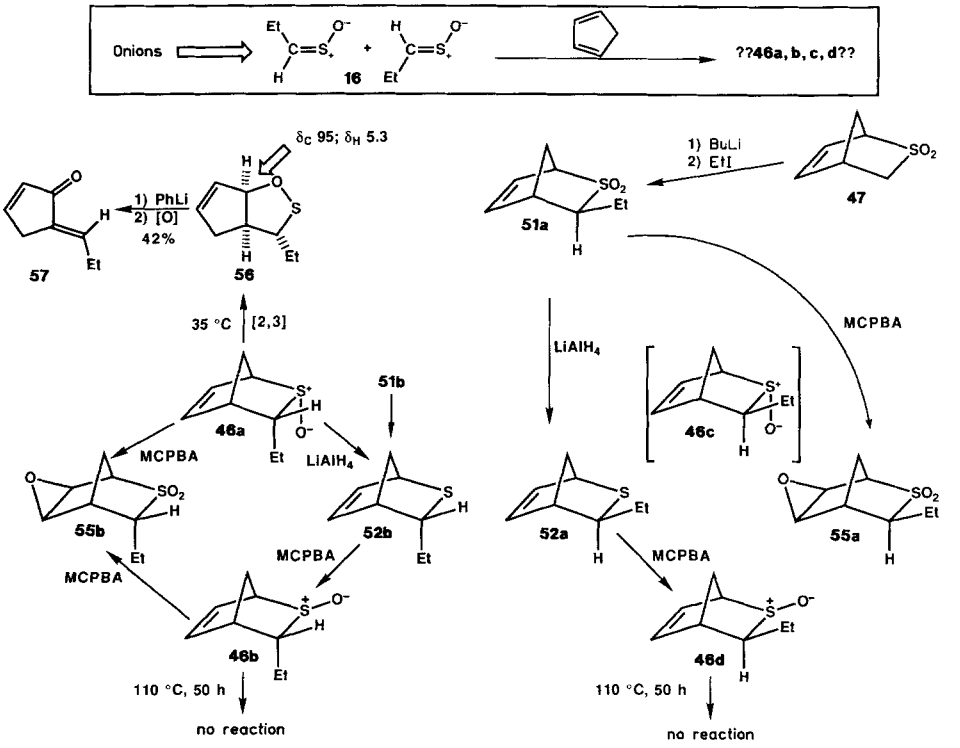
the CHSO framework is identical to that of thioformaldehyde *S*-oxide (**40**) and that the methyl groups are tetrahedral with C–H = 1.093 Å. The structures of (*Z*)-**44** and the onion LF, (*Z*)-**16**, determined by microwave spectroscopy, are given in Figure 3 (also see Section 5.1.4).[72] The *E* (*anti*) isomer of **44** could not be detected by microwave spectroscopy. The dipole moment of (*Z*)-**44** is 3.23(2) D, slightly larger than that determined for **40** (2.994 D). Microwave analysis of **16** is complicated by the fact that internal rotation about the $CH–CH_2$ bond gives this sulfine an additional conformational degree of freedom. Of the four possible conformations/structures for **16**—*Z* skew ((*Z*)-**16a**), *Z cis* ((*Z*)-**16b**), *E* skew ((*E*)-**16a**), and *E cis* ((*E*)-**16b**)—only (*Z*)-**16a** fits the calculated rotational constants and fulfills the heavy-atom nonplanarity implied by the observed constants. Unlike **40**, sulfines **16** and **44** are stable in the wave guide at 0.050 torr and 25 °C. Neither ethenesulfenic acid (**15a**/**15b**) nor (*E*)- or (*Z*)-1-propenesulfenic acid (**14**) could be detected in any of the samples examined by microwave spectroscopy (cf. Scheme 4). As will be detailed in Section 5.3.1, ^{1}H-NMR analysis of the onion LF indicated a *Z*:*E* ratio of 95:5 for **16**. Similar *Z*:*E* ratios were obtained for **44** and other thioaldehyde *S*-oxides.

5.1.2. Determination of the Configuration of Onion LF from the Structures of Cyclopentadiene Diels–Alder Adducts

Determination of the configuration of the onion LF by spectroscopic means requires concentration and, in the case of microwave spectroscopy, vaporization. An alternative approach involves directly trapping the LF with cyclopentadiene at low temperature followed by NMR measurement of the adduct *cis*:*trans* ratio [(**46a** + **46d**):(**46b** + **46c**), Scheme 16]. As we have already mentioned in Section 4.3, sulfine **40** is readily trapped by cyclopentadiene giving thermally labile *endo*-adduct **42** which undergoes a facile [2,3]-sigmatropic rearrangement to **43** even at 0 °C (see Scheme 14).

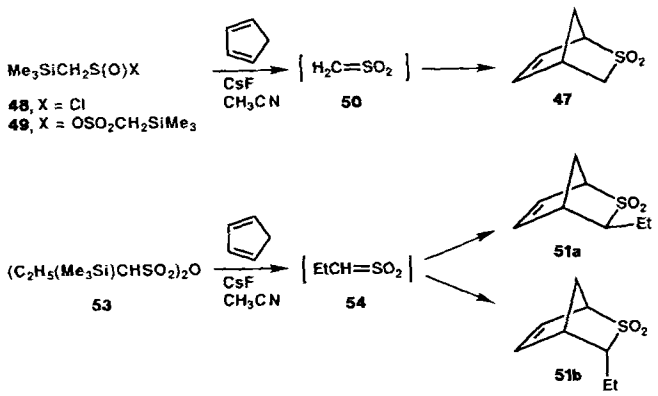
Adducts **46b** and **46d** were independently synthesized and characterized (Schemes 16 and 17); adduct **46c** could not be prepared.[73] A novel procedure was used to prepare 2-thiabicyclo[2.2.1]hept-5-ene 2,2-dioxide (**47**). Thus, treatment of (trimethylsilyl)methanesulfonyl chloride (**48**) or (trimethylsilyl)methanesulfonic anhydride (**49**) with cesium fluoride and excess cyclopentadiene gave **47** in 64% isolated yield from **48** or 75% isolated yield from **49** by a reaction which must involve thioformaldehyde *S*,*S*-dioxide (**50**, sulfene) as an intermediate.[74] This reaction represents the first instance of Diels–Alder trapping of sulfene.[48b] Compound **47** could also be prepared by oxidizing the unstable adduct **42** of cyclopentadiene and sulfine (**40**) or by oxidation of the known 2-thiabicyclo[2.2.1]hept-5-ene.[75] Sequential treatment of **47** with butyllithium followed by ethyl iodide gave *exo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene 2,2-dioxide (**51a**), which was reduced with lithium aluminum hydride to *exo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene (**52a**) and then oxidized with MCPBA to *exo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene *exo*-2-oxide (**46d**).

A 23:77 mixture of **51a** and its *endo*-isomer (**51b**) could be prepared in 76% yield by treatment of 1-(trimethylsilyl)propanesulfonic anhydride (**53**) with cesium fluoride and excess cyclopentadiene, a reaction which must involve propanethial *S*,*S*-dioxide (**54**) as an intermediate (Scheme 17). When the product from the Diels–Alder reaction of cyclopentadiene with the onion LF or **16**, prepared from propanesulfinyl chloride (**20**), was oxidized with one



Scheme 16. Cyclopentadiene-LF adducts of type **46**: their synthesis, interconversion, and rearrangement.

equivalent of MCPBA, **51b** could be isolated in 79% yield. Lithium aluminum hydride reduction of the above cyclopentadiene-LF or cyclopentadiene-**16** adduct gave *endo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene (**52b**)[76] which on reoxidation with one equivalent of MCPBA gave *endo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene *exo*-2-oxide (**46b**). Oxidation of **51a** and **51b** with excess MCPBA gave *exo*-5,6-epoxy-*exo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene 2,2-dioxide (**55a**) and *exo*-5,6-epoxy-*endo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene 2,2-dioxide (**55b**), respectively. The structure of **55b** was established by X-ray crystallography.[73, 77a]



Scheme 17. Synthesis of **47** (64–75% yield) and **51a,b** (76% yield) by trapping of thioformaldehyde *S,S*-dioxide (**50**) and propanethial *S,S*-dioxide (**54**) with cyclopentadiene. The sulfenes are generated by fluorodesilylation.

While compounds **46b** and **46d** were unchanged after refluxing in deuteriotoluene for 50 hours, the adducts of cyclopentadiene with LF or **16** rearranged upon refluxing in methylene chloride for 1.5 hours to give *exo*-4-ethyl-2-oxa-3-thiabicyclo[3.3.0]oct-7-ene (**56**), isolated in 50% yield. The same type of rearrangement was also observed for the adducts of cyclopentadiene with ethanethial *S*-oxide (**44**), and butanethial *S*-oxide.[77a] This novel rearrangement forms the basis for a useful synthesis of 5-alkylidene-2-cyclopentenones, e.g. **57** (Scheme 16).[77a]

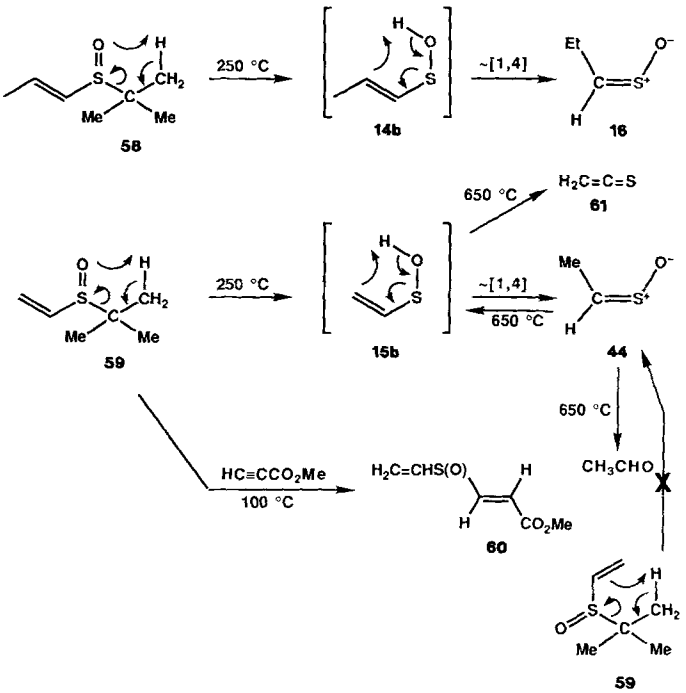
When an onion slurry, prepared from frozen chopped onions, was extracted with Freon-11 and the dried extract treated with cyclopentadiene at −78 °C followed by low-temperature concentration, a 15:1 mixture of *endo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene *endo*-2-oxide (**46a**) and *exo,exo*-adduct **46d** could be detected through coincidence of ^{13}C-NMR peaks in the olefinic region with corresponding peaks of authentic samples. We were unable to detect NMR peaks corresponding to *exo,endo*-adduct **46b**. The reason for the absence of **46b** is clear if we assume that formation of *exo*-3-ethyl-2-thiabicyclo[2.2.1]hept-5-ene *endo*-2-oxide (**46c**) is significantly favored by secondary orbital interactions over **46b** and that substantially less **46c** is formed than **46a**. While we could not prepare an authentic sample of **46c**, in the LF-cyclopentadiene adduct mixture we observed several minor unidentified olefinic ^{13}C-NMR signals which disappeared on warming, and could be due to **46c**. We estimate that the concentration of **46c** is less than 5%, reflecting a *Z*:*E* ratio for the LF of at least 95:5, in agreement with the NMR data (see Section 5.3.1).[77b]

5.1.3. *Mechanism for the Formation of Onion LF from (E)-1-Propenesulfenic Acid*

And if the boy have not a woman's gift to rain
a shower of commanded tears,
An onion will do for such a shift,
which in a napkin being close conveyed,
Shall in despite enforce a watery eye.

"The Taming of the Shrew", Introduction, 122.
William Shakespeare (1564–1616)

We examined the pyrolysis of (*E,Z*)-*tert*-butyl-1-propenyl sulfoxide (**58**) and *tert*-butyl-2-vinyl sulfoxide (**59**) with the hope of generating (*E,Z*)-1-propenesulfenic acid (**14b**) and ethenesulfenic acid (**15b**) (which, by analogy with the structure of methanesulfenic acid (**10**), should possess dicoordinate sulfur) and determining the relationship, if any, between these sulfenic acids and propanethial *S*-oxide (**16**) and ethanethial *S*-oxide (**44**), respectively. Both **58** and **59** are efficiently converted by FVP at 250 °C into the respective (*Z*)-sulfines (*Z*)-**16** and (*Z*)-**44**, as characterized by both microwave and NMR spectroscopy (Scheme 18). A 97:3 (*Z*)-

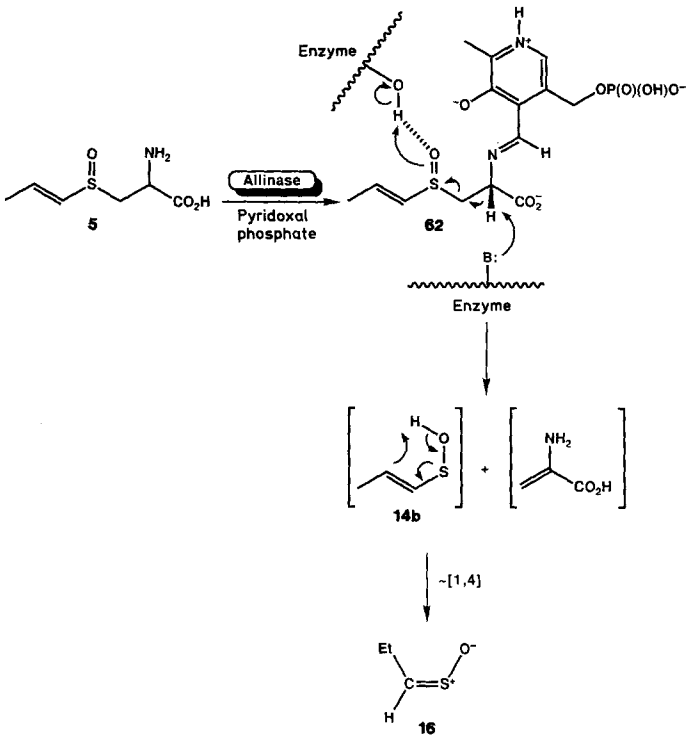


Scheme 18. Flash vacuum pyrolysis of 1-alkenyl *tert*-butyl sulfoxides such as **58** and **59** as a route to 1-alkenesulfenic acids such as **16** and **44**, respectively.

16:(*E*)-**16** ratio and a 95:5 (*Z*)-**44**:(*E*)-**44** ratio was established by ^{1}H-NMR analysis (discussed in Section 5.3.1). Heating a solution of **59** in excess methyl propiolate at 100 °C affords sulfenic acid adduct **60**. Neat **59** decomposes within 4 h at 100 °C to give, among other products, acetaldehyde, which we have separately found to be a major decomposition product of ethanethial *S*-oxide (**44**). Finally, microwave spectroscopic analysis indicates that sulfine **44** decomposes under high-temperature FVP conditions (650–750 °C) to both acetaldehyde and thioketene (**61**).[72]

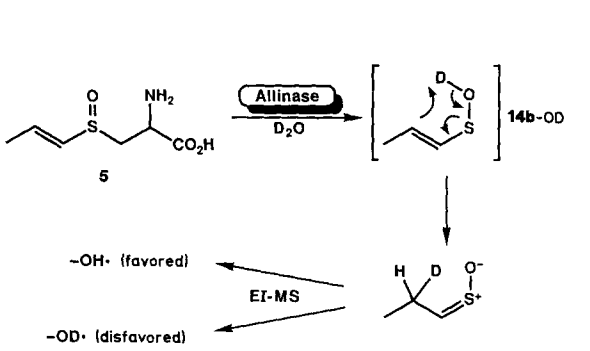
The above results are most simply explained in terms of a [1,4]-sigmatropic rearrangement of **14b** and **15b** (Scheme 18), a reaction leading to (*Z*)-sulfines. The conversion of **58** via **14b** into **16**, and of **59** via **15b** into **44** finds precedence in the known tautomerism of thioamide *S*-oxides[78] and the isomerization of other α,β-unsaturated sulfenic acids to sulfines.[79] At high temperatures **15b** undergoes unimolecular dehydration to thioketene (**61**), in analogy with the previously noted high-temperature dehydration of methanesulfenic acid (Scheme 13). McLafferty et al. have examined the formation of **15b** and **44** from **59** by tandem FVP and neutralization-reionization mass spectrometry and ab initio calculations.[80] Their studies exclude an alternative retro-ene route from **59** to **2** (Scheme 13) and indicate that **44** is 12 kJ mol^{-1} (2.9 kcal mol^{-1}) more stable than **15b** with a transition state interconversion barrier of 137 kJ mol^{-1} (33 kcal mol^{-1}) and that **15b** has a near-orthogonal geometry with a CSOH dihedral angle of 88°. When **15b**-OD is examined in the mass spectrometer under conditions allowing conversion into **44**, OH loss predominates >2:1 over OD loss.

A mechanism for the genesis of the onion LF from precursor **5** is proposed (Scheme 19). Our mechanism is consistent

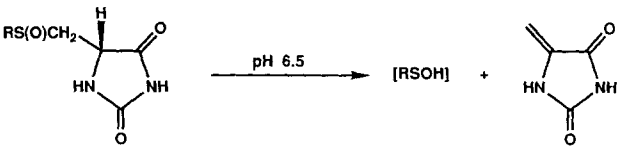


Scheme 19. Mechanism for allinase catalyzed conversion of **5** into the onion LF **16**.

with the deuteration studies of Virtanen if it is assumed that rearrangement of deuterated 1-propenesulfenic acid **14b**-OD precedes electron-impact-induced fragmentation (Scheme 20). Our mechanism also has the advantage of allowing a common mode of enzymatic decomposition for LF precursor **5** and cysteine sulfoxides **2**, **6**, and **7**. The intermediacy of Schiff base **62** is consistent with the requirement for pyridoxal phosphate as a cofactor for the enzymatic reaction[3h, i] and the demonstration that sulfenic acids can be eliminated from related structures (Scheme 21) in vitro at neutral pH and ambient temperatures.[81]



Scheme 20. Mechanisms of the allinase-catalyzed conversion of **5** into LF **16** in the presence of deuterium oxide.



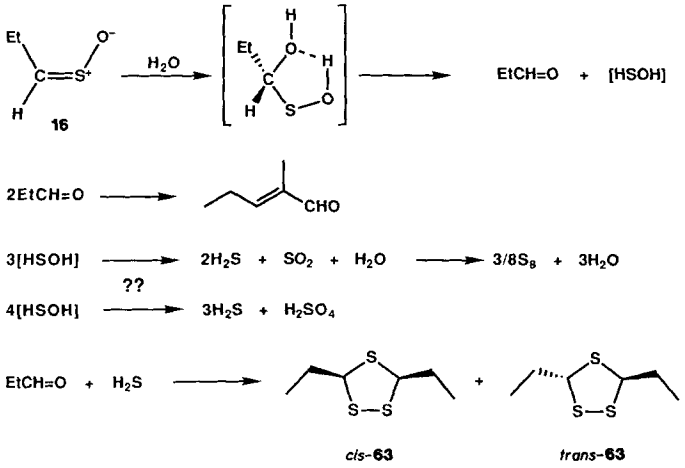
Scheme 21. Formation of sulfenic acids from hydantoins at room temperature in almost pH neutral solution.

5.1.4. The "Syn Effect" of Onion LF and Other Sulfines

While the [1,4]-sigmatropic rearrangements of **14b** to (*Z*)-**16** and **15b** to (*Z*)-**44** are aesthetically appealing and accommodate most observations (Scheme 18), it is curious that (*Z*)-**16** and (*Z*)-**44** are also the predominant products formed upon treatment of propanesulfinyl chloride (**19**) and ethanesulfinyl chloride (**45**), respectively, with triethylamine, reactions that should not involve the intermediacy of **14b** and **15b**! Theoretical calculations were therefore performed to examine the relative energies of the conformers of **44**.[82] Restricted Hartree-Fock calculations on **44** indicate that conformer (*Z*)-**44a** is more stable than conformers (*Z*)-**44b**, (*E*)-**44a**, and (*E*)-**44b** by 0.8, 1.7, and 3.1 kcal mol^{-1}, respectively (Fig. 3). These calculations are in good agreement with microwave spectroscopic studies of **44**-CH_2D ($CH_2DCH{=}S^+{-}O^-$), in which **44a** was the only conformation to be observed. The conformational preference for *Z*-**44a** can be explained in terms of orbital and electrostatic interactions between the terminal oxygen and methyl hydrogens, which are negligible in the (*E*)-form. Calculations indicate substantial negative charge on the sulfine oxygen (Fig. 3). It is suggested that there is an attractive electrostatic interaction between the methyl hydrogens (which according to the calculations bear a positive charge) and the negatively charged oxygen. A σ-type interaction, characterized by the formation of six σ-MOs, of which the HOMO is 1,5-bonding, also favors conformer (*Z*)-**44a**.[82] Both of these types of interactions are missing in the (*E*)-conformers. The general phenomenon of enhanced stability of (*Z*)- or *syn* isomers, the "*syn*-effect", is in fact well known.[82, 83] An important consequence of the above theoretical findings is that alternative routes from **14b** to (*Z*)-**16**, e.g. by protonation of the enolate of the (*E*)-1-propenesulfenate anion, cannot be excluded.

5.1.5. The Hydrolysis of Onion LF

When **16** is allowed to remain in contact with water, sulfur is split off, perhaps initially as HSOH, leaving behind propanal, which readily undergoes aldol condensation. In the medium following hydrolysis of **16**, sulfur is found as the free element as well as (in minor quantities) sulfate and sulfite. Hydrogen sulfide, detected in onion volatiles and presumably a decomposition product of **16**, may be trapped by propanal, forming *cis*- and *trans*-3,5-diethyl-1,2,4-trithiolane (**63**). **63** has likewise been isolated from volatiles of onion and other *Allium* spp. (Scheme 22).[84]

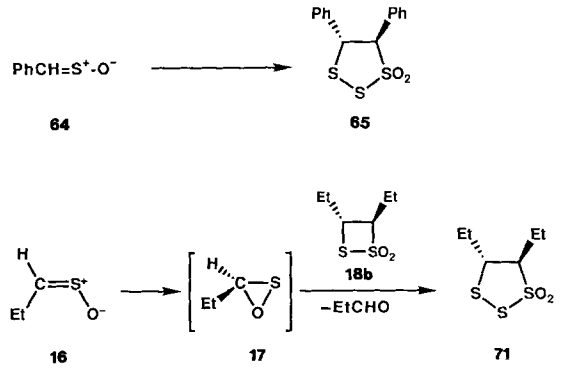


Scheme 22. Hydrolysis of LF **16** and formation of 1,2,4-trithiolanes *cis*- and *trans*-**63**.

5.1.6. The Dimer of Onion LF

As already noted, in 1961 Wilkens reported that the onion LF dimerized, affording a compound claimed to be 2,4-diethyl-1,3-dithietane 1,3-dioxide (**18a**) (cf. Scheme 5).[47] The proposed structure seemed to us to be at odds with the IR spectrum of the dimer, which indicated the presence of a sulfonyl group, and our examination of the IR spectra of authentic *cis*- and *trans*-1,3-dithietane 1,3-dioxide (**38a/b**) (cf. Scheme 12),[59] which failed to show the type of unusual "pseudo-sulfone infrared absorption" proposed by Wilkens to explain the spectrum of **18a**. Furthermore, the stability of the **38a/b** contrasts with the instability of **18a**. Finally, it is mechanistically difficult to reconcile the formation of **18a** from **16** with the reported formation of *trans*-4,5-diphenyl-1,2,3-trithiolane 1,1-dioxide (**65**) from thiobenzaldehyde *S*-oxide (**64**, Scheme 23).[85] In view of the uncertainty about the structure of the LF-dimer we re-examined the self-condensation of **16**.

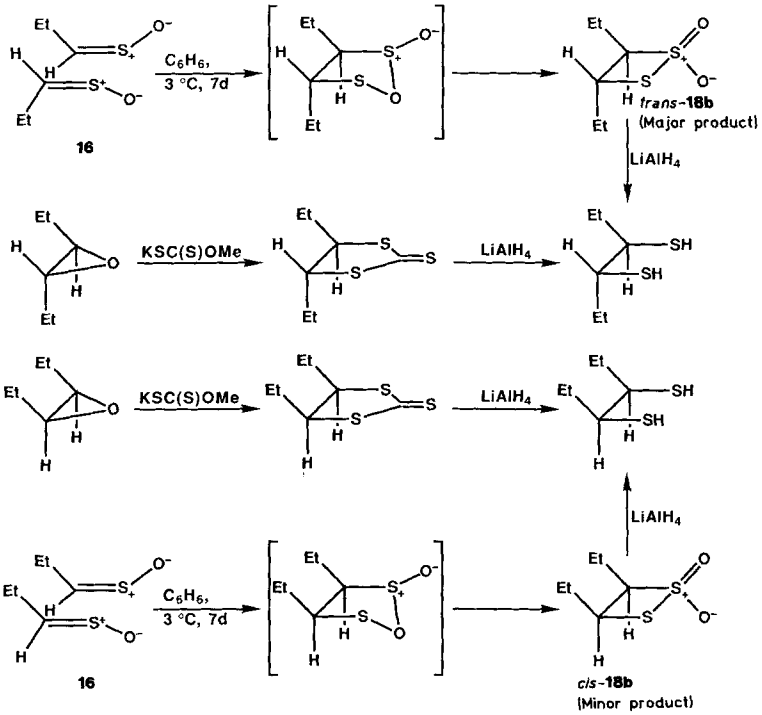
A sample of **16** from natural or synthetic sources was purified by trap-to-trap distillation at −30 °C, dissolved in about twice its volume of freshly dried benzene and kept in the dark at 3 °C for 7 days. The slightly yellow solution, now devoid of lachrymatory properties, was concentrated in vacuo and the residue subjected to molecular distillation, affording a clear, practically colorless liquid with a strong onion-like odor. Analysis by GC indicated a single major



Scheme 23. Formation of 1,2,3-trithiolane 1,1-dioxides **65** and **71** from sulfines **64** and **16**, respectively.

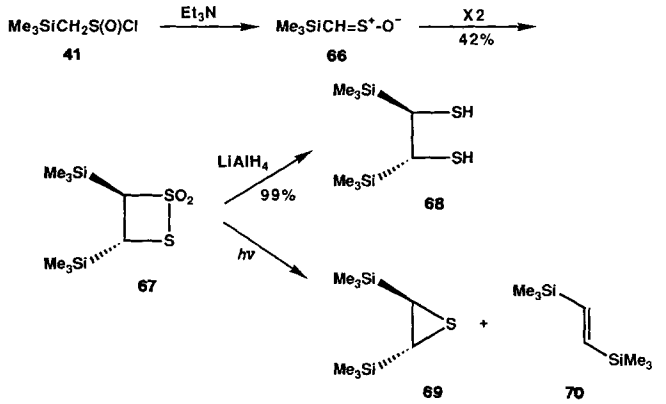
product with retention time slightly longer than that of propyl propanethiosulfonate. High resolution mass spectrometry confirmed the formula $C_6H_{12}S_2O_2$ for the LF dimer. The IR spectrum, showing sulfonyl bands, was very similar to that published by Wilkens.[47] The LF dimer gave a positive thiosulfonate test[86] and absorbed in the UV (EtOH or hexane) at $\lambda_{max} = 280$ (ε 100, sh).[87] Reduction of the compound with $LiAlH_4$ in ether gave 90% (±)-hexane-3,4-dithiol and 10% *meso*-hexane-3,4-dithiol. The above data and the ^1H- and ^{13}C-NMR spectra, discussed in Section 5.3.2, are most consistent with *trans*-3,4-diethyl-1,2-dithietane 1,1-dioxide (**18b**) as the structure of the LF dimer.[88a] Compound **18b** is formed by a process that begins with 1,3-dipolar addition of **16** to itself followed by rearrangement (Scheme 24).[88b] Minor amounts of *cis*-**18b** are also formed.

(*Z,E*)-(Trimethylsilyl)methanethial *S*-oxide (**66**), prepared by treatment of (trimethylsilyl)methanesulfinyl chloride (**41**)



Scheme 24. Mechanism for the dimerization of propanethial *S*-oxide **16** to **18b**.

with one equivalent of triethylamine. also dimerizes on storage at room temperature for several days to afford *trans*-3,4-bis(trimethylsilyl)-1,2-dithietane 1,1-dioxide (**67**) in 42% yield as a colorless, crystalline solid of m.p. 100–101 °C (Scheme 25).[77b, 89] Compound **67** affords (±)-1,2-bis-

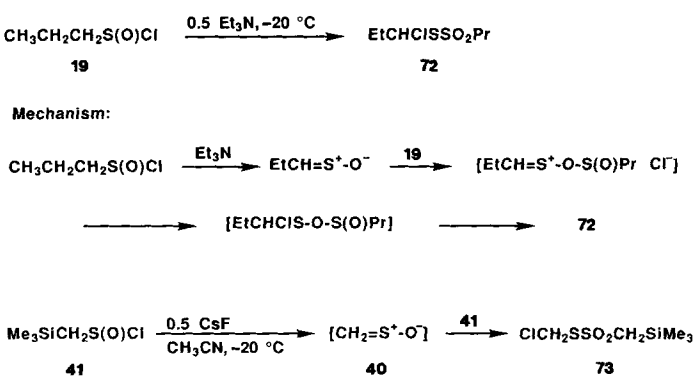


Scheme 25. Synthesis of silylated 1,2-dithietane 1,1-dioxide **67** from (trimethylsilyl)methanethial *S*-oxide (**66**); conversion of **67** into 2,3-bis(trimethylsilyl)thiirane (**69**) and the compounds (±)-**68** and **70** (only the *S,S* forms are shown).

(trimethylsilyl)-1,2-ethanedithiol (**68**) on reduction and *trans*-2,3-bis(trimethylsilyl)thiirane (**69**) and *trans*-1,2-bis(trimethylsilyl)ethene (**70**) on photolysis.[89] In benzene solution, the LF **16** may also undergo unimolecular rearrangement giving oxathiirane **17**, which in turn could donate sulfur to LF dimer **18b** giving *trans*-4,5-diethyl-1,2,3-trithiolane 1,1-dioxide (**71**, Scheme 23).

5.1.7. α-Chloroalkyl Alkanethiosulfonates: By-products in the Synthesis of Onion LF and Other Alkanethial S-Oxides from Alkanesulfinyl Chlorides

In the course of preparing onion LF **16** by treatment of propanesulfinyl chloride (**19**) with triethylamine we noticed the formation of small quantities of 1-chloropropyl propanethiosulfonate (**72**). We found that the formation of α-chloroalkyl alkanethiosulfonates was a general reaction with optimum yields when an alkanesulfinyl chloride was



Scheme 26. Synthesis of α-chloroalkyl alkanethiosulfinates such as **72** and **73** from sulfines such as **19** and **41**, respectively.

treated at low temperature with *one-half an equivalent* of triethylamine.[90] Thiosulfonates such as **72** result from reaction of the sulfine, functioning as a nucleophile, with the sulfinyl chloride, functioning as an electrophile (Scheme 26). In support of this mechanism we found that separately generated sulfines react with sulfinyl chlorides forming the expected chlorinated thiosulfonates. If thionyl chloride is substituted for the sulfinyl chloride, the product is a bis(α-chloroalkyl) disulfide. In another variant, we found that slow addition of 0.5 equivalent of cesium fluoride to (trimethylsilyl)methanesulfinyl chloride (**41**) in acetonitrile at −20 °C gave *S*-chloromethyl (trimethylsilyl)methanethiosulfonate (**73**) in nearly quantitative yield. Here the sulfine being trapped is the parent compound **40**.[70] We have recently utilized this reaction to establish the formation of cyclopropanethione *S*-oxide from cyclopropanesulfinyl chloride.[91]

5.2. Organosulfur Constituents of *Allium* Homogenates Separated by HPLC and GC-MS

If Leekes you like but do their smell dis-leeke
Eat Onyuns and you shall not smell the Leeke.
If you of Onyuns would the scent expelle
Eat Garlicke and that shall drowne the Onyun's smelle.

Anonymous

A variety of procedures have been examined for the separation of compounds formed in solution from cut *Allium* spp. The plant can be finely cut using a Waring Blender, a food processor or a tissue homogenizer. While the Waring Blender gives satisfactory results with "softer" plants, garlic and shallot bulbs are best cut first with a food processor followed by a tissue homogenizer. The plant is chopped using a 2:1 water:plant ratio. For the preparation of an *extract*, the homogenate is squeezed through cheese cloth or nylon mesh, saturated with sodium chloride, and shaken twice with dichloromethane, filtering/centrifuging each time. The separated dichloromethane layers are combined, dried and concentrated in vacuo at room temperature and then analyzed by FT-NMR and HPLC and/or GC (with a modified injector; see Section 5.2.1). Supercritical carbon dioxide can also be used as the extraction solvent.[92] For preparation of *a room temperature "steam distillate"*, the above homogenate is subjected to distillation at high vacuum using an oil bath to keep the pot at room temperature. The distillate is collected at −196 °C,[93, 94] saturated with sodium chloride and extracted and analyzed as above. For a particular plant the extract and room-temperature distillate were analytically quite similar (cf. Fig. 4). Although the distillates were generally cleaner with less component isomerization, in some cases more material was lost by distillation than by extraction, or other differences were observed.

5.2.1. Thiosulfinates: Primary Products in Cut Allium spp.

In addition to LF **16**, detected exclusively in the case of the onion but probably formed in other *Allium* spp., the primary

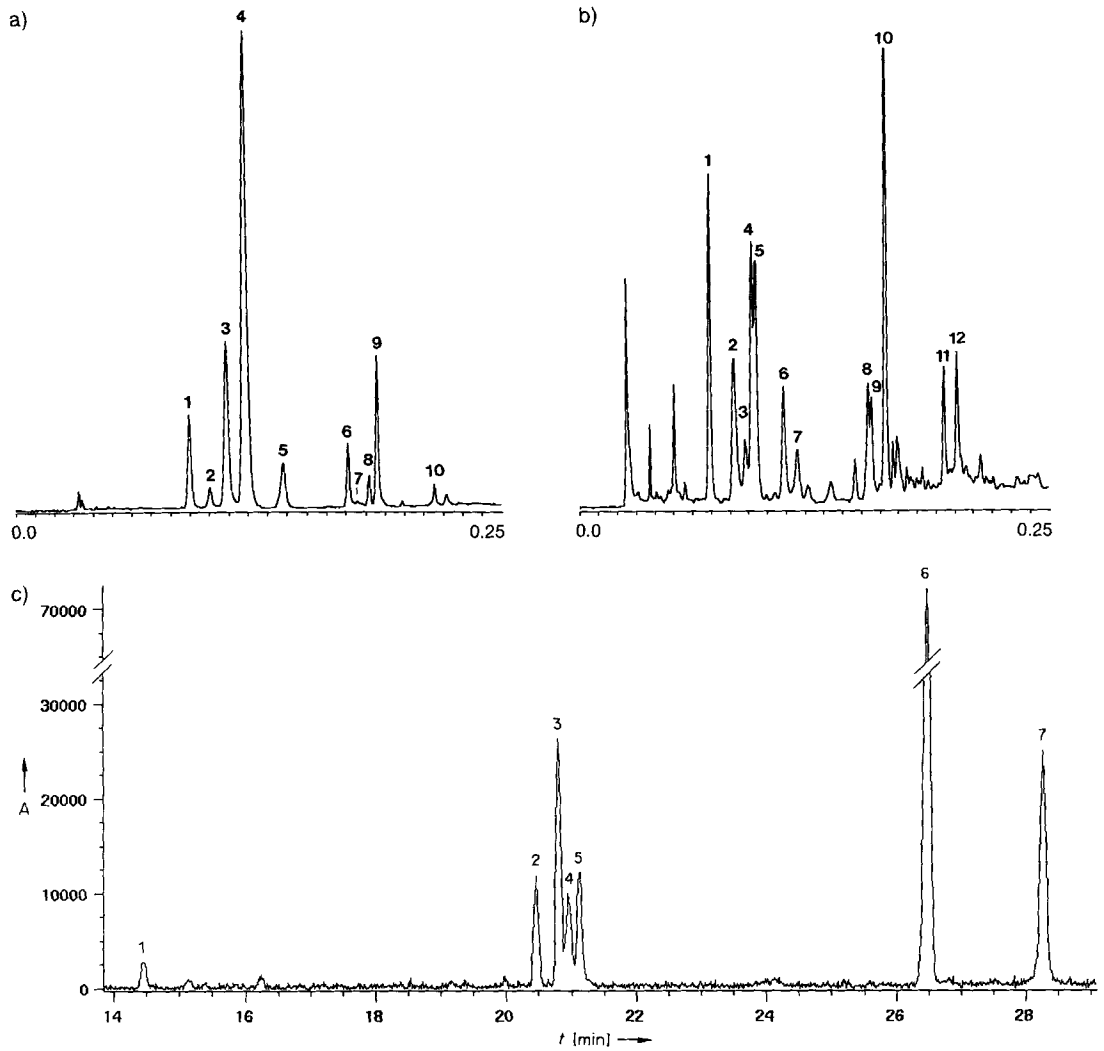


Fig. 4. a) HPLC separation of an extract of store-purchased garlic containing benzyl alcohol as internal standard. Conditions: 250 × 4.6 mm, 5 μm Rainin Microsorb silica gel column, UV detection at 254 nm; 1.6 mL min^{-1}, gradient from 2:98 2-propanol:hexane (10 min hold), to 20:80 during 10 min (5 min hold). Peak identification: 1, (*E*)-**105**, R = All); 2, (*Z*)-**106**, R = All); 3, (*E*)-**106**, R = All); 4, allicin **1**; 5, benzyl alcohol, internal standard; 6, **102**; 7, (*Z*)-**106**, R = Me; 8, (*E*)-**106**, R = Me; 9, **101**, 10, **12** (cf. Schemes 1, 4, 34, and 37). b) HPLC separation of a distillate of white onion (conditions as above). Peak identification: 1, (*E*)-**105**, R = Pr; 2, (*Z*)-**106**, R = Pr; 3, **16**; 4, (*E*)-**106**, R = Pr; 5 (shoulder), **13**; 6, (*E*)-**105**, R = Me; 7, benzyl alcohol, internal standard; 8, **30**; 9, (*Z*)-**106**, R = Me; 10, (*E*)-**106**, R = Me and **29** (overlapping peaks); 11, **123**; 12, **12** (cf. Schemes 4, 5, 10, 37, and 46). c) GC-EI-MS total ion chromatogram of the same sample of white onion as in Figure 4b. A = abundance. Conditions: 30 m × 0.53 mm methyl silicone gum capillary column, cryogenic on-column injection at 0 °C, column programmed from 0–200 °C at 5 °C min^{-1}; column head pressure 34.5 × 10^3 Pa (5 psi), GC-MS transfer line temperature, 100 °C. Peak identification: 1, **12**; 2, **29**; 3, (*E,Z*)-**106**, R = Me; 4, **30**; 5, (*E*)-**105**, R = Me; 6, (*E*)-**106**, R = Pr and *trans*-zwiebelane (**118**); 7, *cis*-zwiebelane (**117**) (cf. Schemes 4, 10 and 37, and Fig. 7).

products detected by HPLC, NMR, and GC-MS from the above procedures are thiosulfinates (Table 1) with negligible di- and polysulfides or thiosulfonates. Together with LF **16**, these thiosulfinates closely duplicate the taste and aroma of the freshly cut *Allium* spp. and serve as progenitors of virtually all of the organosulfur compounds formed in the cut plants. In view of the thermal instability of allicin **1** and other thiosulfinates it is surprising that vacuum "steam distillation" succeeds so well. Room-temperature steam distillation is successful because of the stabilizing effect of water, through hydrogen bonding, on the thiosulfinates; mildly acidic conditions (e.g. pH 2–4) also seem to stabilize thiosulfinates.[28] Since the thiosulfinates are water soluble, the physical laws applied to steam distillation of water-insoluble compounds are not applicable. It is likely that thiosulfinates form azeotropes under our vacuum "steam distillation" conditions.[21b]

Some comments are necessary regarding the "best" chromatographic methods for characterizing and quantifying unstable aroma and taste substances such as thiosulfinates produced on cutting *Allium* spp. Because of their excellent resolving powers, GC and GC-MS have dominated studies on *Allium* headspace volatiles and room-temperature extracts, despite early cautionary notes that many of the compounds seen by GC may be "artifacts of analysis"[39] and that more recent work suggests that equivalent or superior resolution of *Allium* components may be achieved at room temperature using HPLC![95, 96, 121] We have already noted in Section 4.1 that some, but not all, aliphatic thiosulfinates possessing up to eight carbons survive GC analysis using short columns and low injection port and column temperatures.[29, 54e] Unfortunately most studies on *Allium* volatiles employ long, narrow bore capillary columns (e.g. 0.20 mm × 50 m) and/or injection port temperatures as high

Table 1. Relative concentrations of thiosulfinates and other compounds in *Allium* spp. (in mol-% referred to total RS(O)SR′). Data from Ref. [21b,c]. **105** MeCH=CHS(O)SR **106** RS(O)SCH=CHMe

RS(O)SR	Garlic (NY) [b]	Garlic (NY) D [b]	Garlic (NY) R [b, c]	Garlic (S) [b]	Garlic (S)R [b, c]	Garlic (Ind. 1) [b, e]	Garlic (Ind. 2) [b, e]	"Elephant"-garlic [b]	"Elephant"-garlic (NY) D [b]	Wild garlic [b]
12 MeS(O)SMe	–	–	–	2.2	0.9	2	4	10	8.6	20
101 MeS(O)All	2.9	3.0	3.9	18	11	20	27	27	28	34
102 AllS(O)SMe	1.4	1.7	1.6	8.1	7.5	9	11	15	16	16
(*E,Z*)-**106**, R = Me [a]	x	x	x	1.2 [a]	1.9 [a]	1 [a]	1 [a]	3.6 [a]	1.5 [a]	1 [a]
(*E*)-**105**, R = Me	–	–	–	x	0.6	–	–	1.7	x	x
29 MeS(O)SPr	–	–	–	–	–	–	–	–	–	–
30 PrS(O)SMe	–	–	–	–	–	–	–	–	–	–
1 AllS(O)SAll	89	89	79	62	59	64	53	38	43	28
(*E,Z*)-**106**, R = All [a]	5.3 [a]	5.5 [a]	13 [a]	5.9 [a]	18 [a]	3 [a]	3 [a]	4.5 [a]	2.6 [a]	1 [a]
(*E*)-**105**, R = All	1.6	0.8	3.1	2.1	1.6	1	1	0.6	0.6	–
13 PrS(O)SPr	–	–	–	–	–	–	–	–	–	–
(*E,Z*)-**106**, R = Pr [a]	–	–	–	–	–	–	–	–	–	–
(*E*)-**105**, R = Pr	–	–	–	–	–	–	–	–	–	–
16 LF	–	–	–	–	–	–	–	–	–	–
123 Bissulfine	–	–	–	–	–	–	–	–	–	–
117/**118** *cis*/*trans*-Zwiebelane	–	–	–	–	–	–	–	–	–	–
Total-% Allyl	94	95	89	80	78	80	74	61	67	54
Total-% Methyl	2	2	3	16	11	18	24	34	31	45
Total-% 1-Propenyl	3	3	8	4	11	2	2	5	2	1
Total-% Propyl	–	–	–	–	–	–	–	–	–	–
Total-RS(O)SR′ [μmol g^{-1}]	14.3 [f]	7.5 [f]	22.1 [f]	25.6 [f]	20.7 [f]	15.5 [f]	36.5 [f]	5.2 [f]	2.7 [f]	20.8 [g]

RS(O)SR′	Onion (white) [b–d]	Onion (yellow) [b–d]	Shallot [b–d]	Scallion [b–d]	Chive [b–d]	Leek [b–d]	Chinese chive [b–d]
12 MeS(O)SMe	1	14	9	1	1.2	3	74
101 MeS(O)SAll	–	–	–	–	–	–	12
102 AllS(O)SMe	–	–	–	–	–	–	9
(*E,Z*)-**106**, R = Me [a]	34 [a]	25 [a]	15 [a]	18 [a]	4.4 [a]	27 [a]	5 [a]
(*E*)-**105**, R = Me	14	24	9	2.5	1.3	12	–
29 MeS(O)SPr	1	1	1.2	7.5	6.8	5	–
30 PrS(O)SMe	1	1	2.8	7.5	3.8	5	–
1 AllS(O)SAll	–	–	–	–	–	–	–
(*E,Z*)-**106**, R = All [a]	–	–	–	–	–	–	–
(*E*)-**105**, R = All	–	–	–	–	–	–	–
13 PrS(O)SPr	9	13	27	35	57	25	–
(*E,Z*)-**106**, R = Pr [a]	33 [a]	10 [a]	22 [a]	28 [a]	23 [a]	15 [a]	–
(*E*)-**105**, R = Pr	7	12	14	1.5	2.4	8	–
16 LF	+ +	+ +	+ +	+ +	–	+	–
123 Bissulfine	8% TS	0.5% TS	0.2% TS	x	x	x	–
117/**118** *cis*/*trans*-Zwiebelane	29% TS	20% TS	4% TS	8% TS	4% TS	11% TS	–
Total-% Allyl	–	–	–	–	–	–	11
Total-% Methyl	19	33	22	17	9	27	87
Total-% 1-Propenyl	59	47	33	30	19	31	3
Total-% Propyl	22	20	45	53	72	42	
Total-RS(O)SR′ [μmol g^{-1}]	0.20 [f]	0.35 [f, h]	0.25 [f, h]	0.08 [f]	0.26 [f]	0.15 [f, h]	2.0 [f]

[a] Typical *E*:*Z* ratio 2–3:1. [b] by HPLC analysis; [c] by NMR analysis; [d] by GC-MS analysis; [e] Ind. 1 = from farm in mountainous region of India with 22–23 °C average growing temperatures; Ind. 2 = from farm in plains region of India with 30–32 °C average growing temperatures; [f] fresh weight; for comparison, average fresh weight values reported for garlic and elephant garlic by Lawson by extraction are 34 μmol g^{-1} and 11 μmol g^{-1}, respectively; since garlic and elephant garlic contain ca. 60% water, approximate dry weight values are obtained by multiplying fresh weight values by 2.5 [121b]; [g] dry weight; [h] average fresh weight values reported by Lawson for *1-propenyl thiosulfinates* from scallion, shallot, leek, yellow onion, and white onion are 1.65, 1.89, 1.77, 0.50, and 0.40 μmol g^{-1}, respectively [121a]; *, trace level detected; + +, substantial amounts of LF detected; not quantitated due to variable loss on workup; zwiebelanes and bis-sulfine **123** not included in calculation of total number of moles present but indicated as % total thiosulfinates (TS) present; D, distilled then extracted (if not indicated, sample prepared by direct extraction of homogenized plant); R, refrigerated for 8 weeks; S, typical store purchased garlic (Mexican or Californian origin); NY, from farm in upstate New York (average growing temperature 19–22 °C); Total, percent of total thiosulfinates found as allyl-, methyl- 1-propenyl- and propyl group, respectively.

as 280 °C,[71, 92b, 97, 98] conditions which are especially conducive to thiosulfinate decomposition.

Our comparison of the results of both GC and HPLC analyses of fresh extracts and room-temperature distillates of *Allium* spp., using authentic samples of the thiosulfinates thought to be present to evaluate analysis conditions, reveal that *gas chromatography, as typically performed with high injector and column temperatures, presents a highly inaccurate picture of the composition, both of the headspace volatiles as well as of the room-temperature extracts from Allium species.*[21b] Thus, analysis of *Allium* extracts or vacuum distillates by both normal (Si) and reverse phase (C-18) HPLC, using diode-array UV detection, indicate that the predominant constituents are thiosulfinates. *We find no evidence from HPLC for the presence in these samples of the polysulfides claimed by prior GC-MS studies*! Using Si-HPLC, almost all of the thiosulfinates from *Allium* spp. can be separated and quantified using an internal standard.

While some thiosulfinates survive gas chromatography using short columns and low temperatures, these earlier GC analyses frequently suffered from peak broadening and tailing, indicative of partial sample decomposition. We find that

by using a standard polymethylsilicone column (30 m, 0.53 mm internal diameter, "Megabore") with *on-column injection ramped from 0 °C (liquified CO_2 cooling) with a 5 °C min^{-1} temperature injector and column program and a GC-MS transfer line temperature of 100 °C*, nicely resolved, clean GC-MS total ion chromatograms could be obtained for pairs of thermally unstable C_4 regioisomers such as **105**/**106**, R = Me, and **29**/**30**.[21c] While some C_6 compounds

RSS'(O)CH=CHMe **105**, R = Me

RS(O)SCH=CHMe **106**, R = Me

MeS(O)SPr **29**

MeSS(O)Pr **30**

could also be resolved under the above conditions, compounds such as PrS(O)SPr **13** required a slower temperature program (2 °C min^{-1}) and higher flow rates or a shorter (15 m) column for analysis. The various allylic thiosulfinates from garlic, such as allicin, could not be satisfactorily analyzed even under the mildest GC conditions.[21c]

The Si-HPLC and cryogenic-injector silicone capillary column GC-MS *Allium* analyses are complementary since the former separates on the basis of polarity and uses UV detection, while the latter separates on the basis of boiling point and uses EI/CI-MS detection. Peaks that are not resolved using one technique can often be separated using the other technique. Furthermore, ion extraction and selective ion MS methods (SIMS) can be employed to resolve overlapping GC peaks, especially when authentic samples are available for calibration purposes. Because of the great thermal instability of allylic thiosulfinates, HPLC represents the preferred method of analysis for garlic, elephant garlic, wild garlic, and Chinese chive extracts. HPLC peaks can also be identified by LC-MS, although the volatility of the C_2 and C_4 components limit the utility of this technique at present.[21b] Representative analyses of *Allium* extracts under our HPLC and GC-MS conditions are shown in Figure 4a–c and Table 1. An important conclusion from these analyses is that *thiosulfonates and di- and polysulfides are not detected in the fresh Allium extracts examined by us.* Thiosulfonates are seen in some samples that have been allowed to stand for some time. These compounds therefore may contribute to the flavor (or off-flavor!) of processed or cooked *Allium* spp.

The *Allium*-derived thiosulfinates are of four types: 1) fully saturated, RS(O)SR' (R,R' = Me or Pr) such as **12**, **13**, **29**, and **30**; 2) mono- or bis-β,γ-unsaturated thiosulfinates AllS(O)SMe **102**, AllSS(O)Me **101** or AllS(O)SAll **1**; 3) mono-α,β-unsaturated thiosulfinates, (*E*)-**105** or (*E,Z*)-**106** (R = Me or Pr); 4) mixed α,β- and β,γ-unsaturated thiosulfonates, (*E*)-**105** or (*E,Z*)-**106**, R = All. Notable in their omission from this listing are the isomeric bis-α,β-unsaturated thiosulfinates, MeCH=CHS(O)SCH=CHMe. These are thought to be formed and to rapidly rearrange; they will be considered separately (see Section 5.2.5). The chemistry of the fully saturated thiosulfinates has already been discussed above (Section 4.1). The chemistry of the other classes of *Allium* thiosulfinates will be considered in Sections 5.2.3 and 5.2.4 following some general observations on thiosulfinates from garlic, wild garlic, elephant garlic, onion, shallot, scallion, chive, leek, and Chinese chive (see Table 1).

5.2.2. *General Observations on Thiosulfinates from Each Allium spp.*

One way to categorize the different *Allium* spp. is by the types of alkyl groups present in the thiosulfinates, or less reliably (using gas chromatography), in derived compounds such as polysulfides. This type of chemotaxonomic information has been used to establish relationships between different members of the *Allium* genus.[39, 99, 100] Only the Chinese chive showed a predominance of *methyl* groups, although all of the *Allium* species examined contain methyl groups.[101] In three of the plants, garlic, elephant garlic, and wild garlic, the *allyl* group is the major alkyl group (Fig. 5). The only

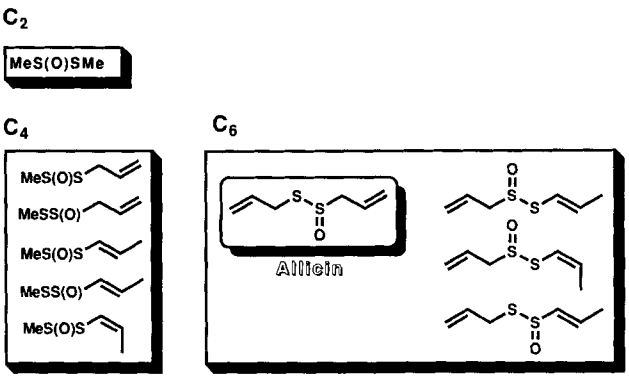


Fig. 5. C_2, C_4, and C_6 thiosulfinates in garlic extracts.

other plant containing detectable quantities of allyl groups is Chinese chive. The *propyl* group is the major alkyl group in chive, scallion, shallot, and leek, and is present in onion. Contrary to earlier reports[3i, 38] but consistent with Lawson's observation[121] the *propyl* group is *absent* in garlic as well as in elephant garlic, wild garlic and Chinese chive, the *1-propenyl* group being present instead. While *all* of the plants contain *1-propenyl* groups, it is the dominant group only in onion (Fig. 6). The total percentage of the 1-propenyl

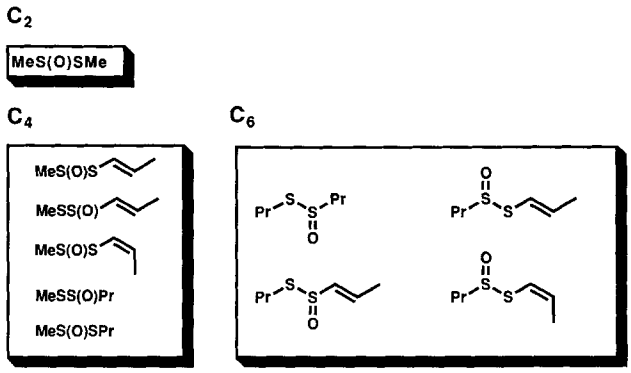


Fig. 6. C_2, C_4, and C_6 thiosulfinates in onion extracts.

group incorporated in onion thiosulfinates, zwiebelanes and bissulfine (e.g. 59% for white onions) is somewhat misleading since the majority of the 1-propenyl group generated as

1-propenesulfenic acid ends up as the LF, which is not included in the calculation because most is lost during analysis. However, in one experiment using ether as solvent to extract white onion, 0.5 $\mu mol\,g^{-1}$ of LF was isolated compared to ca. 0.2 $\mu mol\,g^{-1}$ total thiosulfinate! Small quantities of bissulfine were also found in some of the extracts. When the plant homogenates were allowed to stand in *methanol* for 24 hours before extraction and workup by chromatographic methods, a number of other organosulfur compounds were isolated as described below.

In view of the ephemeral nature of *Allium* thiosulfinates, the significance of the numbers in Table 1 can be questioned both with regard to variation in isolation techniques and in plant specimens. *Allium* homogenates prepared from the trimmed bulbs (garlic, elephant garlic, wild garlic, onion, shallot) or the trimmed plants (scallion, chive, leek, Chinese chive; roots and tips of stalks removed) were typically allowed to stand at room temperature for 30 min and then analyzed after rapid extraction and extract concentration. The analytical results were not altered upon increasing the interval between homogenization and extraction to 6 h. When the homogenate was allowed to stand overnight at room temperature, the only significant change was the disappearance of thiosulfinates of type MeCH=CHS(O)SR **105** (see Section 5.2.5). For quantitative analysis, some variation is seen between different methods of homogenization. Lower yields of thiosulfinates and, in some cases, minor qualitative differences were obtained using distillation rather than extraction methods. Organoleptic evaluation of the room temperature "steam distillate" of the onion indicated that the taste and smell closely duplicate that of the freshly cut plant. Thus, for a given plant sample, reasonable reproducibility is achieved and the analytical data so obtained is relevant to plant flavor.

The situation with regard to the plant specimens is more ambiguous. Thus, the relative percentages for different alkyl groups can vary with the part of the plant, e.g. in Chinese chives the methyl:allyl ratio varies from 71:29 to 36:64 with the leaves, roots, and rhizomes,[102] with the plant variety (e.g. yellow, white or red onion), with the developmental stage[45] and, as we shall discuss below, with the growing and storage conditions.[28c] In particular, we find considerable variation in methyl group percentages between plant samples.

Despite limitations in the reproducibility of the data in Table 1, a number of interesting features can still be noted. The following data, extracted from Table 1 and from more extensive studies, will be considered in more detail in Sections 5.2.3 to 5.2.5:

a) There is excellent qualitative agreement in the thiosulfinate composition of extracted and room temperature "steam-distilled" garlic (see Table 1) and elephant garlic (NY extract not shown).
b) For thiosulfinates of type **106** both *E* and *Z* isomers are found, with *E*:*Z* ratios varying from 9:1 to 1.1:1, with an average value of 2:1. Since pure *E* and *Z* isomers undergo rapid isomerization in solution (see Section 5.2.4) only the *E* + *Z* sum is reported. For thiosulfinates of type **105**, only the *E* isomer is found in plant extracts or distillates. In all but one case, significantly more (*E*,*Z*)-**106** is found than (*E*)-**105**.
c) Store-purchased garlic (origin: Mexico) shows a typical allyl:methyl:1-propenyl ratio of 80:16:4; the ratio of **101**:**102** is 2.2:1.
d) Refrigerated store-purchased garlic shows an allyl:methyl:1-propenyl ratio of 78:11:11; the ratio **101**:**102** is 1.4:1.
e) New York grown garlic (average growing temperature 19–22 °C) shows an allyl:methyl:1-propenyl ratio of 95:2:3; the ratio **101**:**102** is 1.8–2.1:1.
f) Refrigerated New York grown garlic shows an allyl:methyl:1-propenyl ratio of 89:3:8; the ratio **101**:**102** is 2.4:1.
g) Garlic grown in a plains region of India (average growing temperature 30–32 °C) shows an allyl:methyl:1-propenyl ratio of 74:24:2; the ratio **101**:**102** is 2.5:1.
h) Garlic grown in a mountainous region of India (average growing temperature 22–23 °C) shows an allyl:methyl:1-propenyl ratio of 80:18:2; the ratio **101**:**102** is 2.2:1.
i) "Deodorized" garlic[103] shows an allyl:methyl:1-propenyl ratio of 84:11:6 (not listed in Table 1).
j) Store-purchased elephant garlic shows an allyl:methyl:1-propenyl ratio of 61:34:5; the ratio **101**:**102** is 1.8:1.
k) New York grown elephant garlic shows an allyl:methyl:1-propenyl ratio of 67:31:2; the ratio **101**:**102** is 1.8:1.

5.2.3. *Mono- and Bis-β-γ-unsaturated Thiosulfinates and Their Derivatives*

The first thiosulfinate to be discovered was allicin (**1**), so it is appropriate to consider its chemistry first. As already noted, **1** is a colorless, odoriferous, unstable antibacterial substance with a characteristic garlic odor (cf. Section 3).[30] While **1** was first described as being optically inactive[30] recent work suggests that *natural* **1** *is in fact optically active* as determined qualitatively by HPLC with a chiral detector and quantitatively using a polarimeter.[104] Natural **1** shows a specific rotation of $-3.90°$; its optical purity is unknown. Thiosulfinates such as methyl 2-methyl-2-propanethiosulfinate (**23**) have been prepared in optically active form.[105] In the absence of *tert*-butyl or other bulky groups they tend to be optically unstable. If the optical activity of **1** is real, what is its origin? Based on mechanisms suggested above for thiosulfinate formation (Scheme 8), if natural **1** originates from free, achiral 2-propenesulfenic acid (**2**) or its anion, it must also be achiral. On the other hand, if the sulfenic acid remains bound to the allinase via hydrogen bonding (cf. Scheme 19) when it is attacked by a second, free sulfenic acid, asymmetric induction giving optically active **1** is possible.[105b] Further research is necessary to clarify these possibilities.

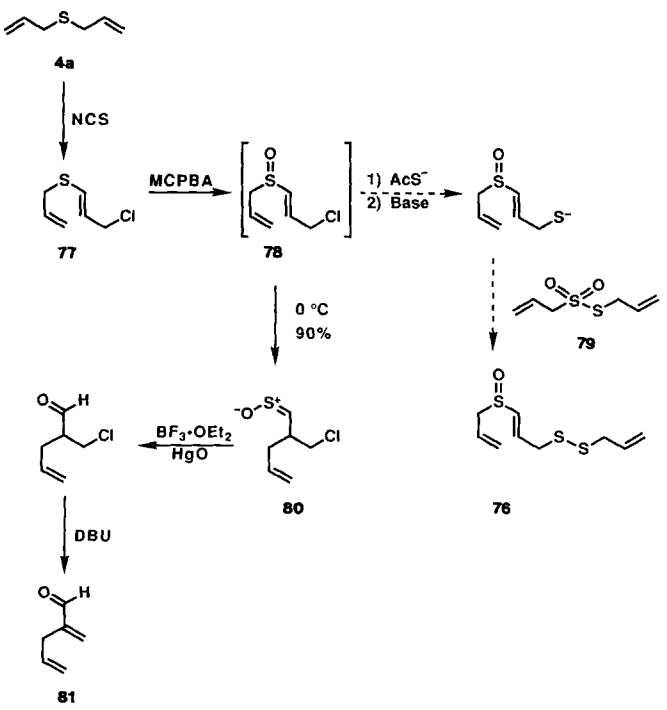
Decomposition of neat allicin is said to afford sulfur dioxide along with allyl alcohol, dimethyl trisulfide, diallyl mono-, di- and trisulfides (**4a–c**), and allyl methyl di- and trisulfides, while passage through a gas chromatograph is said to furnish a 2.4:1 mixture of 3-vinyl-3,4-dihydro-1,2-dithiin (**9**) and 3-vinyl-3,6-dihydro-1,2-dithiin (**9a**) (Scheme 3).[35a] Thiosulfonates (RSO_2SR'), typically produced along with disulfides upon disproportionation of most thiosulfinates (cf. Scheme 11), were not formed from **1**.

Compounds **9** and **9a** were thought to be dehydration products of **1** formed according to the following equation akin to

$$\underset{\mathbf{1}}{C_6H_{10}S_2O} \longrightarrow \underset{\mathbf{9/9a}}{C_6H_8S_2} + H_2O$$

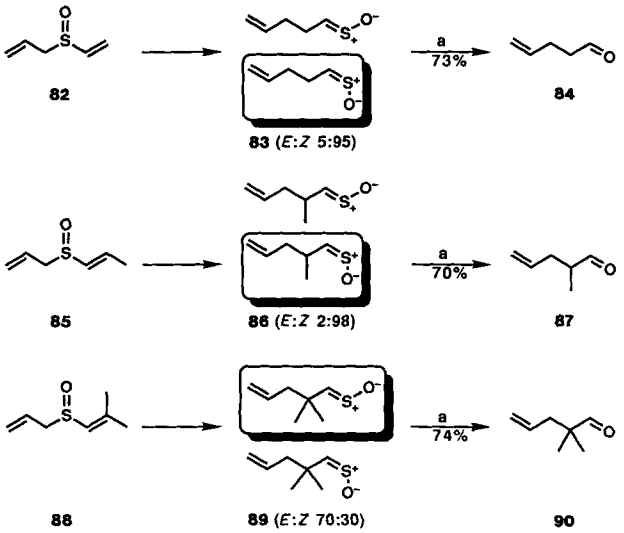
the formation of 1-propenyl propyl disulfide from propyl propanethiosulfinate (**13**).[35a] (cf. Ref. [35b]). Our investigation of the mechanism of decomposition of **1** was prompted by a collaborative study with M. K. Jain and R. Apitz-Castro on the identity of several antithrombotic substances they had isolated from garlic extracts[106] and it is this work that is presented first. The chromatographic separation of solutions prepared by soaking chopped garlic in methanol afforded allicin (**1**), diallyl di-, tri-, and tetrasulfides (**4b–d**), allyl methyl trisulfide, 2-vinyl-2,4-dihydro-1,3-dithiin (**74**), 3-vinyl-3,4-dihydro-1,2-dithiin (**9**) along with two isomeric polar compounds, showing the greatest antithrombotic activity. The substances were named (*E*)- and (*Z*)-ajoene (based on the Spanish word for garlic, ajo, pronounced "aho"), ultimately characterized as (*E*)- and (*Z*)-4,5,9-trithiadodeca-1,6,11-triene 9-oxide (**75**) (cf. Scheme 31) by spectroscopic and synthetic methods.[107]

The sulfoxide thio-Claisen rearrangement: Two pairs of structures, (*E,Z*)-**75** and (*E,Z*)-4,5,9-trithiadodeca-1,7,11-triene 9-oxide (**76**), seemed compatible with the spectroscopic data for (*E,Z*)-ajoene and we sought syntheses of both. A proposed synthesis of **76** involved oxidation of allyl 3-chloro-1-propenyl sulfide[108] (**77**) to allyl 3-chloro-1-propenyl sulfoxide **78**, displacement of chloride by thioacetate, and hydrolysis of thioacetate to thiolate followed by use of allyl 2-propenethiosulfonate (**79**) to construct the S–S bond (Scheme 27). To our surprise MCPBA oxidation of **77** at 0 °C did not lead to **78** but rather to (*Z*)-2-chloromethyl-4-pentenethial *S*-oxide (**80**) in 90% isolated yield. This sulfine could be converted into 2-methylene-4-pentenal (**81**) by sequential desulfurization with boron trifluoride etherate-mercuric oxide[109] and dehydrochlorination with DBU.[110]



Scheme 27. Discovery of the sulfoxide thio-Claisen rearrangement.

The conversion of **78** into **80** is an example of a sulfoxide-accelerated thio-Claisen rearrangement,[79] a stereospecific [3,3]-sigmatropic process occurring under unusually mild conditions. Additional examples of the sulfoxide thio-Claisen rearrangement include conversion of allyl vinyl sulfoxide (**82**) into lacrymatory (*E,Z*)-4-pentenethial *S*-oxide (**83**; *E,Z* = 5:95) and then aldehyde **84**, of allyl (*E*)-1-propenyl sulfoxide (**85**) into (*E,Z*)-2-methyl-4-pentenethial *S*-oxide (**86**; *E,Z* = 2:98) and then aldehyde **87**, and of allyl 2-methyl-1-propenyl sulfoxide (**88**) into (*E,Z*)-2,2-dimethyl-4-pentenethial *S*-oxide (**89**; *E,Z* = 70:30) and then aldehyde **90** (Scheme 28).[110]

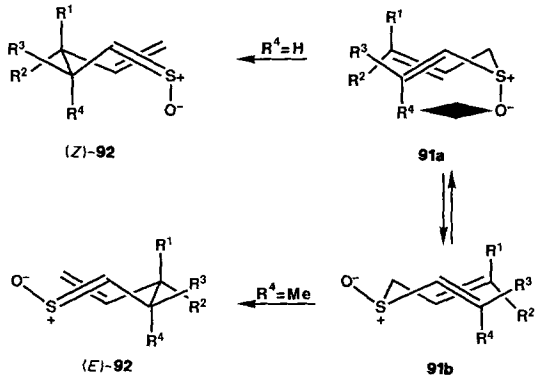


Scheme 28. Examples of the sulfoxide thio-Claisen rearrangement. a: $BF_3 \cdot OEt_2$, HgO.

While the activation enthalpy for the thio-Claisen reaction is typically greater than that for the Claisen rearrangement,[111] the activation energy for the sulfoxide thio-Claisen reaction of allyl vinyl sulfoxide **82** ($\Delta H^{\neq} = 19.32\ kcal\,mol^{-1}$, $\Delta S^{\neq} = -4.3\ cal\,mol^{-1}K^{-1}$) is *lower* than that for the Claisen rearrangement of allyl vinyl ether ($\Delta H^{\neq} = 25.40\ kcal\,mol^{-1}$, $\Delta S^{\neq} = -15.9\ cal\,mol^{-1}K^{-1}$[112]). The sulfoxide thio-Claisen rearrangement, an example of a zwitterion-accelerated Cope process,[113] proceeds with comparable substrates at 23 °C ca. 50 times faster than the thio-Claisen rearrangement under neutral conditions and 39 times faster under acidic conditions. The low $\Delta H^{\neq}$ for this reaction reflects, in part, the low C_{sp^3}–S(O) bond strength (ca. 46 $kcal\,mol^{-1}$ in **82**).

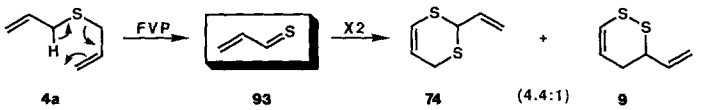
We have noted (Section 5.1.4) that the *Z*-stereochemistry is favored for sulfines. Thus, it is of interest to observe that **88** (and several other similarly substituted 1-alkenyl allyl sulfoxides) prefer the *thermodynamically less stable E-configuration* in the rearranged sulfine **89**. If it is assumed that the sulfoxide thia-Claisen rearrangement involves a pseudo chair transition state then pseudoaxial or pseudoequatorial

orientations are possible for sulfoxide oxygen. For thiane *S*-oxides an axial oxygen orientation is favored *except* when there are substituents at the 3- or 5-positions *cis* to sulfoxide oxygen, such as 3,3-dimethylthiane *S*-oxide where the equatorial/axial oxygen ratio is $>95:5$.[114] Similar effects should prevail in the sulfoxide thio-Claisen favoring **91a** → (*Z*)-**92** when $R^4 = H$ but favoring **91b** → (*E*)-**92** when $R^4 = Me$ (Scheme 29).[110, 115]



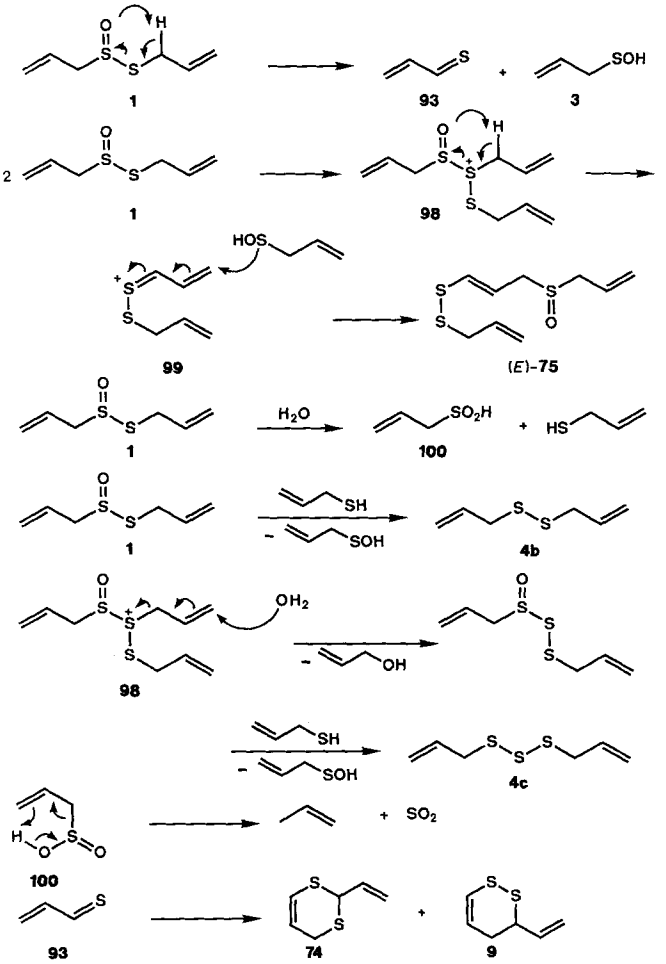
Scheme 29. Steric arrangement of the transition state **91a** ⇌ **91b** for the sulfoxide thio-Claisen rearrangement.

Synthesis of ajoenes, 2-vinyl-2,4-dihydro-1,3-dithiin and 3-vinyl-3,4-dihydro-1,2-dithiin and mechanistic considerations: Our discovery of the significant facilitating effect of the sulfinyl oxygen on the thio-Claisen rearrangement made it apparent that structure **75** (cf. Scheme 31) was to be preferred to **76** for (*E,Z*)-ajoene as there was no indication of rearrangement of this material to a sulfine upon heating. Since allicin (**1**) is the first isolable product formed when garlic is cut, we suspected that **1** might be the immediate precursor of **75**. Indeed, we found that when synthetic **1** was refluxed with 3:2 acetone:water for 4 hours, (*E,Z*)-**75** could be isolated in 34% yield.[107, 116] Other products included 2-vinyl-2,4-dihydro-1,3-dithiin (**74**) and 3-vinyl-3,4-dihydro-1,2-dithiin (**9**), in a 4.4:1 ratio, diallyl di- and trisulfides (**4b** and **4c**), and propene. The structures of **74** and **9** were established by comparison with the known products of the dimerization of thioacrolein (**93**) at −180 °C *which likewise affords* **74** *and* **9** *in a 4.4:1 ratio*. **93** is formed in the flash vacuum pyrolysis of diallyl sulfide (**4a**) (Scheme 30).[117]

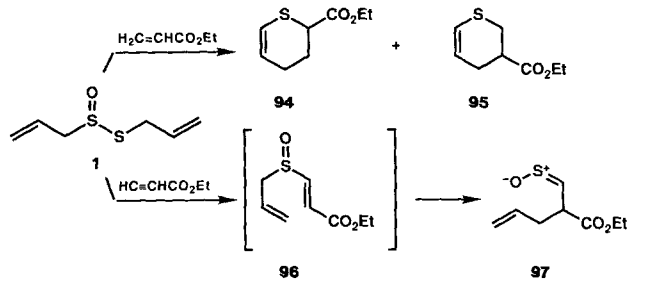


Scheme 30. Dimerization of thioacrolein (**93**) from flash vacuum pyrolysis of diallyl disulfide (**4a**).

The isolation of **74** and **9** as decomposition products of **1** and the identity of the **74**:**9** ratio to that observed upon dimerization of **93** suggests that the first step in the decomposition of **1** involves Cope-elimination to give 2-propenesulfenic acid (**3**) and **93** (Scheme 31). This postulate, which is consistent with our suggestion for the decomposition of methyl methanethiosulfinate (**12**) (Scheme 6), finds additional support in our observation of the characteristic sapphire blue color of **93** when **1** is distilled into a liquid nitrogen cooled trap, and our isolation of ethyl-3,4-dihydro-2*H*-thiopyran-2- (**94**) and -3-carboxylates (**95**) and (*Z*)-ethyl-2-thioformyl-4-pentenoate *S*-oxide (**97**) when solutions of **1** in ethyl acrylate and ethyl propiolate, respectively, are kept overnight at room temperature (Scheme 32).[118] Presumably **97** results from sulfoxide thio-Claisen rearrangement of the initial adduct **96** of ethyl propiolate and **3**. The earlier work of Brodnitz[35a] (Scheme 3) on the decomposition of **1** in a gas chromatograph must be corrected by replacing his incorrect structure **9a** with **74**.

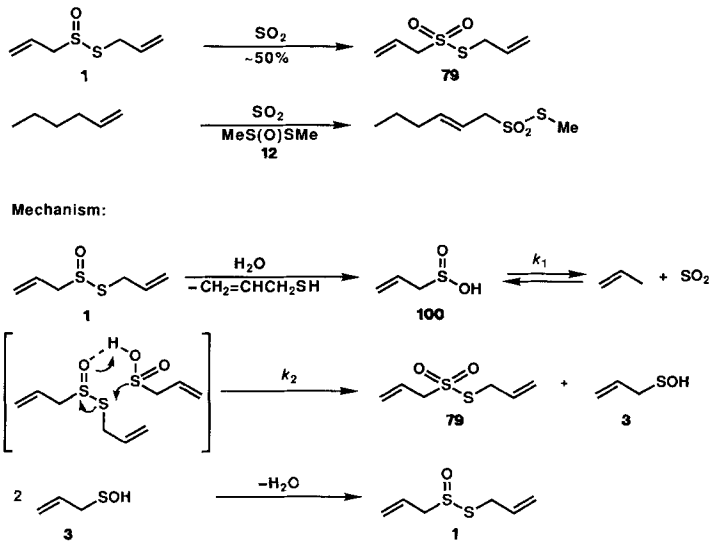


Scheme 31. Mechanism for the decomposition of allicin (**1**) and formation of ajoene (**75**).



Scheme 32. Trapping of thioacrolein (**93**) (H_2C=CH-CH=S) and 2-propenesulfenic acid (**3**) (H_2C=CH-CH_2SOH) from allicin (**1**) as **94** + **95** and **97**, respectively.

With the mechanism proposed by us for the decomposition of **12** (Scheme 11) as a model, a detailed scheme for the decomposition of allicin **1** can be suggested (Scheme 31). A key step involves *S*-allylthiolation of **1** to give the sulfonium ion **98**, which can: a) undergo β-elimination to give carbocation **99** followed by γ-addition of **3** to give (*E*,*Z*)-**75**; b) undergo S_N2' hydrolysis giving allyl alcohol and then **4c**; c) undergo hydrolysis to 2-propenesulfinic acid (**100**) and **4b**.[119a] Direct hydrolysis of **1** can give **100** and 2-propenethiol. β,γ-Unsaturated sulfinic acids such as **100** are known to readily lose sulfur dioxide by retro-ene type reactions.[119c] A search was made for the presence of allyl 2-propenethiosulfonate (**79**) among the decomposition products of **1**, but none was found. This observation can be rationalized by assuming that the rate of loss of sulfur dioxide from **100** (k_1) is more rapid than its rate of nucleophilic attack on **1** (k_2; Scheme 33).[119d] It is noteworthy that when **1** is dissolved in liquid sulfur dioxide and the solution is allowed to stand at room temperature in a sealed vial, **79** can be isolated in good yield (Scheme 33).[135d] Compound **79**, sometimes referred to as pseudoallicin, has only 50% of the antibacterial activity of alliicin.[120]

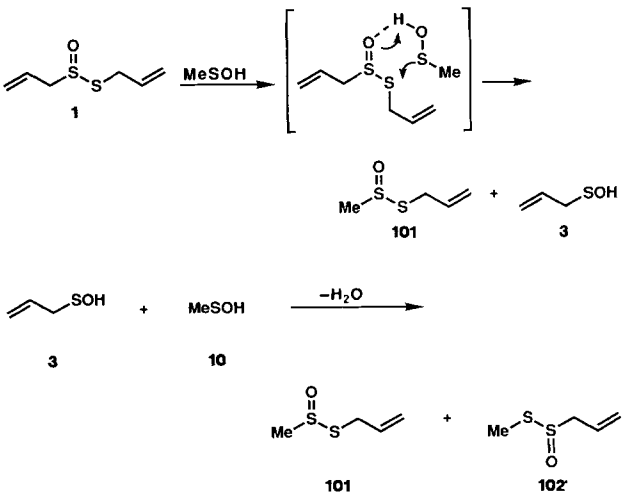


Scheme 33. Formation of allyl 2-propenethiosulfonate (**79**) from allicin (**1**) and sulfur dioxide.

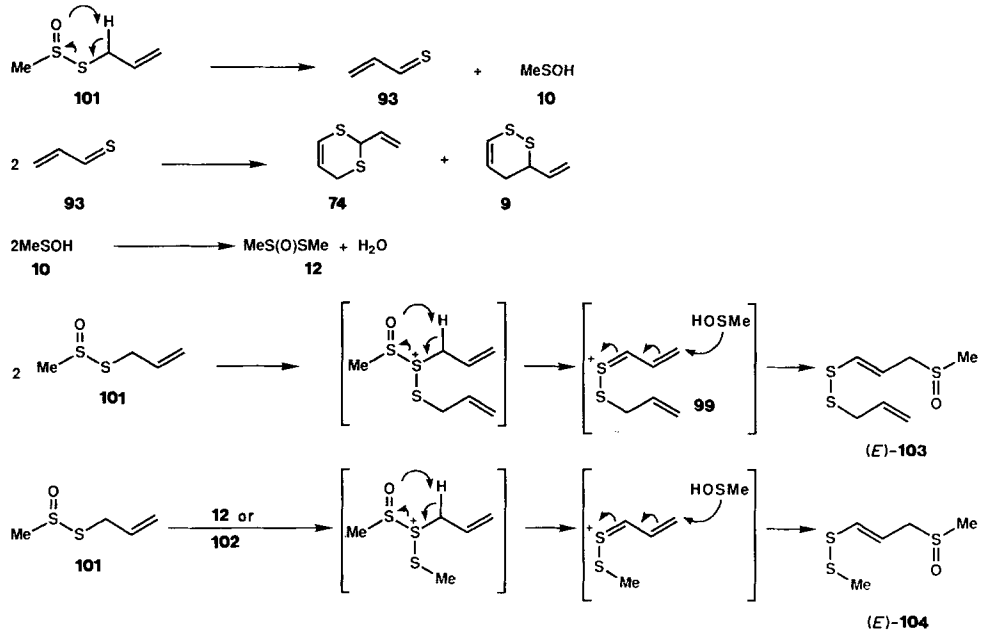
Other allyl thiosulfinates in garlic, elephant garlic, and wild garlic: We have previously noted (Section 2.1) that garlic *grown* in colder climates contains far less (+)-*S*-methylcysteine *S*-oxide (**6**) than garlic grown in more temperature climates.[21] This lower concentration of **6** translates into diminished levels of methyl group-containing thiosulfinates. Thus, some garlic grown in New York State (cooler climate: 19–22 °C average growing temperatures) shows an allyl:methyl:1-propenyl ratio of 94:2:3, which differs dramatically from the more typical ratio of 80:16:4 seen in store-purchased garlic of Mexican origin. A similar but smaller decrease in methyl group levels is seen when the composition of New York State grown elephant garlic (allyl:methyl:1-propenyl ratio of 67:31:2) is compared to that of store-purchased elephant garlic (allyl:methyl:1-propenyl ratio of 62:35:3), grown in a warmer climate. A comparison of samples of Indian garlic obtained from a mountainous area (22–23 °C average) and from an area with a climate averaging 10 °C warmer show a similiar trend: the allyl:methyl ratio is larger for the garlic grown in a cooler climate. Finally, garlic treated to allegedly make it "odorless"[103] also shows a lower relative methyl content (allyl:methyl:1-propenyl ratio of 84:11:6). It can therefore be concluded that when garlic (and elephant garlic) is grown under harsher conditions or treated with certain chemicals the specific enzymes associated with formation or hydrolysis of *S*-methylcysteine *S*-oxide (**6**) are attenuated or destroyed.[21, 28b]

Lawson has observed that γ-glutamyl-*S*-(*E*)-1-propenylcysteine and γ-glutamyl-*S*-2-propenylcysteine (see **e** and **c**, respectively, in Scheme 2), the dominant γ-glutamyl peptides in homogenates of fresh garlic, decrease markedly when freshly picked garlic is refrigerated.[11, 121] This decrease is coupled with a corresponding increase in (+)-*S*-(*E*)-1-propenylcysteine *S*-oxide (**5**) and (+)-*S*-2-propenylcysteine *S*-oxide (**2**), respectively, which in turn afford 1- and 2-propenesulfenic acids. Thus, for store-purchased garlic of Mexican origin the allyl:methyl:1-propenyl ratio of 80:16:4 changes to 78:11:11 after refrigeration for two months; for New York grown garlic the allyl:methyl:1-propenyl ratio of 94:2:3 changes to 90:3:8 after refrigeration for this same period.

In addition to **1** and α,β-unsaturated thiosulfinates, two isomeric thiosulfinates, allyl methanethiosulfinate **101**, and methyl 2-propenethiosulfinate **102**, are important components of some *Allium* homogenates. Interpretation of the data in Table 1 is facilitated if it is recognized that in garlic, thiosulfinates containing only the 1- and 2-propenyl groups are formed *ten times more rapidly* than thiosulfinates containing methyl groups.[122] There would therefore be little 1- or 2-propenesulfenic acid available to condense with the more slowly forming methanesulfenic acid (**10**). A mechanism involving reaction of **10** with allicin **1** (Scheme 34) accommodates the facts that: 1) after **1** is maximally formed in 0.5 min it decreases until the mixed allyl methyl thiosulfinates are maximally formed after 5 min;[122] 2) for each mole of **1** lost, 1.9 moles of mixed allyl methyl thiosulfinates are formed;[122] 3) the **101**:**102** ratio increases to ca. 2:1 after



Scheme 34. Formation of allyl methanethiosulfinate (**101**) and methyl 2-propenethiosulfinate (**102**) in garlic.

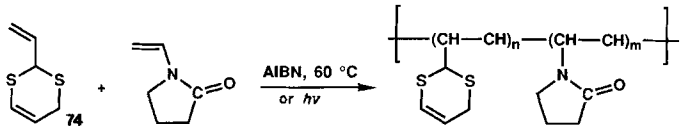


Scheme 35. Formation of methylajoene (**103**) and dimethylajoene (**104**) from allyl methanethiosulfinate **101**.

1–5 min and **101** dominates; 4) when powdered garlic (e.g. alliin/allinase) is added to excess aqueous methyl methanethiosulfinate (**12**), the major product is **102** (Scheme 34).[21a]

Decomposition of an authentic sample of **101** in acetone/water affords **9**, **74**, **12**, **4b**, **4c**, allyl methyl trisulfide and two new polar compounds identified as (*E*,*Z*)-2,6,7-trithiadeca-4,9-diene 2-oxide (**103**, "methyl ajoene") and (*E*,*Z*)-2,3,7-trithiaocta-4-ene 7-oxide (**104**, "dimethyl ajoene") (Scheme 35). Compounds **103** and **104**, thought to be present in low concentrations in garlic extracts, have recently been found in extracts of ramsons or wild garlic (*Allium ursinum*) and are derived from the isomers **101**/**102**, which predominate over allicin **1** in this plant (ratio of **1**:**101**/**102**:**12** is 1.26:0.14:0.01 in garlic and 0.53:0.70:0.27 in ramsons).[123]

After our identification of **74** as one of the antithrombotic components of garlic extracts, the novel use of **74** in a copolymer with *N*-vinylpyrrolidone was described (Scheme 36).[124] This copolymer is proposed as an anti-



Scheme 36. Copolymer of 2-vinyl-2,4-dihydro-1,3-dithiin (**74**) and *N*-vinyl pyrrolidone [124].

thrombogenic and antibiotic composition for use as a coating for artificial prostheses and implants which remain in contact with blood.

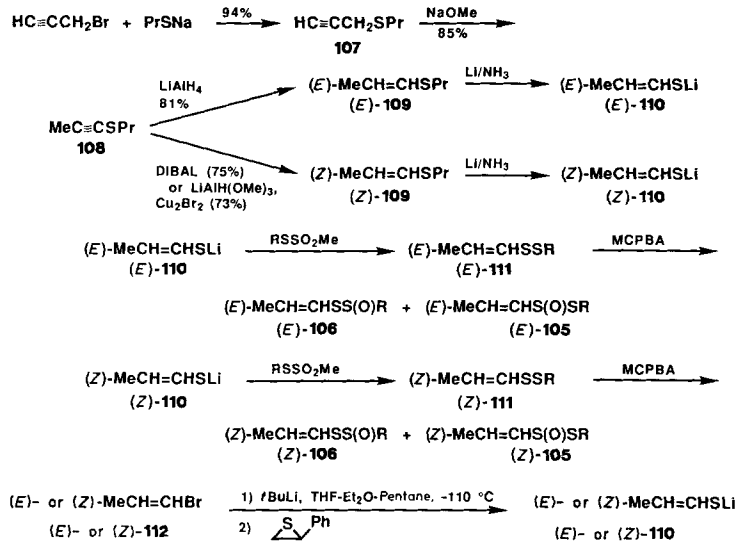
5.2.4. *Mono-α,β-unsaturated Thiosulfinates*

While saturated aliphatic and allylic thiosulfinates have been known for many years, little work has been carried out on α,β-unsaturated thiosulfinates, despite the fact that such compounds are present in onion and garlic extracts and display significant inhibitory activity toward lipoxygenase and cyclooxygenase enzymes.[28, 125] We therefore conducted a systematic study of the natural occurrence, synthesis and properties of these compounds.

Natural occurrence of mono-α,β-unsaturated thiosulfinates: Considerable quantities of α,β-unsaturated thiosulfinates of type (*E*)-**105** (alkyl (*E*)-1-propenethiosulfinate) and (*E*,*Z*)-**106** ((*E*,*Z*)-1-propenyl alkanethiosulfinates, R = Me, Pr, or All) are present in fresh extracts or room-temperature steam distillates of all of the *Allium* spp. examined as noted in Table 1. The thiosulfinates **106** (R = Me, Pr) have been identified in yellow onion extracts by Wagner et al.[150] and by Kawakishi et al.;[149d] Wagner also noted the rapid interconversion of geometric isomers. Lawson reports the presence of **105** and **106** (R = Me and Pr) in scallion, shallot, leek, yellow onion, boiling onion, white onion and red onion[121] and of **105** and **106** (R = Me, All) in garlic, and also comments on the ease of geometric isomerism in **106**.[121b]

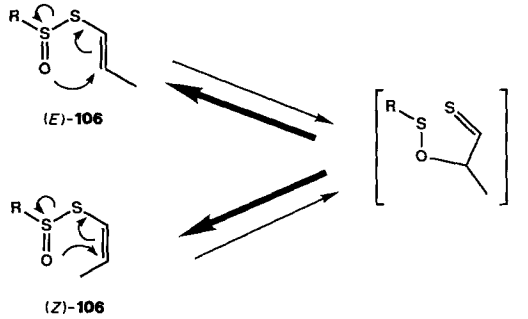
Synthesis of mono-α,β-unsaturated thiosulfinates: Synthetic routes to the stereoisomers **105** and **106** (R = Me, Pr, All) are summarized in Scheme 37. One approach involves propyl 1-propynyl sulfide (**108**), available from base-catalyzed isomerization[126] of propyl 2-propynyl sulfide (**107**), as the key intermediate. Lithium aluminum hydride converts **108** into (*E*)-1-propenyl propyl sulfide ((*E*)-**109**) while diisobutylaluminum hydride or trimethoxyaluminum hydride-cuprous bromide[127] converts **108** into (*Z*)-**109**. Lithium-liquid ammonia reduction of (*E*)- and (*Z*)-**109** gives lithium (*E*)- and (*Z*)-1-propenethiolate (**110**), which are treated with the appropriate thiosulfonate to afford alkyl (*E*)- and (*Z*)-1-propenyl disulfides (**111**). Oxidation of (*E*)- and (*Z*)-**111** affords (*E*)-**105**/(*E*)-**106** and (*Z*)-**105**/(*Z*)-**106**, respectively. A second approach to (*E*)- and (*Z*)-1-propenethiolate (**110**) involves lithiation at −110 °C of readily available pure (*E*)- and (*Z*)-1-bromo-1-propene[128, 129] (**112**) followed by treat-

ment of each lithio compound with styrene sulfide. The unique ^{1}H- and ^{13}C-NMR chemical shifts for **105**/**106** are useful[130] in determining the composition of *Allium* extracts.[21, 135a]



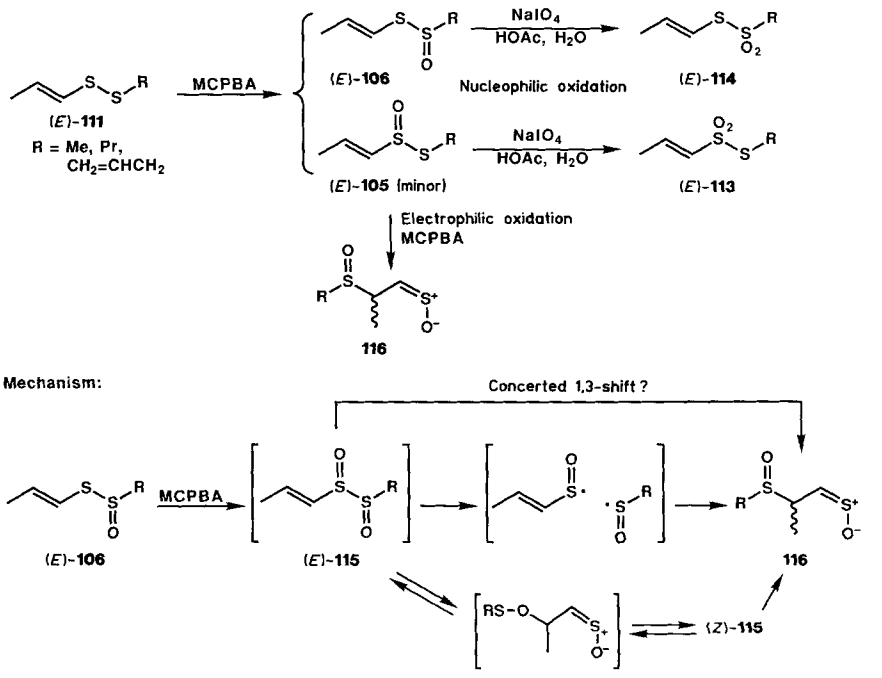
Scheme 37. Synthesis of the α,β-unsaturated thiosulfinates **105** and **106**.

E,Z-Isomerization of mono-α,β-unsaturated thiosulfinates: All attempts to isolate pure samples of (*E*)- or (*Z*)-**106** from mixtures with **105** always led to mixtures of (*E,Z*)-**106**. Furthermore stereochemically pure samples of (*E*)-**105**/(*E*)-**106** or (*Z*)-**105**/(*Z*)-**106** were converted during the course of one hour at 25 °C into (*E*)-**105**/(*E,Z*)-**106** or (*Z*)-**105**/(*E,Z*)-**106**, respectively. This facile isomerization of isomers of **106**, but not **105** or precursor disulfides **111**, can be explained by a [2,3]-sigmatropic rearrangement (Scheme 38) analogous to reactions of allylic sulfoxides or methallyl 2-methyl-2-propenethiosulfinate.[131] This isomerization explains the puzzling observation that although only (+)-*S*-(*E*)-1-propenyl-L-cysteine *S*-oxide (**5**) occurs naturally, affording, it is assumed, only (*E*)-1-propenesulfenic acid ((*E*)-**14b**), both (*E*)- and (*Z*)-**106**, but only (*E*)-**105**, are found in *Allium* extracts and distillates. Compound **105**, of course, is incapable of isomerization by the mechanism of Scheme 38.



Scheme 38. Interconversion of (*E*)- and (*Z*)-1-propenyl alkanethiosulfinate geometric isomers **106**. The half-life at 25 °C is ca. 1 h.

Oxidation of mono-α,β-unsaturated thiosulfinates: We have examined the oxidation of **105**/**106** as a route to the corresponding thiosulfonates **113**/**114**, of interest as natural products themselves (e.g. methyl (*E*)-propenethiosulfonate, (*E*)-**113**, R = Me, has been isolated from *Allium grayi*)[132] as well as synthetic reagents for preparation of α,β-unsaturated disulfides. "Nucleophilic" oxidation[133] of (*E*)-**105**/(*E*)-**106** or (*Z*)-**105**/(*Z*)-**106** using sodium metaperiodate/acetic acid gave (*E*)-**113**/(*E*)-**114** or (*Z*)-**113**/(*Z*)-**114** (R = Me, Pr, All) with no stereoisomerization (Scheme 39). Unlike (*E*)- and (*Z*)-**106**, stereoisomers of **114** were configurationally stable, showing no tendency to undergo *E,Z*-isomerization. "Electrophilic" oxidation[133] of either (*E*)-**105**/(*E*)-**106** or (*Z*)-**105**/(*Z*)-**106** with MCPBA gave identical 1:1 mixtures of



Scheme 39. Nucleophilic and electrophilic oxidation of 1-propenyl alkanethiosulfinates (**106**) and alkyl 1-propenethiosulfinates (**105**) furnishing thiosulfonates **113**/**114** and α-sulfinylsulfines **116**.

compounds characterized as (*Z*)-2-(alkanesulfinyl)propanethial *S*-oxide (*Z*)-**116** (see below for NMR assignment of sulfine stereochemistry as *Z*). We presume that initial oxidation of **105**/**106** gives α-disulfoxide **115**. While **115** could undergo pseudopericyclic[134] rearrangement to **116**, stereochemistry would be expected to be conserved, which is not the case. Therefore either: 1) stereochemistry in **115** is lost through [2,3]-sigmatropic rearrangement (Scheme 39) which is more rapid than pseudopericyclic processes; 2) *two* diastereomers of **115** are formed initially; or 3) a free radical mechanism (Scheme 39) is involved in conversion of **115** into **116**.[135a]

5.2.5. *Bis-α,β-unsaturated Thiosulfinates*

"Is there any point to which you would wish to draw my attention?"
"To the curious incident of the dog in the nighttime."
"The dog did nothing in the nighttime."
"That was the curious incident," remarked Sherlock Holmes.

"Silver Blaze"
Sir Arthur Conan Doyle (1859–1930)

What is unusual about the thiosulfinates isolated from cut *Allium* spp. is the *complete absence* of bis-α,β-unsaturated derivatives, despite the preeminence of the bis-β,γ-unsaturated thiosulfinate allicin (**1**) from garlic and the abundance of mono-α,β-unsaturated thiosulfinates from onion. Our curiousity piqued, we examined synthetic approaches to 1-propenyl 1-propenethiosulfinates. Serendipitously, while these efforts were underway, Professor Hildebert Wagner invited our participation in a study of some unusual organosulfur compounds isolated by his doctoral student, Thomas Bayer.[136] This collaborative study led to some fascinating chemistry, detailed below.

2,3-Dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxides ("zwiebelanes"): Two isomers **117** and **118** (smaller amounts of latter) were isolated as colorless oils of formula $C_6H_{10}OS_2$ following chromatography of onion extracts. Compound **117** showed intense IR bands at 1065 and 1085 cm^{-1} (S=O) and UV $\lambda_{max} = 250$ nm. NMR data for **117** and **118** are discussed in Section 5.3.3. The above spectroscopic data, the chemical shifts in presence of $Eu(fod)_3$ shift reagent and aromatic solvents, as well as the synthetic results described below point to **117** and **118** having the structures (1α,2α,3α,4α,5β)- and (±)-(1α,2α,3β,4α,5β)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide, respectively (Fig. 7). These two compounds were given the trivial names *cis*- and *trans*-zwiebelane ("zwiebel" is German for onion), respectively.[137] Compounds **117** and **118** have been isolated by us from extracts of shallot, scallion and chive as well. The mixture of **117** and **118** showed a 65–90% inhibition of thrombin-induced TXB_2 biosynthesis in human platelet rich plasma at a concentration of 0.1–1.0 $mg\,mL^{-1}$. Recently, other examples of substituted 5,6-dithiabicyclo[2.1.1]hexanes have been reported.[138]

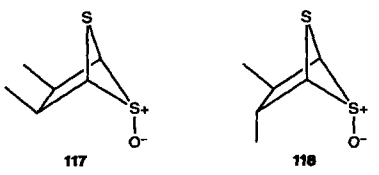
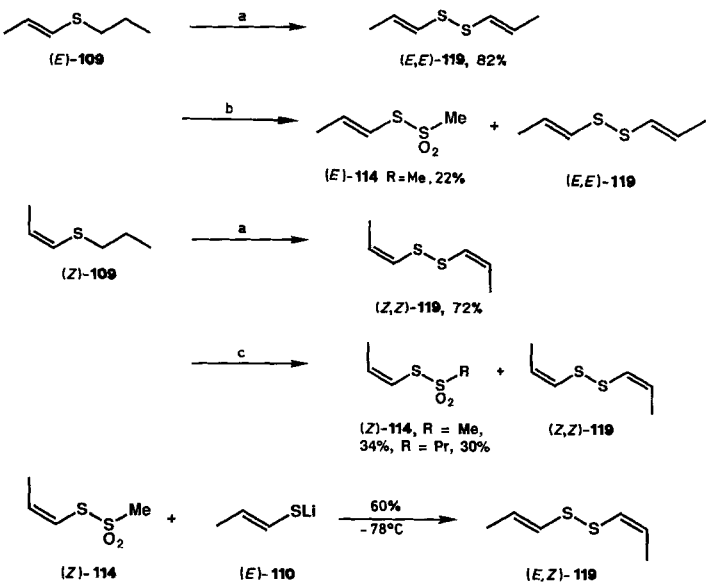


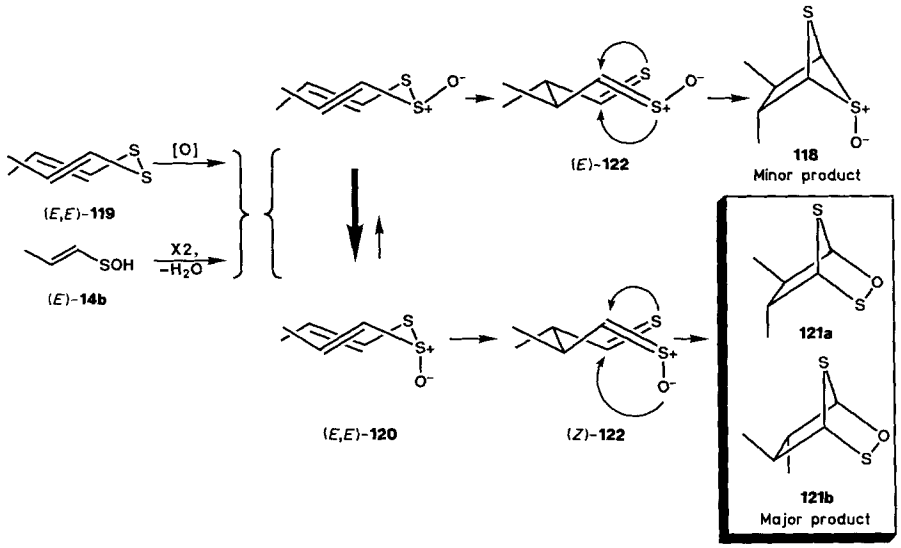
Fig. 7. Isomeric "zwiebelanes" **117** and **118** isolated from onion extracts.

Monooxidation of the isomeric bis(1-propenyl) disulfides: The isomeric bis(1-propenyl) disulfides (*E,E*)-**119** and (*Z,Z*)-**119** were prepared by oxidation of lithium (*E*)- and (*Z*)-1-propenethiolate ((*E*)-**110** and (*Z*)-**110**) while (*E,Z*)-bis(1-propenyl) disulfide ((*E,Z*)-**119**) was prepared by reaction of (*E*)-**110** with (*Z*)-1-propenyl methanethiosulfonate ((*Z*)-**114**) at −78 °C (Schemes 37 and 40).[135d] Compound (*Z*)-**114** can be conveniently synthesized through reaction of (*Z*)-**110** with methanesulfonyl chloride; the latter reagent can also be used for the conversion of (*E*)-**110** and (*Z*)-**110** into (*E,E*)-**119** and (*Z,Z*)-**119**, respectively (Scheme 40).[135c] Isomers of **119** can be separated by preparative HPLC on a C-18 reverse phase column. While (*E,E*)-**119** and (*Z,Z*)-**119** are relatively stable at room temperature, (*E,Z*)-**119** disproportionates on standing to a mixture of all three isomers of **119**.



Scheme 40. Synthesis of (*E,E*)-, (*Z,Z*)-, and (*E,Z*)-bis(1-propenyl) disulfide **119**. For the reaction **109** → **110** cf. Scheme 37. a: 1) Li/NH_3; 2) $2\,MeSO_2Cl$, −78 °C; 3) H_2O. b) 1) Li/NH_3; 2) $20\,MeSO_2Cl$, −78 °C; 3) H_2O. c) 1) Li/NH_3; 2) $20\,RSO_2Cl$, −78 °C; 3) H_2O.

Solutions of pure isomers of **119** in $CDCl_3$ at −60 °C were treated with chilled solutions of MCPBA in the presence of one equivalent of anhydrous sodium carbonate. After 5 min the reaction mixture was transferred to an NMR tube cooled to −60 °C and placed in a −60 °C NMR probe. Thus, (*E,E*)-**119** gave (*E*)-1-propenyl (*E*)-1-propenethiosulfinate ((*E,E*)-**120**) (Scheme 41), (*Z,Z*)-**119** gave the (*Z,Z*)-isomer, ((*Z,Z*)-**120**) (Scheme 42), and (*E,Z*)-**119** gave a ca. 2:1 mixture of (*Z*)-1-propenyl (*E*)-1-propenethiosulfinate ((*E,Z*)-**120a**) and (*E*)-1-propenyl (*Z*)-1-propenethiosulfinate ((*E,Z*)-**120b**) (Scheme 43). Qualitative studies indicate that the relative rates of oxidation are (*E,E*)-**119** > (*E,Z*)-**119** > (*Z,Z*)-**119**. Assignment of structures to isomers

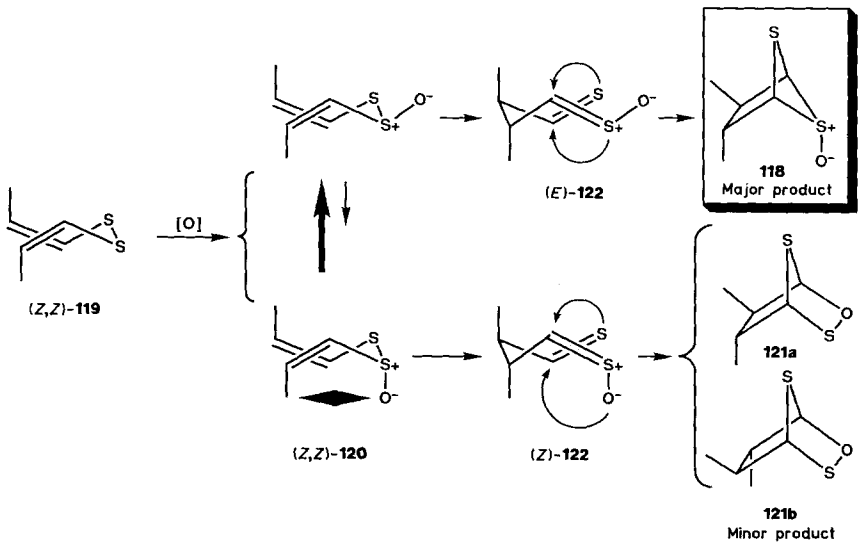


Scheme 41. Oxidation of (*E,E*)-bis(1-propenyl) disulfide (*E,E*)-**119** giving **121a** (via (*E,E*)-**120**). **122** always shown as the (2*S*,3*R*) form.

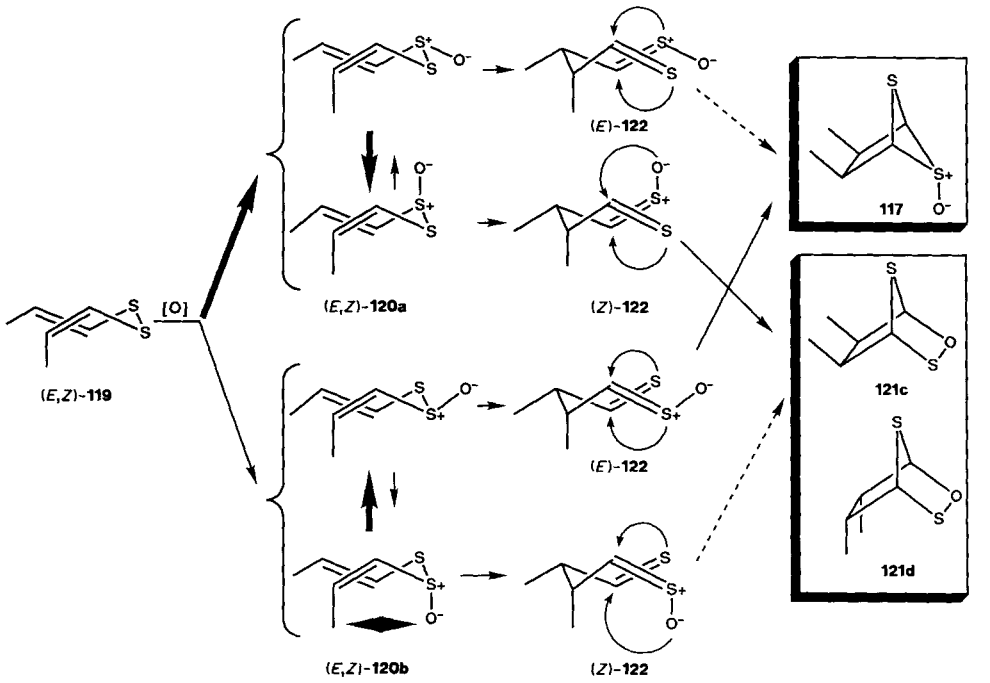
(*E,Z*)-**120a,b** is based both on kinetic considerations that the disulfide sulfur adjacent to a *cis* double bond is oxidized at a slower rate than the disulfide sulfur adjacent to a *trans* double bond, as well as on careful comparison of the ^{1}H and ^{13}C chemical shift data for thiosulfinates (*E,E*)-**120**, (*Z,Z*)-**120**, (*E,Z*)-**120a,b**, and the methyl 1-propenethiosulfinates (*E*)-**106** and (*Z*)-**106**, R = Me.

Solutions of thiosulfinates (*E,E*)-**120**, (*Z,Z*)-**120**, and (*E,Z*)-**120a,b** in NMR tubes with dioxane as internal standard were warmed to −15 °C. The disappearance of peaks associated with the thiosulfinates was followed with time. The so-determined first order rate constants for disappearance of thiosulfinates at −15 °C are $8.22\times10^{-4}\,s^{-1}$ for (*E,E*)-**120**, $4.13\times10^{-4}\,s^{-1}$ for (*E,Z*)-**120a,b**, and $3.02\times10^{-4}\,s^{-1}$ for (*Z,Z*)-**120**. From the rate data for disappearance (rearrangement) of (*Z,Z*)-**120** we calculate: $E_a = 16\,kcal\,mol^{-1}$, $\Delta H^{\neq} = 15.5\,kcal\,mol^{-1}$, $\Delta S^{\neq} = -15.3\,cal\,mol^{-1}K^{-1}$, and $\Delta G^{\neq} = 19.5\,kcal\,mol^{-1}$, all at 273 K. These values may be compared to those described in Section 5.2.3 for the Claisen and sulfoxide thio-Claisen rearrangements. If the ratio of these rate constants, 2.7:1.4:1, is compared to the analogous ratio for Claisen rearrangement of isomeric 1-propenyl 2-butenyl ethers,[139] it is apparent that the rate ratio for the rearrangement of thiosulfinates is contracted suggesting a more *advanced* transition state than for the Claisen rearrangement. The initial products of rearrangement are a 4.5:1 mixture of *endo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**121a**) and its *exo,endo*-isomer **121b** from (*E,E*)-**120** after 3 h at −40 °C, a 27:3:1 mixture of (±)-**118**, **121a** and **121b** from (*Z,Z*)-**120** after 3 h at −40 °C, and a 10:10:1 mixture of **117**, *exo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**121c**) and its *endo,endo*-isomer **121d** from (*E,Z*)-**120a,b** after 3 h at −40 °C (Schemes 41–43). Isomers **121** are bicyclic sultenes similar to compounds **43** and **56** (see Sections 4.4 and 5.1.2 and Schemes 14 and 16). Isomers **121** react rapidly with thiophenol giving ring-opened thiolane derivatives.

Mechanistic considerations: We propose that—following the oxidation of (*E,E*)-**119** with *one* equivalent of peroxy acid—the thiosulfinate ((*E,E*)-**120**) oxygen assumes a pseudoaxial orientation for the [3,3]-sigmatropic rearrangement since this orientation is also favored in 1,2-dithiane 1-oxides



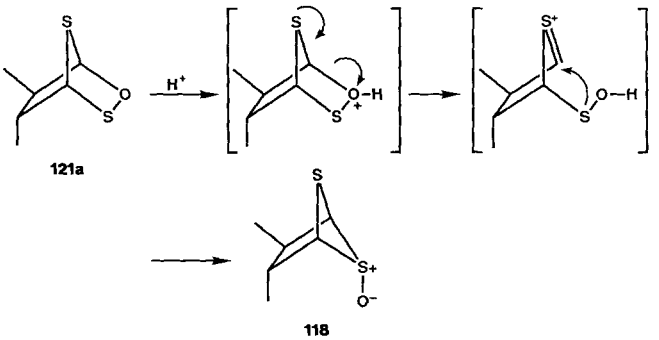
Scheme 42. Oxidation of (*Z,Z*)-bis(1-propenyl) disulfide (*Z,Z*)-**119** giving **118** (via (*Z,Z*)-**120**). **122** always shown as the (2*R*, 3*S*) form.



Scheme 43. Oxidation of (*E,Z*)-bis(1-propenyl) disulfide (*E,Z*)-**119** giving **117** and **121c** (via (*E,Z*)-**120a,b**). **122** always shown as (*R,R*) form.

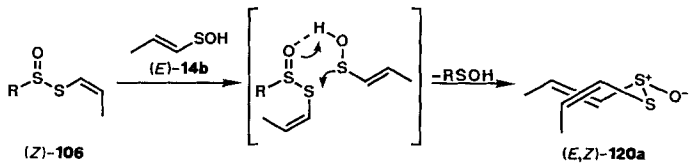
and in sulfoxide thio-Claisen rearrangements.[115,135b] Rearrangement from this transition state gives (*Z*)-(2*R*,3*S*/2*S*,3*R*)-2,3-dimethyl-1,4-butanedithial *S*-oxide ((*Z*)-**122**), which can assume an appropriate conformation to undergo a very facile intramolecular 1,3-dipolar cycloaddition of the $C{=}S^{+}{-}O^{-}$ group to the C=S function[88b] with formation of **121a,b** (Scheme 41), a structure similar to the well-known 2,5-dimethylthiophene–singlet oxygen adduct[140] and to 5,6-dimethyl-2,3,7-trithiabicyclo[2.2.1]heptane, recently isolated from scallion distillates.[141] Rearrangement of (*E,E*)-**120** should be facilitated by the weak S–S bond (the bond dissociation energy would be expected to be quite similar to that of phenyl benzenethiosulfinate, e.g. 35 kcal mol^{-1}). Subsequent cyclization should be aided by the very high reactivity of the thial group of (*Z*)-**122** as a 1,3-dipolarophile.[142] Precedence exists for formation of heterobicyclo[2.2.1]heptanes via intramolecular 1,3-dipolar cycloaddition reactions.[143] On the other hand, on analogous oxidation of (*Z,Z*)-**119**, steric effects associated with the *cis* double bonds lead the intermediate to adopt a transition state geometry in which thiosulfinate ((*Z,Z*)-**120**) oxygen is pseudoequatorial, resulting in the formation of (*E*)-(2*R*,3*S*/2*S*,3*R*)-2,3-dimethyl-1,4-butanedithial *S*-oxide ((*E*)-**122**), where the (*E*)-geometry of the $C{=}S^{+}{-}O^{-}$ group favors the [2+2] process yielding **118** over the sterically now more difficult 1,3-dipolar cycloaddition (Scheme 42). In the case of (*E,Z*)-**119** either pseudoaxial or pseudoequatorial thiosulfinate ((*E,Z*)-**120a**, (*E,Z*)-**120b**) oxygen transition state geometry is possible with the consequence that the heterobicyclo[2.1.1]hexane and heterobicyclo[2.2.1]heptane systems (**117** and **121c** respectively) are formed in comparable amounts (Scheme 43). While there is variation in the type of ring system formed on monooxidation of (*E,E*)-, (*Z,Z*)- and (*E,Z*)-**119**, there is complete stereoselectivity in carbon–carbon bond formation.[135b]

Problems are encountered in extending the above concepts of the mechanism of the monooxidation of stereoisomers of **119** to reactions that occur when onions are cut. We have shown that zwiebelane **118** originates from (*Z,Z*)-**120**. Formation of this latter compound in onion homogenates would require condensation of two molecules of (*Z*)-1-propenesulfenic acid ((*Z*)-**14b**). However, since (*Z*)-(+)-*S*-1-propenyl-L-cysteine *S*-oxide ((*Z*)-**5**) is not found in onions, and the barrier to interconversion of (*E*)- to (*Z*)-1-propenesulfenic acid is anticipated to be substantial (a 33 kcal mol^{-1} activation energy barrier separates ethenesulfenic acid and ethanethial *S*-oxide;[80] a similar barrier should exist for interconversion of (*E*)- and (*Z*)-**14b** by way of LF **16**), it is unlikely that the concentration of (*Z*)-**14b** would suffice for *self condensation* to take place. Furthermore, the detection of substantial amounts of alkyl (*E*)-1-propenethiosulfinates ((*E*)-**105**), *but not a trace of the Z-isomers* in *Allium* spp. extracts, also argues against the formation of significant amounts of (*Z*)-**14b** and thus of (*Z,Z*)-**120**. It is possible, under the conditions existing when onions are cut, that **121a** can isomerize to **118** (Scheme 44), and that **117** is similarly formed by isomerization of **121c**. Alternatively, a molecule of (*E*)-**14b** could react with a second molecule of (*E*)-**14b** that is hydrogen bonded to allinase (see Scheme 19; the



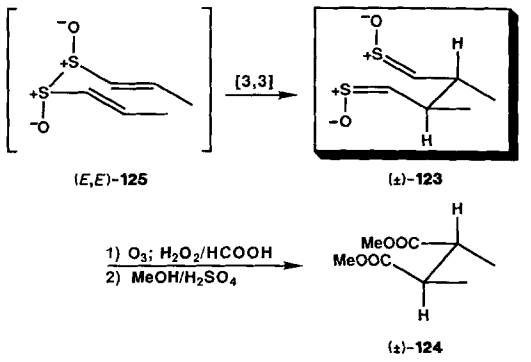
Scheme 44. Possible isomerization of **121a** to **118**.

dimeric/tetrameric structure proposed for allinase is consistent with the presence of more than one sulfenic acid molecule within the enzyme at any given time). The resultant (*E,E*)-**120**, if still associated with the allinase, may undergo a [3,3]-sigmatropic process from a more compact transition state, with the sulfoxide oxygen pseudoequatorial, to give **118**. (*E,Z*)-**120a**, the postulated precursor to **121c**, could be formed in onion homogenates through reaction of (*E*)-**14b** with (*Z*)-**106** (Scheme 45).



Scheme 45. Reaction of (*E*)-**14b** with (*Z*)-**106** giving (*E,Z*)-**120a**.

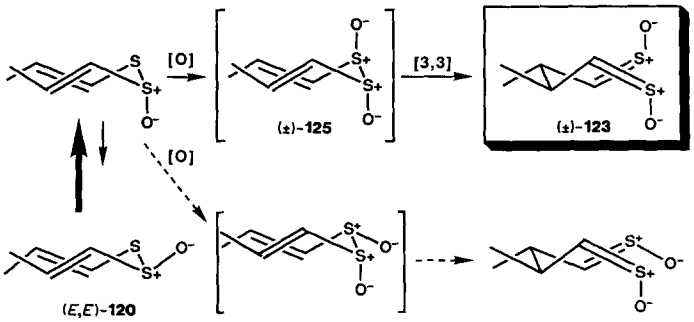
(Z,Z)-(±)-2,3-Dimethylbutanedithial S,S'-dioxide: Examination of the ^{1}H-NMR spectrum of onion extracts revealed the presence of a doublet at $\delta = 8.09$ just upfield from the position of the triplet for the methine proton in LF **16** ($\delta = 8.21$), suggesting the natural occurrence of a second sulfine.[77b, 144] Ultimately, compound **123** was isolated as a colorless solid of formula $C_6H_{10}S_2O_2$ which showed absorption bands at 1103 and 1120 cm^{-1} (C=S=O) in the IR spectrum. Sequential treatment of synthetic **123** (see below) with ozone (at −50 °C), H_2O_2/HCOOH and MeOH/H_2SO_4 gave in 88% yield a compound which according to GC-MS and ^{13}C-NMR was identical with an authentic sample of (±)-dimethyl 2,3-dimethylsuccinate ((±)-**124**), but different from an authentic sample of *meso*-**124**, thereby establishing **123** as (*Z,Z*)-(±)-2,3-dimethylbutanedithial *S,S'*-dioxide ((±)-**123**) (Scheme 46). The *Z,Z* arrangement of the CSO



Scheme 46. Proof of structure of bis-sulfine **123** by ozonolysis. **123** and **125** always shown as (*R,R*) form.

group was established by NMR methods similar to those used with **16** (see Section 5.3.1). Compound **123** is unique as the first example of a bis(thial *S*-oxide); so far, also only a single example of a bis(thione *S*-oxide) is known.[145]

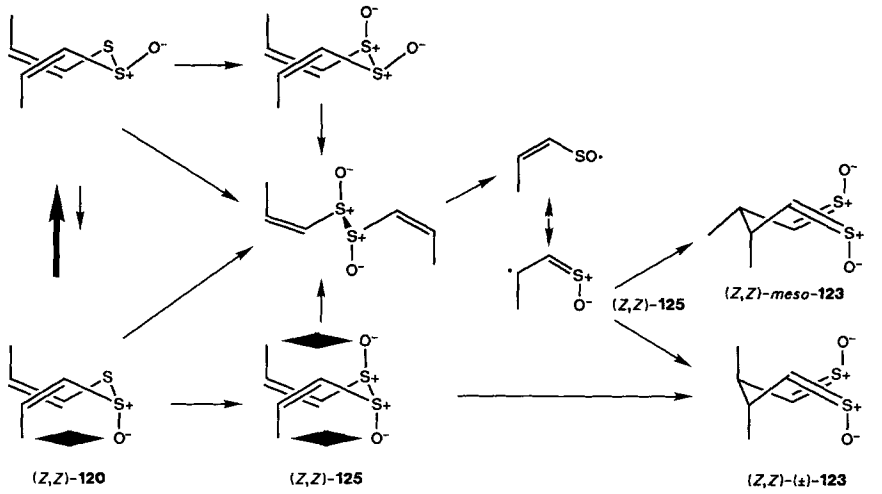
Bis-oxidation of bis(1-propenyl) disulfides; mechanistic considerations: The close relationship that **123** bears to intermediate (*Z*)-**122** in Scheme 41 suggests that **123** originates via a novel double sulfoxide-accelerated dithio-Claisen rearrangement of (*E,E*)-bis(1-propenyl) *vic*-disulfoxide ((*E,E*)-**125**) (Scheme 46). Indeed, oxidation of (*E,E*)-**119** with 2.2 equivalents of MCPBA at −60 °C or of (*E,E*)-**120** with one equivalent of MCPBA (Scheme 47) leads to a product identical to **123** isolated from onion extracts.[144] Oxidation of (*E,E*)-**120** should give (*E,E*)-**125** with an *anti* (diaxial) arrangement of the oxygens, which represents an energy minimum according to theoretical calculations on model systems.[146] This geometry of (*E,E*)-**125** correlates with (*Z*)-CSO geometry in **123** (Scheme 47). Compound (*E,E*)-



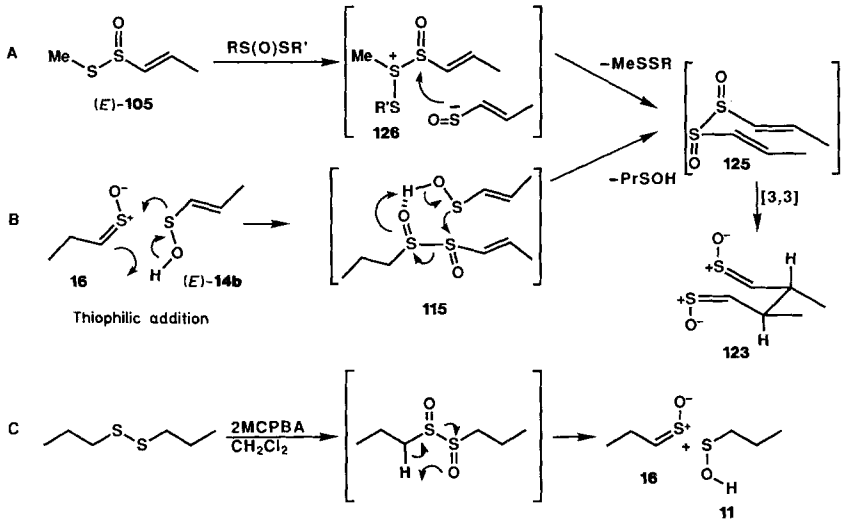
Scheme 47. Oxidation of (*E,E*)-**120** to (±)-**123** (shown as (*S,S*) form).

125 should undergo particularly facile [3,3]-sigmatropic rearrangement due to the weakness of the S–S bond (comparable with the S–S bond in diphenyl *vic*-disulfoxide, i.e. ca. 26 kcal mol^{-1}) as well as the rate-enhancing effect of the two zwitterionic sulfinyl functions.[113] This assumption is in agreement with the observation that (*E,E*)-**125** could not be detected in low-temperature NMR studies[147] of the oxidation of (*E,E*)-**120**. In contrast, to the stereospecificity seen in the oxidation of (*E,E*)-**120** or its precursor (*E,E*)-**119**, oxidation of (*Z,Z*)-**119** with two equivalents of MCPBA gives a 2:1 mixture of (±)-**123** and *meso*-**123** (Scheme 48).[135b] In this case, for the second oxygen to be antiperiplanar to the first, the bis(1-propenyl) *vic*-disulfoxide (*Z,Z*)-**125** would have to assume an open conformation unsuitable for [3,3]-sigmatropic rearrangement, and favoring a homolytic process.[135b]

How is **123** formed in onion extracts? One possibility would involve thioalkylation of (*E*)-**105** (R = Me) giving thiosulfonium ion **126**, which could undergo nucleophilic displacement at the sulfinyl sulfur by (*E*)-1-propenesulfenate (Scheme 49A). A second possibility would involve "thiophilic" addition of (*E*)-**14b** to **16** (Scheme 49B; the reverse of *vic*-disulfoxide decomposition,[148] shown in Scheme 49C) followed by nucleophilic attack of a second molecule of (*E*)-**14b** on *vic*-disulfoxide intermediate **115**. A weakness of both mechanisms is the need for one reactive intermediate ((*E*)-**14b** or its anion) to attack another one (**126** or **115**). An additional problem with the second mechanism is that attack of (*E*)-**14b** on **115** would have to occur more readily than the rate of rearrangement **115** to **116** (see Scheme 39), since the latter is not found in onion extracts.



Scheme 48. Oxidation of (*Z*,*Z*)-**120** to (±)-**123** (shown as (*R*,*R*) form) and *meso*-**123**.

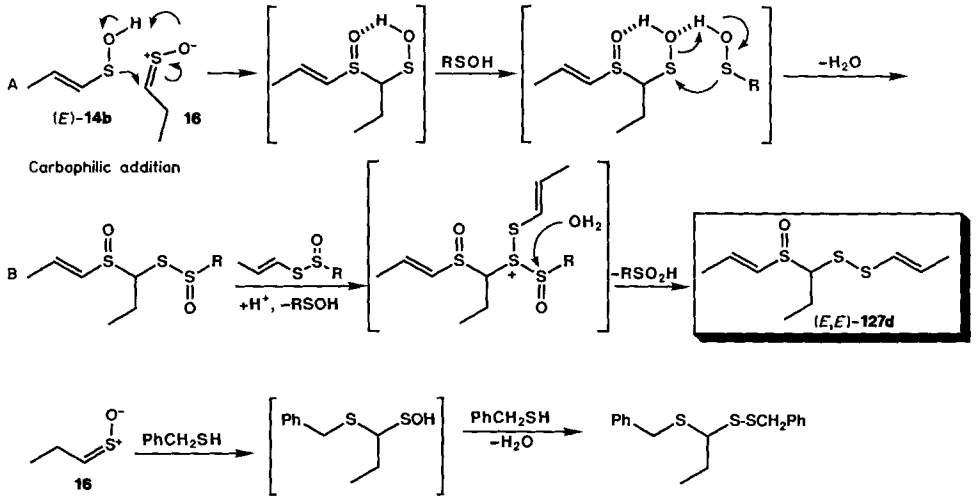


Scheme 49. Proposed mechanisms for formation of bissulfine **123** in onion homogenates. A–C, see text.

5.2.6. Cepaenes

Isolation of cepaenes and mechanisms of formation: In 1988 Kawakishi and Morimitsu identified methyl 1-(methylsulfinyl)propyl disulfide (**127a**, R = R′ = Me) as a new platelet aggregation inhibitor from onion extracts.[149a] Simultaneously, Wagner et al. reported the isolation of diastereomeric pairs 1-((*E*)-1-propenylsulfinyl)propyl propyl disulfide (**127c**) (R = (*E*)-MeCH=CH, R′ = Pr) and 1-((*E*)-1-propenylsulfinyl)propyl (*E*,*Z*)-1-propenyl disulfide (**127d**) (R = (*E*)-MeCH=CH, R′ = (*E*,*Z*)-MeCH=CH) as cyclooxygenase and 5-lipoxygenase inhibitors from onion extracts.[125c, 136] Wagner proposed that the onion α-sulfinyl disulfides be called "cepaenes". Later it was reported that: 1) other cepaenes could be isolated including 1-(methylsulfinyl)propyl (*E*,*Z*)-1-propenyl disulfide (**127b**, R = Me, R′ = (*E*,*Z*)-MeCH=CH);[149b] 2) individual enantiomers of diastereomeric pairs showed only a twofold to fourfold difference in biological activity, contrary to expectations of substantial differences associated with stereospecific enzymatic recognition;[149c] 3) cepaenes display a variety of types of interesting biological activity (see Section 7.3);[125a, b, 149d, 150] 4) by combining fresh onion and garlic juice, various mixed cepaenes, including some with allylic groups, can be prepared.[149d] A mechanism for formation of cepaenes in onion juice is proposed (Scheme 50A).[135c, 144, 149c, d] Precedence for "carbophilic" addition of (*E*)-**14b** to **16** includes addition of thiols to **16** (Scheme 50B)[151] and sulfenic acids to thiones.[152] α-Alkylthiodisulfides ("deoxycepaenes") are found in distilled oils of shallot and scallion, e.g. ethyl-1-(methylthio)propyl disulfide,[95] methyl 1-(methylthio)propyl disulfide, 1-(methylthio)propyl propyl disulfide,[153] 1-(methylthio)-propyl 1-propenyl disulfide, 1-propenyl-1-(propylthio)-propyl disulfide, and 1-propenyl-1-(1-propenylthio)propyl disulfide.[141, 153, 154] It is not known whether these compounds originate via deoxygenation of cepaenes, either in solution or in the inlet of a gas chromatograph, or through entirely different mechanisms.

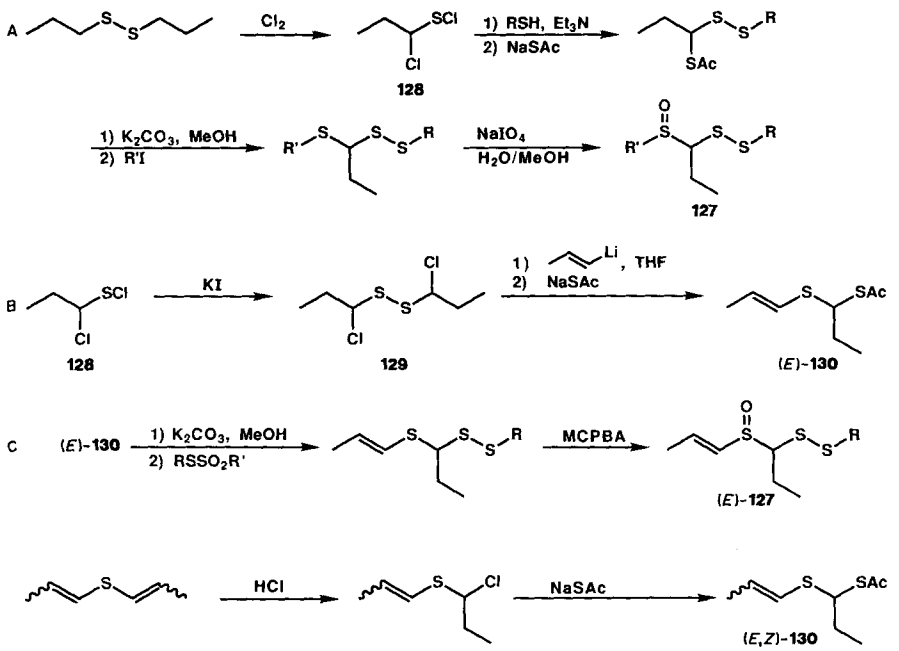
Synthesis of fully saturated cepaenes: In 1973 we reported that refluxing alkyl alkanethiosulfinates in benzene/water affords α-sulfinyl disulfides, e.g. **33** or **34** (Scheme 11).[54d] The isolated yield of **33** was high, whereas the yield of **34** was quite low. A more efficient synthesis of the saturated cepaenes such as **127a** was developed starting from 1-chloropropanesulfenyl chloride (**128**) via: 1) nucleophilic attack on



Scheme 50. Proposed mechanism for formation of cepaenes **127** in onion homogenates. A, B see text.

the sulfenyl chloride group by an alkanethiol with formation of an alkyl 1-chloropropyl disulfide; 2) replacement of the α-chloride by thioacetate; 3) hydrolysis and alkylation of the latter giving an alkyl 1-(alkylthio)propyl disulfide; 4) oxidation of the latter to the alkyl 1-(alkylsulfinyl)propyl disulfide **127**, formed as diastereomeric pairs (Scheme 51 A). When methanethiol was used, **128** could be directly converted into methyl 1-(methylthio)propyl disulfide.[155a]

chloride by thioacetate to give **130**; 3) hydrolysis of **130** followed by thioalkylation with an alkyl alkanethiosulfonate to give an alkyl 1-((*E*)- or (*Z*)-1-propenylthio)propyl disulfide; 4) oxidation of the latter to the alkyl 1-((*E*)- or (*Z*)-1-propenylsulfinyl) propyl disulfide diastereomers (Scheme 51 B). An alternative non-stereospecific synthesis of **130** involves addition of one equivalent of HCl to bis(1-propenyl) sulfide followed by displacement of the α-chlo-

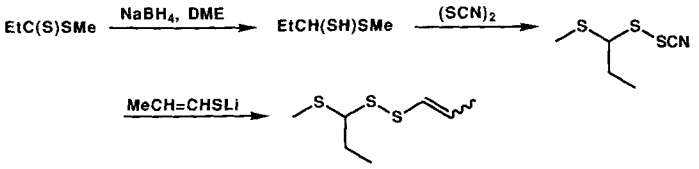


Scheme 51. Synthesis of fully saturated and singly unsaturated cepaenes. A–C see text.

Synthesis of singly unsaturated cepaenes: In the above syntheses, the sulfenyl chloride group becomes the disulfide function of **127** while the α-chloride of **128** becomes the alkylsulfinyl group. The fate of these groups is reversed in a synthesis of singly unsaturated cepaenes, which involves: 1) oxidation of **128** to bis(1-chloropropyl) disulfide (**129**); 2) treatment of **129** with (*E*)- or (*Z*)-1-propenyllithium at low temperature followed by immediate displacement of the α-

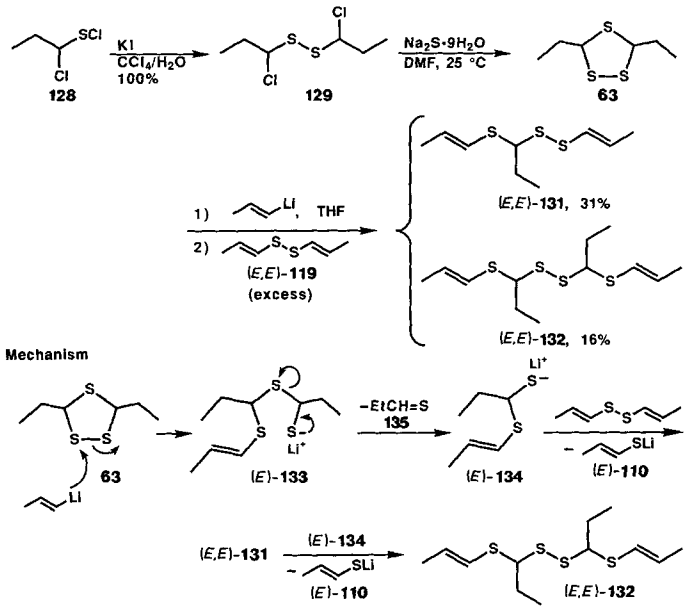
rides by thioacetate (Scheme 51 C). 1-(Methylthio)propyl (*E,Z*)-1-propenyl disulfide (a deoxycepaene) has been synthesized from methyl dithiopropionate (Scheme 52).[156]

Synthesis of doubly unsaturated cepaenes: Two novel syntheses of doubly unsaturated cepaenes have been developed. The first involves 3,5-diethyl-1,2,4-trithiolane (**63**), a component of onion oil. Treatment of **63** with (*E*)-1-propenyllithium followed by bis((*E*)-1-propenyl) disulfide ((*E*)-**119**) gives



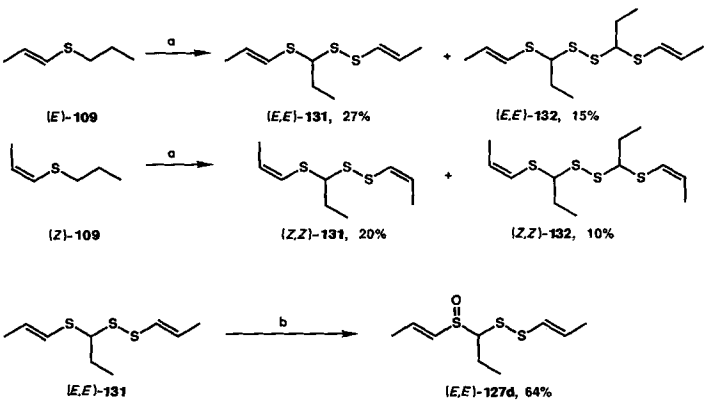
Scheme 52. Synthesis of the deoxycepaene 1-(methylthio)propyl (*E,Z*)-1-propenyl disulfide; total yield 36%.

the deoxycepaenes (*E,E*)-6-ethyl-4,5,7-trithiadeca-2,8-diene (**131**; 31%) and (*E,E*)-6,8-diethyl-4,6,7,9-tetrathiadodeca-2,10-diene (**132**; 16%) (Scheme 53).[135d, 155b] We suggest that the initial product (**133**) from ring-opening of **63** fragments to **134** and propanethial (**135**) at a rate competitive with nucleophilic attack on (*E,E*)-**119** to form **132**. The reverse of the fragmentation reactions, carbophilic addition to **135**, may also take place.

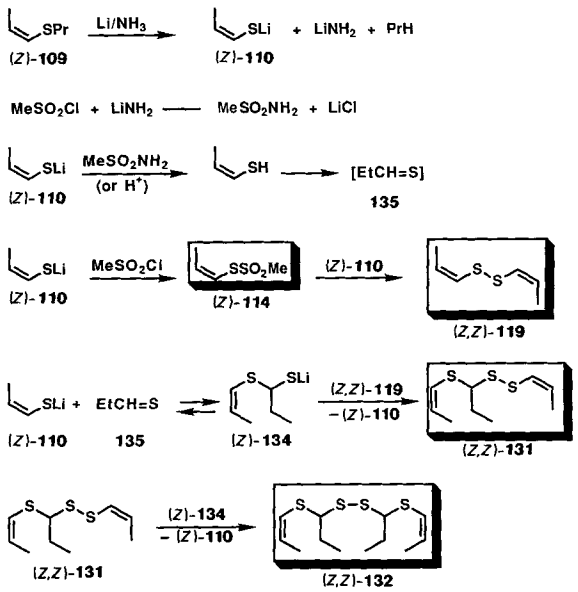


Scheme 53. Synthesis of doubly unsaturated deoxycepaenes **131** and **132** via 3,5-diethyl-1,2,4-trithiolane **63**.

A second synthesis of **131** and **132** also involves fragmentation of α-(alkenylthio)alkanethiolates such as **134** to thials such as **135**. This synthetic route was developed in connection with a study concerning the use of mesyl chloride as an alternative to iodine for stereospecific conversion of (*E*)- or (*Z*)-1-propenethiolate (**110**) into (*E,E*)- or (*Z,Z*)-**119**, respectively (Schemes 37 and 40).[135d] While treatment of (*E*)-**110** (from lithium-ammonia cleavage of (*E*)-**109**) with two equivalents of mesyl chloride gave (*E,E*)-**119** in 82% yield, use of 0.7 equivalents of mesyl chloride led instead to a mixture of (*E,E*)-**131** (27%) and (*E,E*)-**132** (15%). Similarly, while treatment of (*Z*)-**110** (from (*Z*)-**109**) with 2 equivalents of mesyl chloride gave (*Z,Z*)-**119** in 72% yield, use of 0.7 equivalents of mesyl chloride led to a mixture of (*Z,Z*)-**131** (20%) and (*Z,Z*)-**132** (10%). Oxidation of (*E,E*)-**131** with MCPBA led to a 2:1 diastereomeric mixture of the cepaene (*E,E*)-6-ethyl-4,5,7-trithiadeca-2,8-diene 7-oxide **127d** (64%) which could be separated by chromatography. The results in Scheme 54 can be explained by the mechanism shown in Scheme 55.[135d]



Scheme 54. Synthesis of **131**, **132**, and **127d**. (*E,E*)-**127d** formed as a chromatographically separable 2:1 mixture of diastereomers. a: 1) Li/NH_3; 2) 0.7 $MeSO_2Cl$, −60 °C; 3) −5 °C 1.5 h; H_2O. b) 100% MCPBA, −78 °C, CH_2Cl_2.



Scheme 55. Mechanism for formation of (*Z,Z*)-**131** and (*Z,Z*)-**132** by reaction of (*Z*)-**110**, obtained by liquid ammonia reduction of (*Z*)-**109**, with mesyl chloride.

5.3. Characterization of Organosulfur Constituents of *Allium* Preparations by Nuclear Magnetic Resonance Spectroscopy

My dear Watson, you see but you do not observe!

Sir Arthur Conan Doyle (1859–1930)

Of the analytical techniques available for the study of such sensitive organosulfur compounds as are associated with *Allium* spp., none is more powerful than NMR spectroscopy. It permits the direct observation of all of the relevant nuclei (H, C, O) at low as well as ambient temperatures. A broad range of chemical shifts are observed, allowing identification of the components of complex mixtures. The configuration

can be determined by analysis of coupling constants, facilitated by two-dimensional NMR methods, and by studying solvent- or reagent-induced chemical shift effects in compounds containing the sulfinyl group. With the more unusual organosulfur components, novel NMR effects abound.

5.3.1. NMR Study of the Onion Lachrymatory Factor (LF) and Related Sulfines

Sulfines (thiocarbonyl *S*-oxides) play an important role in *Allium* chemistry. We have studied the *S*-oxides of ethanethial (**44**), propanethial (**16**), (trimethylsilyl)methanethial (**66**), and 2-(alkanesulfinyl)propanethial (**116**), as well as the bissulfine (±)-2,3-dimethyl-1,4-butanedithial *S,S'-dioxide* (**123**). The stereochemistry about the C=S bonds was established by NMR methods.

The NMR spectrum of onion lachrymatory factor (LF) **16** in $CDCl_3$ shows a downfield methine triplet at $\delta = 8.21$ ($J = 7.81$ Hz), in agreement with the spectrum of **16**, which was prepared from propanesulfinyl chloride (**19**) or by pyrolysis of (*E,Z*)-*tert*-butyl 1'-propenyl sulfoxide (**58**). Examination of the NMR spectrum of the natural **16** in $CDCl_3$ reveals the presence of a second downfield triplet at $\delta = 8.88$ ($J = 8.79$ Hz), with ca. 5% of the area of the triplet at $\delta = 8.21$. This minor triplet, not reported in earlier NMR studies of LF **16**, was found to be present at somewhat lower intensity in the NMR spectrum of synthetic **16**. In C_6D_6, **16** shows downfield triplets at $\delta = 7.61$ (major triplet; $J = 7.82$ Hz) and 8.37 ppm (minor triplet; $J = 8.89$ Hz).[77b, 157]

Thus, the NMR spectrum of **16** reveals a minor triplet $\Delta\delta = 0.67-0.68$ downfield from the major triplet in $CDCl_3$ and $\Delta\delta = 0.77$ downfield from the major triplet in C_6D_6. On using C_6D_6 instead of $CDCl_3$ as solvent, the major triplet was shifted $\Delta\delta = 0.59$, the minor triplet $\Delta\delta = 0.50$ to higher field. From a comparison of this NMR data with NMR data of related structures of the type RCH=N–X (X = OR, NR'R")[158] we concluded that **16** exists as a mixture of *E*- and *Z*-isomers, with the latter dominating. This assignment is consistent with the observation in the nitrogen systems that: 1) protons resonate at lower fields when *syn* than when *anti* to X in RCH=N–X; 2) *anti* protons are shifted further upfield than *syn* protons on changing the solvent from CCl_4 to C_6D_6; and 3) the coupling constant $J_{H_1H_\alpha}$ (e.g. $J_{H_1H_2}$ in **16**) is slightly larger in the *anti* compound than in the *syn* compound.[158] In analogy with the mechanism proposed for the aromatic solvent induced shifts in nitrogen systems[158] and sulfoxides,[73, 159] dipole forces should favor the orientation relative to benzene shown in Figure 8 in which the *anti*-proton in the (*Z*)-isomer (Et) should experience greater shielding than the *syn*-protons (R_2 = H) in the (*E*)-isomer.

Similar conclusions are drawn from consideration of solvent effects on the ^{1}H-NMR spectra of **44**, **66**, **116**, and **123**. In the case of the bissulfine **123** isolated from onion a *Z,Z*-configuration is assumed, since the HC=SO proton is shifted to even lower field ($\delta = 8.09$ in $CDCl_3$, $\delta = 7.06$ in C_6D_6), and this change of solvent influences the chemical shift even more strongly ($\Delta\delta = 1.03$) than in the case of the corresponding proton in (*Z*)-**16**. In the case of the sulfine **116** (R = Me and Pr) a *Z*-configuration is assumed, because of similarity of the chemical shifts of **116** and of (*Z*)-**16** (**116**, R = Me, diastereomer **A**: HC=SO appears as a doublet at $\delta = 8.27$ in $CDCl_3$ and $\delta = 7.19$ in C_6D_6; diastereomer **B**: HC=SO appears at $\delta = 8.44$ in $CDCl_3$ and $\delta = 7.62$ in C_6D_6; very similar effects are seen for the two diastereomers of **116**, R = Pr). Interestingly, in methanethial *S*-oxide (**40**) the chemical shifts of the two protons ($\delta = 7.84$ and 7.73 in $CFCl_3$[68]) are much closer together in value than in the higher homologs, perhaps due to the slight change in HCS angles. It is also of interest to contrast the chemical shift of the *H*C=S proton in 2,2-dimethylpropanethial (*t*BuCH=S)[160] at $\delta = 11.67$ with the chemical shift of this proton in 2,2-dimethylpropanethial *S*-oxide (*t*BuCH=SO) at $\delta = 7.62$ (*Z*)/9.00 (*E*) (all data recorded in $CDCl_3$ as solvent). While the C=S group deshields an attached proton relative to C=O, the C=SO group has the opposite effect!

The ^{13}C-NMR spectra of (*Z*)- and (*E*)-**16** show the resonances for *C*=SO at $\delta = 180.5$ and 184.5, respectively. The minor *E*-isomer shows deshielding at the sp^2-carbon center compared to the major *Z*-isomer. In the case of the sulfine **116** (R = Me or Pr) and the bissulfine **123** in $CDCl_3$, *C*=SO appears at $\delta = 175.92$ (**116**, R = Me), 176.24 (**116**, R = Pr), and 179.6 (**123**), values more consistent with a *Z*- rather than an *E*-configuration. These ^{13}C-NMR values for *C*=SO differ markedly from the value for H*C*=S in 2,2-dimethylpropanethial[160] ($\delta_C = 255.6$).

In the ^{17}O-NMR spectrum the signal for the sulfine oxygen atom of (*Z*)-**16** and (*Z*)-**44** appears at $\delta_O = 196$ and 199, respectively. These values may be compared to the ^{17}O chemical shifts of $SOCl_2$, $(MeO)_2S{=}O^*$, $Me_2S{=}O$, thiane *S*-oxide and thiolane *S*-oxide which have been determined as $\delta_O = 292$, 176, 13, −3, and 15, respectively.[49, 161] The strong deshielding of the oxygen in sulfines compared to that in simple sulfoxides may be a consequence of the enhanced electronegativity of carbon sp^2 orbitals attached to the sulfine sulfur compared to carbon sp^3 orbitals utilized in the sulfoxides, since other sulfinyl compounds containing electronegative substituents on sulfur are also deshielded relative to simple sulfoxides.

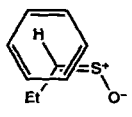


Fig. 8. Aromatic solvent induced shift (ASIS) effects on onion LF (*Z*)-**16**.

5.3.2. NMR Spectroscopy of the Dimer of LF: the Four-Membered Ring Sulfone Effect

The ^{1}H- and ^{13}C-NMR data of the LF dimer **18b** (see Scheme 24) and of the homolog *trans*-3,4-bis(trimethylsilyl)-1,2-dithietane 1,1-dioxide (**67**) (see Scheme 25) clearly indicate the presence of two substantially different, coupled, "CHR" groups, i.e. $-SO_2CHR$ and $-SCHR$. The difference in the δ_c values of the two pairs of methine carbon atoms (e.g. 97.9 and 39.2 in **18b** and 88.4 and 14.8 in **67**) is quite striking. While part of the difference is due to deshielding of the α-sulfonyl carbon atoms of thiosulfonates compared with sulfones,[162] and a vicinal deshielding effect due to the *trans*-ethyl or *trans*-trimethylsilyl groups (e.g. 2-methyloxetane and *cis*- and *trans*-2,3-dimethyloxetane show ^{13}C shifts

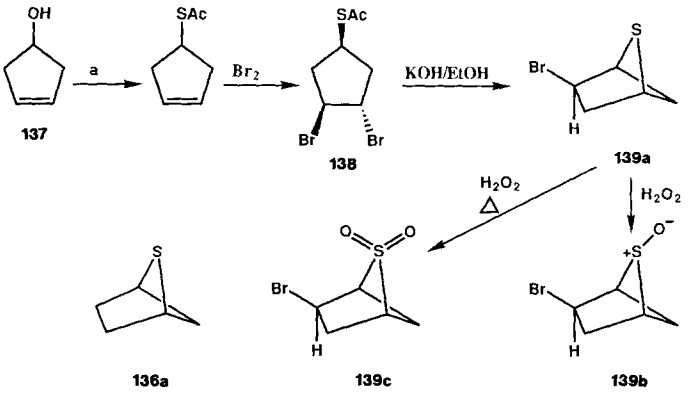
for C-2/C-3 at δ_c = 78.3/29.2, 79.6/31.8 and 85.0/37.4, respectively),[163] it is necessary to invoke an unusual deshielding effect characteristic of four-membered ring sulfones[164] to fully explain the magnitude of the difference.

Consider the ^{13}C-NMR shifts of the α-carbon atoms in the three- to six-membered ring sulfur heterocycles thiirane, thietane, thiolane and thiane (with –S– group), which are 18.1, 26.1, 31.7, 29.1. In the analogous sulfoxides (–S(O)–) and sulfones (–S(O_2)–) the values are 33.8, 52.7, 54.3, 49.0 and 31.6, *65.6*, 51.1, 52.6, respectively.[164] Note the downfield shift of the C_α-signal of $\Delta\delta$ = 40 on oxidation of thietane to thietane 1,1-dioxide and the downfield shift of $\Delta\delta$ = 13 in the oxidation of thietane 1-oxide to the 1,1-dioxide. With most sulfide-sulfoxide-sulfone systems, oxidation of a sulfide to a sulfone results in such a downfield shift of only $\Delta\delta$ = 20–25; very little difference is seen in the chemical shifts of the α-carbon atoms in the sulfoxides and sulfones, the latter sometimes even appearing slightly upfield of the former (cf., e.g., the above data for thiolane 1-oxide and 1,1-dioxide). The so-called "four-membered ring sulfone effect" contributes to the above noted differences in the chemical shifts of the methine carbon atoms in the sulfine dimers **18b** and **67**.

The unusual ^{13}C chemical shift effects for thietane 1,1-dioxides and related four-membered rings such as **18b** and **67** are reflected in similar but smaller effects in the ^{1}H and ^{17}O chemical shifts. Thus, unusually deshielded *H*CSO_2 protons are observed in **18b** (δ = 4.35) and **67** (δ = 5.06). The ^{17}O chemical shifts for thiirane, thietane, thiolane and thiane 1,1-dioxide appear at δ_O = 111, *182*, 165, and 142, respectively, once again showing maximum deshielding for the four-membered ring. Compound **18b** shows bands at δ_O = 210 and 243 which is notable for the substantial deshielding seen as well as the fact that *for the first time discrete ^{17}O chemical shifts are observed for nonequivalent sulfone oxygens.*[164] Additional examples of ^{17}O-NMR investigations on sulfones with diastereotopic protons have subsequently appeared in the literature.[165]

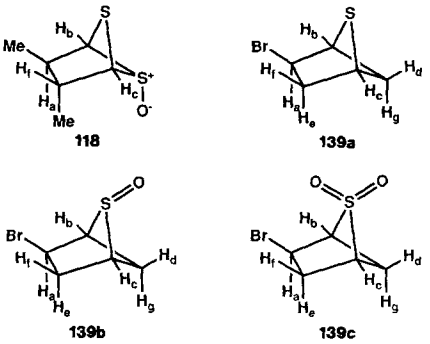
5.3.3. Comparative NMR Spectroscopy of Derivatives of Bicyclo[2.1.1]hexane, 5-Thiabicyclo[2.1.1]hexane, and 5,6-Dithiabicyclo[2.1.1]hexane

In connection with the identification of the zwiebelanes by ^{1}H- and ^{13}C-NMR spectroscopy, heterobicyclo[2.1.1]-hexanes were sought as model compounds for comparison of coupling constants. While 5-thiabicyclo[2.1.1]hexane (**136a**), its *S*-oxide **136b**, and its *S,S*-dioxide **136c** are known, the symmetry of **136** limits the number of H–H couplings seen. The synthesis of a less symmetrical derivative of **136a**, namely **139a**, was therefore developed (Scheme 56).[166] Exposure of 3-cyclopentenol (**137**) to Mitsunobu thioacetylation conditions affords *S*-3-cyclopentenylthioacetate, which was treated directly with bromine in CCl_4 to give the *trans*-1,2-dibromo derivative **138** in 54% overall yield. Treatment of **138** with KOH in aqueous ethanol at reflux for 90 hours afforded *exo*-2-bromo-5-thiabicyclo[2.1.1]hexane (**139a**) in 40% yield. Compound **139a** was oxidized to the corresponding sulfoxide **139b** and sulfone **139c** with H_2O_2/HOAc/CH_2Cl_2 at 0 °C and at reflux, respectively. Table 2 enables a comparison to be made of the NMR data for zwiebelane **118** with those for model compounds **139a–c**. It is noteworthy that



Scheme 56. Synthesis of 2-bromo-5-thiabicyclo[2.1.1]hexane **139a** and its *S*-oxides **139b** and **139c**. a: HSAc, Ph_3P, $EtO_2CN{=}NCO_2Et$.

Tabelle 2. ^{1}H- and ^{13}C-NMR data for compounds **118** and **139a–c**.



Cpd.		Position a	b	c	d	e	f	g
118	^{13}C	48.0	79.4	77.7			39.4	
	^{1}H	2.33	4.25	4.21			2.85	
	J_{HH}	J_{ab} 1.0 J_{af} 4.0	J_{bc} 6.7	J_{cf} 1.0				
139a	^{13}C	51.1	62.4	54.6	49.0	43.6		
	^{1}H	4.79	3.89	3.80	3.09	2.87	2.53	1.88
	J_{HH}	J_{ab} 2.2 J_{ae} 7.3 J_{af} 2.2	J_{bc} 6.2 J_{bd} 2.2	J_{cd} 2.2 J_{ce} 1.7 J_{cf} 0.7	J_{df} 2.2 J_{dg} 7.5	J_{ef} 13.0		
139b	^{13}C	41.3	68.5	63.0	33.6	22.8		
	^{1}H	4.49	3.88	3.66	1.17	2.97	2.79	1.49
	J_{HH}	J_{ab} 2.2 J_{ae} 7.8 J_{af} 3.2	J_{bc} 6.1 J_{bd} 2.2	J_{cd} 2.2 J_{ce} 2.2	J_{df} 2.2 J_{dg} 12.3	J_{ef} 13.4		
139c	^{13}C	38.3	78.5	72.0	33.6	31.8		
	^{1}H	4.49	4.14	3.98	(2.76)	(2.76)	2.65	1.76
	J_{HH}	J_{ab} 2.3 J_{ae} 10.7 J_{af} 4.6	J_{bc} 6.1	J_{cd} 2.3	J_{df} 2.3 J_{dg} 12.8	J_{ef} 12.8		

the $^4J_{HH}$ bridgehead-bridgehead coupling in **118** (6.7 Hz) is quite similar to that in **139a–c** (6.1 Hz) and that reported for bicyclo[2.1.1]hexane (6.23 Hz).[167] Apparently this large "W" long-range coupling is little affected by the nature of the "spacer atoms" between the CH groups.

5.3.4. *Diastereotopic Effects in Polysulfides*

The diastereotopic character of CH_2 protons in sulfinyl compounds is well known, and leads to complex NMR spectra for compounds such as allicin, alliin, and ajoene. It is less well recognized that the helical geometry of polysulfides can also lead to magnetic nonequivalence of methylene protons or enhancement of this effect in molecules containing other chiral centers. In the case of the ^{1}H-NMR spectra of compounds **140a–c** (Fig. 9) found in the distilled oil of garlic, we find that the $SCH_cCH_aH_bS$ group shows the *largest difference* between H_a and H_b in the case of **140c** ($\delta_a = 3.09$, $\delta_b = 3.17$, $J_{ab} = 14.1$ Hz, $J_{ac} = 8.7$ Hz, $J_{bc} = 6.5$ Hz). The

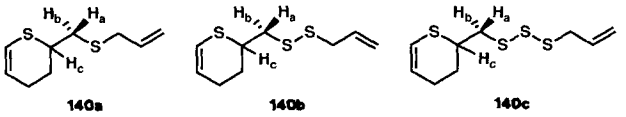


Fig. 9. 3,4-Dihydro-2*H*-thiopyran derivatives **140a–c**.

^{1}H-NMR spectrum of **140a** shows no separation of H_a and H_b while that of **140b** shows a separation of only $\Delta\delta = 0.01$ for these protons.[118]

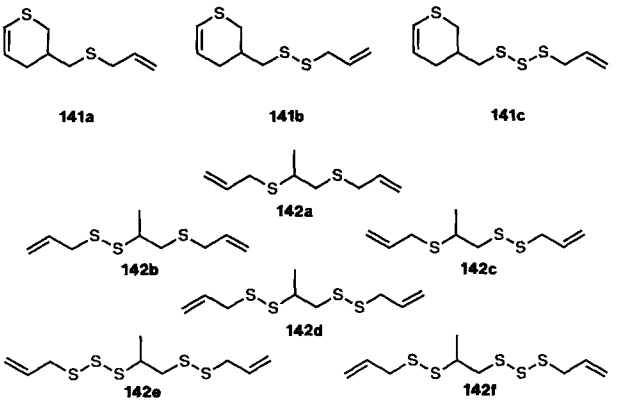
6. Steam-Distilled Oils

The earliest chemical studies on garlic and onion involved distillation procedures. While the first detailed chemical report of the preparation and analysis of the distilled oil of garlic appeared in 1844,[4] it is likely that many centuries earlier alchemists and pharmacists distilled garlic bulbs to produce potions for a plethora of ailments. Wertheim's 1844 paper attributes garlic's appeal to "the presence of a sulfur-containing, liquid body, the so-called garlic oil. All that is known about the material is limited to some meager facts about the pure product which is obtained by steam distillation of bulbs of *Allium sativum*. Since sulfur bonding has been little investigated so far, a study of this material promises to supply useful results for science." The components of garlic oil, separated by Wertheim by fractional distillation, were described as forms of "allylschwefel", establishing the garlic connection to the common name "allyl". Semmler[5] indicated that the principal constituents of the distilled oils of garlic and onion are, respectively, diallyl disulfide (**4b**) and a compound of formula $C_6H_{12}S_2$, structurally unspecified by him but suggested by others to be allyl propyl disulfide.[168] For the onion oil analysis, 5000 kg of onions were steam distilled, affording only 233 g (0.005%) of oil! Today the steam-distilled oils of garlic and onion are items of commercial importance for use both in food and health products.

6.1. Oil of Garlic

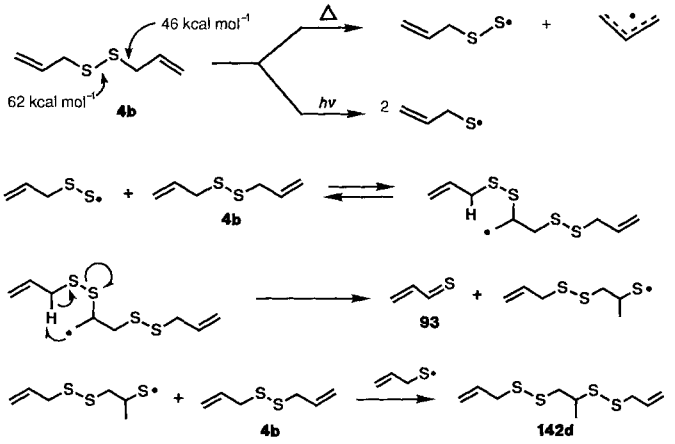
Although distilled garlic oil lacks the antibacterial and antithrombotic activity of the room temperature extract, it possesses equally interesting antitumor and antioxidant properties. Garlic oil and some of its components inhibit lipoxygenase (LO), one of the enzymes involved in arachidonic acid metabolism, which may be related to its antitumor activity and other biological properties. Two observations in particular prompted us to study the effect of heat on garlic oil: 1) Belman and Barany noted that ageing or heating of the garlic oil component allyl methyl trisulfide effected an increased inhibitory activity toward the soybean 15-lipoxygenase (LO) enzyme compared to a freshly synthesized sample;[169] 2) Granroth observed that "diallyl disulfide **4b** is slowly decomposed even at room temperature, and at 100 °C at least 25 reaction products were revealed by gas chromatography, the true number being still greater" and that "allylic compounds may undergo changes upon heating garlic-spiced foods, but the chemistry and possible physiological importance of these changes do not so far appear to have been investigated."[20] Analysis of the thermally more robust heavier compounds in garlic oil by GC and GC-MS suggested the presence of an unusual family of thiaheterocycles and acyclic compounds. The composition and origin of this group of compounds was clarified by examining the behavior of diallyl disulfide upon heating.

We have analyzed distilled garlic oil preparations using the inhibition of soybean lipoxygenase (LO) to determine the compounds responsible for its biological activities. We found that: 1) the LO-inhibitory activity of garlic oil increases upon heating and concentration; 2) GC-MS analysis of garlic oil revealed a group of previously unknown higher boiling cyclic and acyclic organosulfur compounds with two to five sulfur atoms (e.g. **140a–c**, **141a–c**, **142a–f**, Scheme 57); 3) most



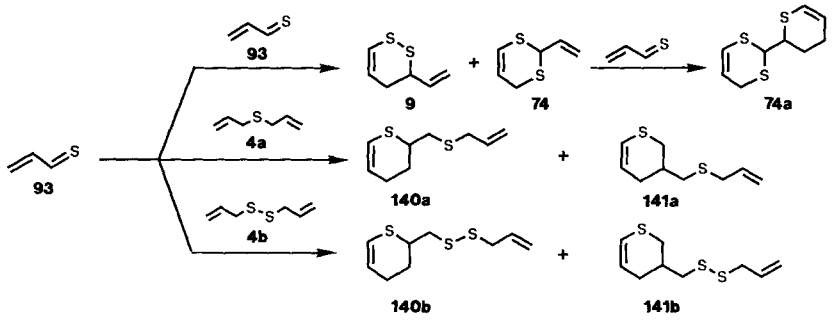
Scheme 57. Higher molecular weight compounds of type **140–142** from the pyrolysis of diallyl disulfide.

of these same compounds are generated upon heating pure samples of diallyl disulfide (**4b**); 4) the formation of these new compounds is best explained by a remarkable sequence involving thermal C–S homolysis of **4b** (rather than S–S homolysis, which only occurs upon photolysis), addition of the allyldithio radical in Markownikoff fashion to **4b**, intramolecular hydrogen atom abstraction-fragmentation of the radical adduct to produce thioacrolein (**93**, Scheme 58), and finally Diels–Alder addition of **93** as a heterodiene to diallyl sulfide (**4a**) and **4b** and dimerization to form **9** and **74** (Scheme 59).[118] The viability of such processes could be independently established using known thermal sources of **93** including allicin (Scheme 32) and diallyl sulfide (in a



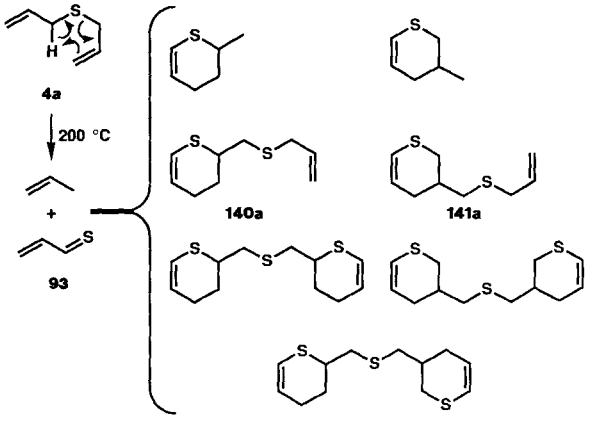
Scheme 58. Mechanism for decomposition of diallyl disulfide (**4b**).

An unexpected dividend to our examination of different thermal sources of **93** was our discovery that one of the most efficient low-temperature sources of **93** is diallyl sulfoxide (**143**)! Thus, when excess **143** is heated at 110 °C with dienophiles such as *N*-phenylmaleimide, dimethyl fumarate or ethyl acrylate, the corresponding thioacrolein Diels–Alder adducts such as **144** can be isolated in good to excellent yields (Scheme 61).[171] We suggest that the sulfur atom of reversibly formed allyl-2-propenesulfenate (**145**) acts as a nucleophile toward a second molecule of **145**, forming thiosulfonium ion **146**, a process similar to that observed with thiosulfinates (Schemes 11 and 31). Hydrolysis of **146** gives allicin **1**, known to be a low-temperature source of **93** (Scheme 32). When garlic oil is examined by HPLC, polysulfides with up to six sulfur atoms (e.g. All_2S_6, **4f**) are



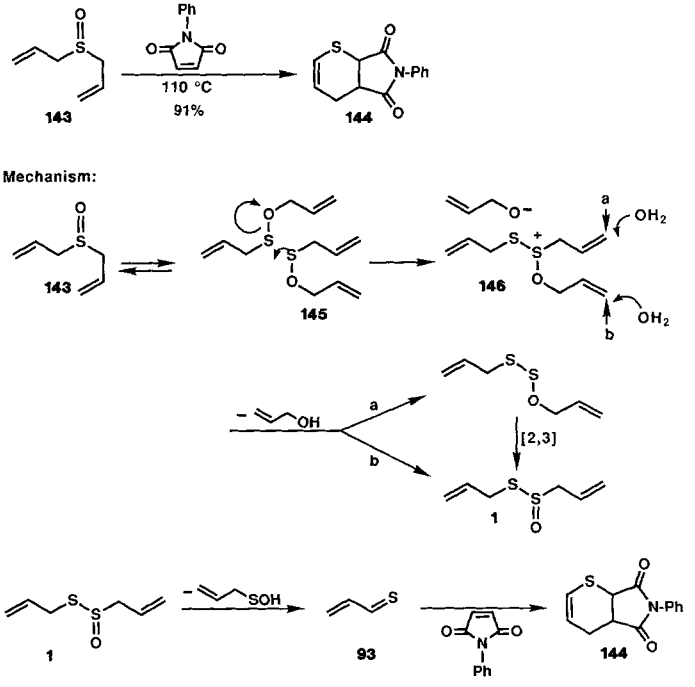
Scheme 59. Diels–Alder reaction of thioacrolein (**93**).

sealed tube; Scheme 60) and by demonstrating by mass spectrometric methods that the C–S and S–S bond dissociation energies in **4b** are 46 and 62 kcal mol^{-1}, respectively.[118] We conclude that the formation of the complex mixture of acyclic and heterocyclic polysulfides in the distilled oil of garlic is a consequence of the action of heat during the distillation process on the allicin and **4b** forming **93** and allyldithio radicals. Obviously any culinary procedure which exposes garlic or garlic-spiced food to heat could also generate the types of compounds described herein with possible health benefits associated with the antioxidant or lipoxygenase-inhibitory activity.[170a]



Scheme 60. Sealed tube pyrolysis of diallyl sulfide (**4a**).

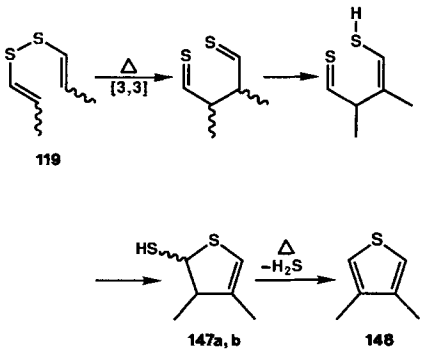
found.[170b] These are difficult to detect by GC because of their thermal instability. They may be formed by known sulfur transfer processes from allylic disulfides.[118, 172]



Scheme 61. Pyrolysis of diallyl sulfoxide (**143**) to give thioacrolein **93**; trapped as 3,4-dihydro-2*H*-thiopyran derivative **144**.

6.2. Pyrolysis of Bis(1-propenyl) Disulfide

When a 1% solution of the isomers of bis(1-propenyl) disulfide **119** in benzene is kept at 85 °C for 3 hours two new compounds, identified as *cis*- and *trans*-3,4-dimethyl-2,3-dihydrothiophene-2-thiol (**147a,b**), are formed in a 1:1 ratio in over 85% yield together with minor quantities of 3,4-dimethylthiophene (**148**).[173] Compound **148** was previously observed as the predominant product formed when **119** is heated to 150–200 °C in the presence of $KHSO_4$.[174] Prolonged heating at higher temperatures results in the conversion of **147a,b** into **148** (Scheme 62). All three isomers of **119** lead to the same mixture of **147a,b**; no isomerization from one isomer of **119** to another occurs under pyrolysis conditions. The relative rates of reaction of the three isomers of **119** were found to be *E,Z* > *E,E* > *Z,Z*.



Scheme 62. Dithio-Claisen reaction of bis(1-propenyl) disulfide (**119**) and formation of *cis*- and *trans*-3,4-dimethyl-2,3-dihydrothiophenethiol (**147a,b**) and 3,4-dimethylthiophene (**148**).

Compounds **147a,b** are thought to be formed from **119** via a [3,3]-sigmatropic dithio-Claisen rearrangement[175] followed by thioenolization and intramolecular addition of SH to CH=S (Scheme 62), similarly to cyclizations involving 1,4-diketones. The similarity of the activation parameters for rearrangement of (*Z,Z*)-**119** (E_a = 19 kcal mol^{-1}, $\Delta H^{\neq}$ = 18.3 kcal mol^{-1}, $\Delta S^{\neq}$ = − 24.8 cal mol^{-1}K^{-1}, and $\Delta G^{\neq}$ = 27.5 kcal mol^{-1}, all at 373 K)[135a] to the corresponding values for (*Z,Z*)-**120** (Section 5.2.5, cf. Schemes 41–43) suggests a similar mechanism. The absence of interconversion of isomers of **119** under the reaction conditions precludes a homolytic route to **147a,b**. Compounds **147a,b** as well as 2-alkyldithio-3,4-dimethylthiophenes (alkyl = Me or Pr) have been detected in steam-distilled volatiles from scallion and Welsh onion.[141] It is likely that the thiophene **148**, one of the significant contributors to the aroma of garlic, leek, and cooked or fried onion,[176] is formed in these plants from **147a,b** by loss of H_2S, although additional routes to **148** and other dimethylthiophenes are conceivable.

7. Physiological Activity

Belief in the preventive or curative effect of vegetables towards disease has persisted for thousands of years. Garlic, onion, cress, and cabbage are examples. In Eastern Europe and Asia Minor, large amounts of raw onion or garlic are a normal feature of the diet. The science of nutrition has paid little serious attention to these beliefs, since, to some extent, they can be explained on the basis of the vitamins and minerals contained in these vegetables, and because other alleged effects, if they exist, seem to be connected with substances better regarded as drugs than foods.

A. Virtanen (1895–1973)[2]

7.1. Antimicrobial Activity

Since things that here in order shall ensue,
Against all poysons have a secret power.
Peare, garlicke, reddish root, nuts, rape and rue—
But garlicke chiefe; for they that it devoure
May drinke, and care not who their drinke do brewe.
May walk in aires infected, every houre
Sith garlicke them have power to save from death,
Bear with it though it maketh unsavory breath,
And scorne not garlicke, like some that thinke
It only maketh men winke, and drinke—and stinke.

"The Englishman's Doctor"
Sir John Harington (1561–1612) [177a]

Before the availability of modern antibiotics, garlic preparations were widely used in epidemics of typhus, cholera, dysentery, amoebic dysentery, diphtheria, and tuberculosis.[3i] Albert Schweitzer first treated amoebic dysentery in Africa with garlic only.[177b] The antimicrobial effect of allicin is considerable.[122b] It has a growth inhibiting effect on both gram-negative and gram-positive bacteria (e.g. *Streptococci, Staphylococci, Eberthella typhosa, B. dysenteriae, B. enteritidis* and *Vibrio chlorae*) even at a 1:100000 dilution.[33] The antimicrobial effect of methyl methanethiosulfinate (**12**), propyl propanethiosulfinate (**13**), and thiosulfinates found in onion extracts (first noted to be antibacterial by Louis Pasteur![178]) are weaker than allicin **1**.[2, 179, 180] Allicin and garlic extracts show anticandidal and antifungal (e.g. anti-*Cryptococcus neoformans*) activity.[181–183] Garlic bulb volatiles have fungicidal properties[184, 185] which may protect the bulb against invading microorganisms. Diallyl trisulfide, **4c**, a constituent of garlic oil, has been used in China to treat viral infections and cryptococcal meningitis.[186]

7.2. Cancer Preventive Properties

Since the 1957 discovery that ethyl ethanethiosulfinate **31** showed anti-tumor activity, considerable attention has focussed on the cancer preventive properties of *Allium* spp.[186, 187] A fascinating epidemiological study conducted in the People's Republic of China reveals that in a region of China where gastric cancer rates are high, a significant reduction in gastric cancer risk parallels increasing consumption of garlic, scallion, and Chinese chive. Persons in the highest quartile of intake of these plants experienced only 40% of the risk of those in the lowest.[188] Since nitrites have been implicated in gastric cancer, it is relevant that gastric juice nitrite concentrations were lower in individuals consuming garlic compared to those who rarely take garlic; the

reduction of nitrite concentration in gastric juice after introduction of fresh garlic homogenate was significantly larger than that of controls.[189a] It is also known that diallyl disulfide **4b** inhibits in vivo activation of nitrosamines.[189b] Unsaturated polysulfides found in *Allium* spp. inhibit tumor promotion,[187, 190-193] perhaps by enhancing glutathione-dependent detoxification enzymes,[194a, b] and also modulate mutagenesis of aflatoxin B1.[194c] Steam-distilled onion oil, but not garlic oil, can also function as a weak tumor *promoter* as well as antipromoter in 7,12-dimethylbenz[*a*]-anthracene-initiated mouse skin.[195]

7.3. Cardiovascular Effects on Lipid and Arachidonic Acid Metabolism, and Platelet Aggregation Inhibitory Activity

Dietary garlic has a lipid- and cholesterol-lowering effect.[3i, 196] γ-Glutamyl-*S*-alkylcysteines inhibit the blood-pressure regulation hormone.[201a] A detailed mortality study[196b] on patients who had prior heart attacks showed that of those given gelatin capsules containing garlic oil (ca. 6 mg/person/day) high in ajoene (**75**) and dithiins (**9**, **74**)[119b] for three years, there was significant reduction in serum lipids, a 35% reduction in new heart attacks, and a 45% reduction in total deaths compared to those consuming placebo capsules. Allicin (**1**) is a specific inhibitor of acetyl-CoA synthetases from plants[197a] while diallyl disulfide (**4b**) inhibits 3-hydroxy-3-methylglutaryl CoA;[197b] in this manner lipid, cholesterol and fatty acid biosynthesis may be inhibited. The inhibitory effect of garlic and onions on human platelet aggregation has been known for two decades and has been variously attributed to adenosine, allicin **1**, alliin **2**, ajoene **75**, polysulfides (such as **4f**), and vinyl dithiins (e.g. **9** and **74**).[28, 198] The identity of the organosulfur compounds found in the blood or tissues after consumption of the plants remains unknown (apart from the compounds found in breath or sweat after ingestion of garlic). In view of the in vivo findings of Lawson[28] and the observations of Cavallito[30] and Wills[199a] that allicin reacts immediately with the SH-group of free or enzyme-bound cysteine forming *S*-(allylthio)cysteine, it is unlikely that allicin itself is found in blood after consumption of garlic. Indeed *S*-(allylthio)-cysteine may well be responsible for much of the biological effects of garlic within the body.[28a] Several studies indicate that the components of freshly cut garlic[199b] and onion[149] inhibit platelet aggregation and smooth muscle contraction through inhibition of cyclooxygenase and related enzymes. The antiasthmatic effects of onion extracts has been demonstrated; some of the most active components are thiosulfinates and cepaenes. These compounds exert a wide range of pharmacological effects such as inhibition of the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, inhibition of histamine release and leukotriene biosynthesis, prevention of bronchial asthma in guinea pigs after inhalation of allergens and platelet-activating factor, and inhibition of inflammatory cell influx.[125] Allicin is reported to inhibit human platelet aggregation in vitro without affecting cyclooxygenase or thromboxane synthase activity or cyclic AMP levels, possibly by influencing calcium movement.[198a]

7.4. Physiological Activity of Ajoene

Ajoene **75** is cytotoxic toward a tumorgenic lymphoid cell line with an EC_{50} of 12 μM;[200] it shows an IC_{50} of 1.6 μM and 5.1 μM towards the 5-lipoxygenase and cyclooxygenase enzymes, respectively;[201] it synergistically potentiates the antiaggregatory action of prostacyclin, forskolin, indomethacin and dypiridamole on human blood platelets.[106] Administration of **75** to dogs under conditions used in open heart surgery prevents the thrombocytopenia induced by contact of blood with artificial surfaces; it shows excellent activity in preventing the loss of platelets and in increasing the rate of restoration of platelet clotting activity.[202a] Other anticlotting agents (aspirin, heparin) had longer lasting effects and did not protect platelets. Ajoene is thought to inhibit platelet activation by impairing the interaction of fibrinogen receptors on the platelet surface with the rest of the membrane signal transduction system and by affecting the plasma-membrane internal microviscosity.[202b-d] Alternatively, it is suggested that ajoene alters the conformation of a hemoprotein implicated in platelet activation.[203a] Ajoene can also inhibit adhesive interactions of human neutrophiles and consequently effect in vivo superoxide anion formation.[203b] Ajoene possesses significant antifungal activity, inhibiting the growth of *Aspergillus niger, Candida albicans, Paracoccidioides-Brasiliensis*, and *Fusarium* species at concentrations of $<20\ \mu g\,mL^{-1}$,[204] possibly by damaging the fungal cell walls.[204b] Ajoene inactivates human gastric lipase (HGL), a sulfhydryl enzyme involved in the digestion and adsorption of dietary fats. This observation corroborates previous reports on the ability of garlic to lower triacylglycerol blood levels ("blood thinning" effect of folk medicine).[205] A garlic preparation prepared by dissolving fresh garlic extract in coconut oil (forming ajoene and dithiins[28]) significantly decreases ADP-induced platelet aggregation in volunteers consuming $0.25\ mg\,kg^{-1}$ daily for 4 weeks.[206]

7.5. Acid Reflux Effect

Eat no onions nor garlic, for we are to utter sweet breath.

"A Midsummer Night's Dream"
William Shakespeare (1564-1616)

Anyone who has overindulged in onions is aware of the consequences. Gastroenterologists refer to the effect as "acid reflux and reflux symptoms", e.g. regurgitation of the stomach contents into the esophagus with resultant "heartburn". A more precise physiological description is inappropriate transient lower esophageal sphincter (LES) relaxation, e.g. erratic opening of the valve separating the esophagus from the stomach.[207] Since, as we have already mentioned in Section 7.3, several of the organosulfur compounds formed when onions are cut are potent inhibitors of the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, raw onions may cause heartburn by blocking these pathways.[208] This inhibition might then result, either singly or in combination, in the transient relaxation of the LES as well as injury to the esophageal mucosa.

7.6. Lachrymatory, Olfactory, and Gustatory Characteristics of *Allium* spp.

Provence with her garlic-scented smile.
Rudyard Kipling (1865–1936)

While it is not known precisely how crying is triggered by an onion, it has been suggested that the onion LF, along with other lachrymators such as tear gases, undergo particularly facile reduction by NADPH following reception in a nerve cell membrane.[209] The organoleptic properties of some fresh onion extract and distilled onion oil components have been evaluated by "expert flavorists" who described odor and taste. The "room-temperature steam distillate" of onion, consisting primarily of α,β-unsaturated thiosulfinates, had an odor and taste quite similar to that of fresh onions. Of the isomeric pair (*E*)-**106**, R = Me/(*E*)-**105**, R = Me, the former had a pronounced fresh raw onion or shallot flavor while the latter had more of a cabbage or radish note. The flavor of (*E,Z*)-**106**, R = Pr, is that of green, raw fresh onions. On the other hand, (*E,Z*)-**114**, R = Pr, lacked the fresh raw onion flavor of the thiosulfinates, having more of an oniony, solvent-like flavor. The cepaene (*E,E*)-**127d** had a fruity melon-like flavor combined with a slight fresh onion flavor.[21] Propyl, propenyl di- and trisulfides possess the odor of cooked onions.[176] The threshold (minimal levels for detection in aqueous solutions by taste) range from 5–10 ppb for the thiosulfinates, the deoxycepaenes (*E,E*)- and (*Z,Z*)-**131** and the cepaene **127d** to 0.01–6 ppb for (*Z,Z*)-**119**, Pr_2S_2, MeSSCH=CHMe, and PrSSCH=CHMe, to an amazing level (for one experienced flavorist) of 0.001 ppb for (*E,Z*)-**114**, R = Pr.[21,176]

MeCH=CHSS(O)R
106

MeCH=CHS(O)SR
105

(*E,Z*)-MeCH=CHSSO$_2$R
114

(*E,E*)-MeCH=CHS(O)CHEtSSCH=CHMe
127d

7.7. Bad Breath and Further Negative Effects of Garlic and Other *Allium* spp.

...edit cicutis alium nocentius.[*]
"Episode 3"
Horace (65 B.C.–8 B.C.)

Eating alliaceous plants causes bad breath and perspiration odors. Components of garlic breath and prespiration include: allyl methyl sulfide and disulfide, diallyl sulfide and disulfide, 2-propenethiol, and *p*-cymene and (+)-limonene (present in garlic distilled oils).[210,211] Garlic breath odor comes from the lungs presumably by way of the blood and not solely from particles of garlic retained in the structures about the mouth.[212] After ingestion of 2 g of raw garlic, garlic odor in human urine was said to persist up to 96 hours while exhaled air no longer had an odor after 24 hours.[213a] When garlic is rubbed on the foot, a garlic taste is soon detected.[213b] Presumably fat-soluble allicin is absorbed through the skin (as in the case of dimethyl sulfoxide) into the lymphatic system which carries it intact to the upper part of the body in a medium where no protein or cysteine is present.[213b] In areas where *Allium* spp. grow wild, cows often eat them, causing a bad flavor in milk. A vacuum treatment can remove these sulfur compounds and the bad taste.[20] Studies on nursing mothers have shown that their milk has a more intense odor 2 hours after having ingested garlic. Furthermore it was found that the nursing babies sucked more and ingested more milk when the milk smelled like garlic.[214]

A few individuals have an allergic response, e.g. dermatitis or asthma, to fresh garlic or onions,[215a] diallyl disulfide, allicin or garlic dust.[3i,215] Freshly ground garlic can cause severe dermatitis on prolonged contact with the skin.[216] In a case associated with excessive garlic ingestion, spontaneous spinal epidural hematoma causing paraplegia following a qualitative platelet disorder has been reported.[217] When given orally to laboratory animals, garlic has been noted to cause anemia,[3i] abdominal hemorrhage and death.[187] In mice, allicin (**1**) has an LD_{50} of 60 mg kg^{-1} i.v. and 120 mg kg^{-1} s.c.[30] An occupational hazard associated with sulfur compounds in the perspiration of a garlic lover has been reported.[211]

[*] That wicked garlic, more poisonous than the hemlock.

7.8. Insect and Animal Attractive/Repulsive Effects

Propyl propanethiosulfinate (**13**) has been identified as the most attractive substance from crushed leek for the leek moth, *Acrolepiopsis assectella*; **13** is repellent to *Ephestia kuehniella* (based on our recent analyses of thiosulfinates from leek, this work may require revision!)[29] Allicin, its homologs, and related sulfur compounds are thought to protect *Allium* spp. against pathogens and predators.[10b,14b] Garlic oil components/metabolites diallyl disulfide and trisulfide are toxic to mosquito and other insect larvae at levels of 2 ppm[218] and are repellant to *Ixodes ricinus*, the tick which carries the encephalitis virus.[219] Diallyl disulfide has been employed to drive away crop-damaging birds.[3i]

8. Summary and Outlook

In the fifty years since the discovery of allicin (**1**)[30] much progress has been made in identifying the various unusual organosulfur compounds formed when garlic and onion are cut (Figs. 10 and 11) and in understanding their origin. Despite this progress, many other compounds remain to be identified in *Allium* extracts. For example, application of field desorption mass spectroscopy to the analysis of onion extracts indicates that the heaviest compounds present have masses of m/z = 325–326 and 298–301, corresponding respectively to molecular formulas $C_{12}H_{20}S_4O_2/C_{12}H_{22}S_4O_2$ and $C_{10}H_{18}S_4O_2/C_{10}H_{20}S_4O_2$. Analysis of these extracts by LC-MS indicate the presence of a series of compounds (perhaps a family of homologous isomers?) with masses 324/326 and 298. Possible structures include *S,S'*-dioxides of **132** (Scheme 53) or isomers **149** (Scheme 63), together with ho-

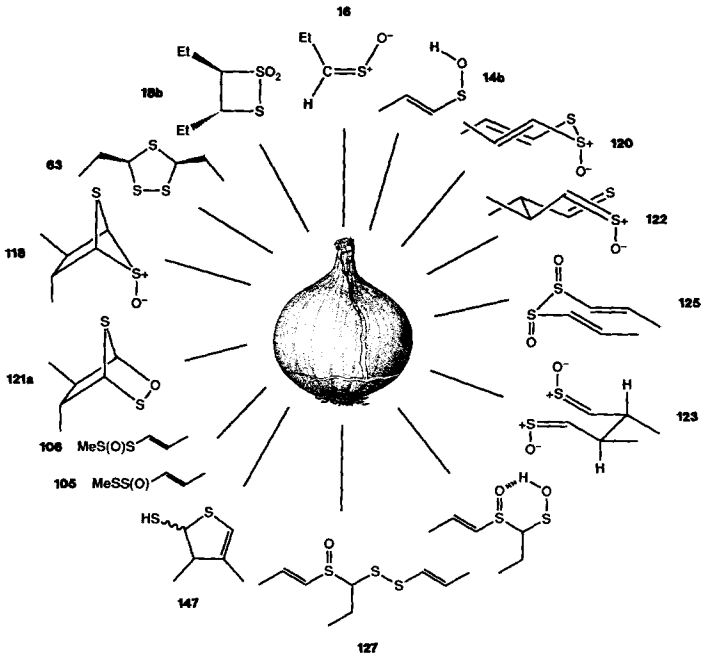


Fig. 10. Collection of some of the principal organosulfur compounds and intermediates associated with onion.

mologs with methyl replacing a 1-propenyl group. Efforts to identify these compounds are underway.

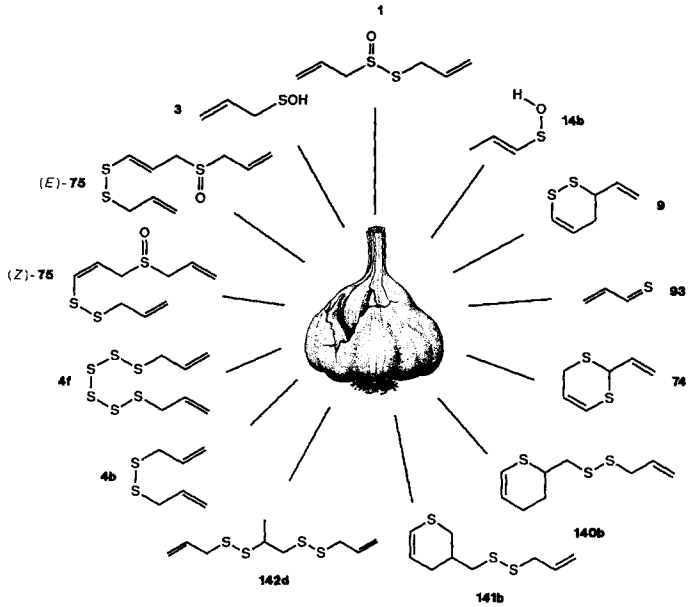
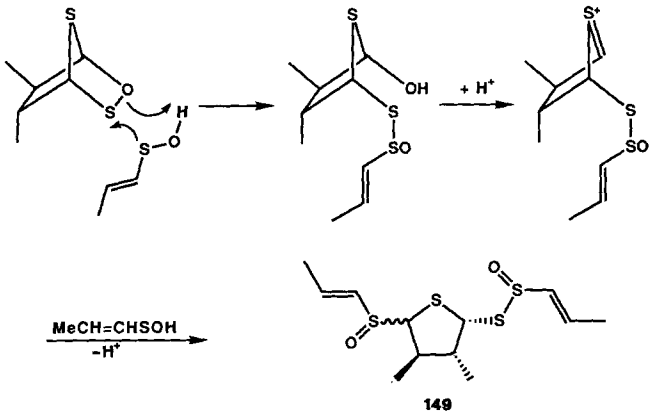


Fig. 11. Collection of some of the principal organosulfur compounds and intermediates associated with garlic.

How might dietary *Allium* spp. benefit us? Consider the following: 1) The *Allium* spp. tissue is not completely crushed when it is eaten, thus allowing a significant portion of the *S*-alk(en)ylcysteine *S*-oxides such as **2**, **5**, **6**, and **7** to pass unchanged into the intestinal tract. While allinases are irreversibly deactivated at the pH of gastric juice, intestinal bacteria have been shown to cleave the sulfoxides, ultimately giving the corresponding disulfides.[10b] 2) Thiosulfinates



Scheme 63. Possible structure for *m/e* 324 compound (**149**) from onion extracts.

which have made their way into the stomach may survive the low pH long enough to act on pathogenic microorganisms present. 3) Alk(en)ylthiolation of certain biological SH groups by thiosulfinates, di- or polysulfides or ajoene might be beneficial. For example, "allylthiolation" of thiamine readily occurs affording allithiamine, which is more easily absorbed from the intestine than thiamine.[3i, 38] 4) Disulfides and other sulfur compounds formed from *Allium* spp. are thought to play an important role in the intestinal tract in deactivating nitrites or other environmental toxins. One thing is clear: tracking the metabolic fate of *Allium* spp. organosulfur compounds is both an important and a fertile area for future research.

I am profoundly grateful to my many excellent co-workers and collaborators, whose names appear in the references, for their valuable contributions to the research described herein. I particularly thank S. Naganathan, D. Putman, and S. H. Zhao for their expert assistance in the preparation of this manuscript. I am deeply appreciative for financial support of this work by the National Science Foundation, the American Heart Assocation, the John Simon Guggenheim Foundation, the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, NATO, Société Nationale Elf Aquitaine, McCormick and Company, Wakunaga Pharmaceutical Company, and the State University of New York at Albany. I thank Dr. Larry Lawson for critically reviewing the entire manuscript and C. T. Ho, W. le Noble, O. Sticher, and L. Lawson for unpublished material.

Received: January 3, 1992 [A 876 IE]
German version: *Angew. Chem.* **1992**, *104*, 1158

[1] For a general overview of organosulfur chemistry, see E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, **1978**.
[2] A. I. Virtanen, *Angew. Chem.* **1962**, *74*, 374–382; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 299–306.
[3] General reviews on *Allium* chemistry: a) E. Block, *Sci. Am.* **1985**, *252*, 114–119; *Spektrum Wiss.* **1985**, 66–72; b) E. Block, *Lect. Heterocycl. Chem.* **1987**, *9*, 27–31; c) E. Block in *Sulfur-Centered Reactive Intermediates in Chemistry and Biology* (Eds.: C. Chatgilialoglu, D. Asmus), Plenum Press, New York, **1991**, S. 282–289 [NATO Conf. Ser.]; d) E. Block, *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *58*, 3–15; e) G. R. Fenwick, A. B. Hanley, *CRC Crit. Rev. Food Sci. Nutr.* **1985**, *22*, 199–271, 273–377; **1986**, *23*, 1–73; f) J. F. Carson, *Food Rev. Int.* **1987**, *3*, 71–103; g) J. L. Brewster, H. D. Rabinowitch (Eds.), *Onions and Allied Crops*, CRC Press, Boca Raton, **1990**, *Vol. 1–3*; h) J. R. Whitaker, M. Mazelis in *Food Enzymology* (Ed.: P. Fox), Elsevier, London, **1991**, Vol. 1. Ch. 13, pp. 479–498; i) J. R. Whitaker, *Adv. Food. Res.* **1976**, *22*,

73–133; j) H. P. Koch, G. Hahn, *Knoblauch*, Urban & Schwarzenberg, München, **1988**; k) M. K. Jain, C. Scanzello, R. Apitz-Castro, *Chem. Unserer Zeit* **1988**, *22*, 193–200; l) E. Block, S. Naganathan, D. Putman, S.-H. Zhao, *Pure Appl. Chem.* **1993**, in press.

[4] T. Wertheim, *Ann. Chem. Pharm.* **1844**, *22*, 193–200.

[5] F. W. Semmler, *Arch. Pharm.* **1892**, *230*, 434–443, 443–448.

[6] C. J. Cavallito, J. H. Bailey, J. S. Buck, *J. Am. Chem. Soc.* **1945**, *67*, 1032–1033.

[7] K. Knobloch, L. Lawson, *Planta Med.* **1990**, *56*, 246.

[8] a) A. Stoll, E. Seebeck, *Experientia* **1947**, *3*, 114–115; b) A. Stoll, E. Seebeck, *Helv. Chim. Acta* **1948**, *31*, 189–210; c) A. Stoll, E. Seebeck, *ibid.* **1949**, *32*, 197–205; d) A. Stoll, E. Seebeck, *Sci. Pharm.* **1950**, *18*, 61–79; e) A. Stoll, E. Seebeck, *Adv. Enzymol.* **1951**, *11*, 377–400.

[9] J. E. Lancaster, H. A. Collin, *Plant Sci. Lett.* **1981**, *2*, 169–176.

[10] a) A. I. Virtanen, C.-G. Spåre, *Suom. Kemistil. B* **1961**, *34*, 72; *ibid.* **1962**, *35*, 28; b) A. I. Virtanen, *Phytochemistry* **1965**, *4*, 207–228.

[11] L. D. Lawson, Z.-Y. J. Wang, B. G. Hughes, *J. Nat. Prod.* **1991**, *54*, 436–444.

[12] a) M. Mütsch-Eckner, *Ph. D. Thesis*, ETH Zürich **1991**; b) M. Mütsch-Eckner, B. Meier, A. D. Wright, O. Sticher, *Phytochemistry* **1992**, *31*, 2389–2391.

[13] Y. Ueda, M. Sakaguchi, K. Hirayama, R. Miyajima, A. Kimizuka, *Agric. Biol. Chem.* **1990**, *54*, 163–169.

[14] a) T. Kasai, P. O. Larsen, *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 173–285; b) J. E. Lancaster, M. L. Shaw, *Phytochemistry* **1991**, *30*, 2857–2859.

[15] J. E. Lancaster, M. L. Shaw, *Phytochemistry* **1989**, *28*, 455–460.

[16] S. J. Ziegler, O. Sticher, *Planta Med.* **1989**, *55*, 372–378.

[17] H. Rennenberg, *Phytochemistry* **1982**, *21*, 2771.

[18] J. W. Anderson in *The Biochemistry of Plants*, (Eds.: E. E. Conn, P. K. Stumpf), Academic Press, New York, **1980**, p. 203.

[19] a) R. J. Parry, G. R. Sood, *J. Am. Chem. Soc.* **1989**, *111*, 4514–4515; b) R. J. Parry, F.-L. Lii, *ibid.* **1991**, *113*, 4704–4706.

[20] B. Granroth, *Ann. Acad. Sci. Fenn. Ser. A 2* **1970**, *154*, 1–71.

[21] a) Garlic cloves from two different New York State farms showed concentrations of **6** of 0.08–0.25 mg/g garlic compared to "normal" values of 1–1.6 mg/g garlic. The concentrations of **2** and the *S*-substituted γ-glutamyl cysteines **e**, **f**, and **g** (see Scheme 2) in the New York garlic samples were within the "normal" range. We thank Dr. L. D. Lawson for performing this analysis [21b] (also see Ref. [28b]); b) E. Block, S. Naganathan, D. Putman, S. H. Zhao, *J. Agric. Food Chem.* **1992**, in press; c) E. Block, D. Putman, S. H. Zhao, *ibid.* **1992**, in press.

[22] a) H. Jansen, B. Müller, K. Knobloch, *Planta Med.* **1989**, *55*, 434–439, 440–445; L. P. Nock, M. Mazelis, *Arch. Biochem. Biophys.* **1986**, 248, 27–33; b) H. Jansen, B. Müller, K. Knobloch, *ibid.* **1987**, *53*, 559–562.

[23] A. Rabinkov, M. Wilchek, D. Mirelman, *FASEB J.* **1991**, *5*, 1149.

[24] M. Fujita, M. Endo, M. Sano, *Agric. Biol. Chem.* **1990**, *54*, 1077–1079.

[25] F. P. Kupiecki, A. I. Virtanen, *Acta Chem. Scand.* **1960**, *14*, 1913–1918.

[26] M. Mazelis, L. Crews, *Biochem. J.* **1968**, *108*, 725–730.

[27] S. Schwimmer, *Arch. Biochem. Biophys.* **1969**, *130*, 312–320.

[28] a) L. D. Lawson, D. K. Ransom, B. G. Hughes, *Thromb. Res.* **1992**, *65*, 141–156; b) Lancaster [28c] also suggests that there is a basic difference in the regulation of *S*-methylcysteine *S*-oxide **6** compared with alliin **2**; c) J. E. Lancaster, E. M. Dommisse, M. L. Shaw, *Phytochemistry* **1988**, *27*, 2123–2124.

[29] a) J. Auger, C. Lecomte, E. Thibout, *J. Chem. Ecol.* **1989**, *15*, 1847–1854; b) J. Auger, F. X. Lalau-Keraly, C. Belinsky, *Chemosphere* **1990**, *21*, 837–843; c) J. Auger, E. Thibout, *C. R. Séances Acad. Sci. Ser. III* **1981**, *292*, 217–220; d) J. Auger, E. Thibout, *Can. J. Zool.* **1979**, *57*, 2223–2229.

[30] a) C. J. Cavallito, J. H. Bailey, *J. Am. Chem. Soc.* **1944**, *66*, 1950–1951; b) C. J. Cavallito, J. S. Buck, C. M. Suter, *ibid.* **1944**, *66*, 1952–1954; c) C. J. Cavallito, US-A 2554088, **May 22, 1951**.

[31] Chemical Abstracts names allicin **1** as 2-propene-1-sulfinothioic acid *S*-2-propenyl ester, **12** as methanesulfinothioic acid *S*-methyl ester, and alliin **2** as L-alanine, 3-(2-propenylsulfinyl)-, (*S*)-. As these names are quite cumbersome to use, we employ here the IUPAC nomenclature. Compounds of the type RS(O)SR′ are named according to Rule C-641 as esters of the thiosulfinic acid RS(O)SH. Accordingly, allicin **1** is named *S*-2-propenyl(or *S*-allyl) 2-propenethiosulfinate. (Since only *S*-esters occur here the *S* will be omitted.) This system of nomenclature is preferable to an alternative system where compounds RS(O)SR are named alk(en)yl alk(en)yl′ thiosulfinate with the first group (R) attached to the sulfinyl sulfur and the second ("primed") group (R′) to the sulfenyl sulfur [121].

[32] V. V. Nosyreva, S. V. Amosova, *Zh. Org. Khim.* **1990**, *26*, 1412–1415 (*Engl. Transl.* 1218–1221).

[33] L. V. Small, J. H. Bailey, C. J. Cavallito, *J. Am. Chem. Soc.* **1947**, *69*, 1710–1713.

[34] C. J. Cavallito, L. V. D. Small, US-A 2508745, **May 23, 1950**.

[35] a) M. H. Brodnitz, J. V. Pascale, L. Van Derslice, *J. Agric. Food Chem.* **1971**, *19*, 273–275. b) We suggest that 1-propenyl propyl disulfide is formed from **13** via the intermediacy of **34** (Scheme 11) rather than by a direct dehydration.

[36] K. Saito, M. Horie, Y. Hoshino, N. Nose, E. Mochizuki, H. Nakazawa, M. Fujita, *J. Assoc. Off. Anal. Chem.* **1989**, *72*, 917–920.

[37] a) Alkylcysteine *S*-oxides have been found in other plants [37b] including cabbage [37c], turnip [37d], and *Phaseolus* [37e]; allinase is not always present [42]. Allicin is produced on cutting the Amazonian garlic bush (*Adenocalymma alliaceum*) [37f]. In nature the –SS(O)– and –SSCH=CH– linkages are uncommon. Examples of the former are all cyclic [37g]; examples of the latter include the powerfull antitumor agents esperamycin [37h] and calicheamicin [37i], and compounds from the plants *Agathosma apiculata* [37j], *Azadirachta indica* [37k], and *Ferula assa-foetida* [37l]; b) R. Gmelin, M. N'Galamulume-Treves, G. Höfle, *Phytochemistry* **1980**, *19*, 553–557; c) R. L. M. Synge, J. C. Wood, *Biochem. J.* **1956**, *64*, 252–259; d) C. J. Morris, J. F. Thompson, *J. Am. Chem. Soc.* **1956**, *78*, 1605–1608; e) H. Rinderknecht, D. Thomas, S. Aslin, *Helv. Chim. Acta* **1958**, *41*, 1; f) M. G. Zoghbi, L. R. Ramos, J. G. S. Maia, M. L. Da Silva, A. I. R. Luz, *J. Agric. Food Chem.* **1984**, *32*, 1009–1010; g) A. Kato, M. Numata, *Tetrahedron Lett.* **1972**, 203–206; H. Yanagawa, T. Kato, Y. Kitahara, *ibid.* **1973**, 1073–1075; S. J. Wratten, D. J. Faulkner, *J. Org. Chem.* **1976**, *41*, 2465–2467; G. H. N. Towers, *Phytochemistry* **1990**, *29*, 2901–2904; F. Balza, G. Pattenden, A. J. Shuker, *Tetrahedron Lett.* **1991**, *32*, 6625–6628; h) J. Golik, G. Dubay, G. Groenewold, H. Kawaguchi, M. Konishi, B. Krishnan, H. Ohkuma, K. Saitoh, T. W. Doyle, *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464; i) M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, W. J. McGahren, D. B. Borders, *ibid.* **1946**, *31*, 3466–3468; j) J. L. B. Smith, D. E. A. Rivett, *Trans. R. Soc. S. Afr.* **1946**, *31*, 111; *Chem. Abstr.* **1946**, *40*, 6752; k) A. M. Mubarak, C. P. Kulatilleke, *Phytochemistry* **1990**, *29*, 3351–3352; M. F. Balandrin, S. M. Lee, J. A. Klocke, *J. Agric. Food Chem.* **1988**, *36*, 1048–1054; l) T. Kajimoto, K. Yahiro, T. Nohara, *Phytochemistry* **1989**, *28*, 1761–1763.

[38] M. Fujiwara, M. Yoshimura, S. Tsuno, *J. Biochem. (Tokyo)* **1955**, *42*, 591.

[39] A. R. Saghir, L. K. Mann, R. A. Bernhard, J. V. Jacobsen, *Proc. Am. Hort. Sci.* **1964**, *84*, 386–398.

[40] a) W. D. Niegisch, W. H. Stahl, *Food. Res.* **1956**, *21*, 657–665; b) Kohmann first identified propanal in onion volatiles: E. F. Kohmann, *Science (Washington D.C.)* **1947**, *106*, 625–627.

[41] a) J. F. Carson, R. E. Lundin, T. M. Lukes, *J. Org. Chem.* **1966**, *31*, 1634–1635; b) J. F. Carson, L. E. Boggs, *ibid.* **1966**, *31*, 2862–2864.

[42] R. Kuttan, N. G. Nair, A. N. Radhakrishnan, T. F. Spande, H. J. Yeh, B. Witkop, *Biochemistry* **1974**, *13*, 4394–4400.

[43] C.-G. Spåre, A. I. Virtanen, *Acta Chem. Scand.* **1963**, *17*, 641–650.

[44] E. J. Matikkala, A. I. Virtanen, *Acta Chem. Scand.* **1967**, *21*, 2891–2893.

[45] J. E. Lancaster, K. E. Kelly, *J. Sci. Food Agric.* **1983**, *34*, 1229–1235.

[46] a) E. Däbritz, A. I. Virtanen, *Chem. Ber.* **1965**, *98*, 781–788; b) E. Däbritz, A. I. Virtanen, *Acta Chem. Scand.* **1964**, *18*, 837–838.

[47] a) W. F. Wilkens: *Ph. D. Thesis*, Cornell University, Ithaca, NY, **1961**; b) W. F. Wilkens, *Cornell Agricultural Experimental Station Memoir*, Ithaca, NY, **Jan. 1964**, 385.

[48] a) W. A. Sheppard, J. Diekmann, *J. Am. Chem. Soc.* **1964**, *86*, 1891–1892; b) J. F. King, R. Rathore in *The Chemistry of Sulphonic Acids, Esters, and their Derivatives* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1991**, S. 697–766; c) B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 1–26; B. G. Lenz, B. Zwanenburg in *Methoden Org. Chem. (Houben-Weyl), Teil 2, Vol. E11*, Thieme, Stuttgart, **1985**, 911; B. Zwanenburg in *Reviews on Heteroatom Chemistry, Vol. 1* (Eds.: S. Oae), Myo, Tokyo, **1988**, pp. 218–234; d) L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 631–636.

[49] E. Block in *Organic Sulfur Chemistry* (Eds.: R. Kh. Freidlina, A. E. Skorova), Pergamon Press, Oxford, **1981**, pp. 15–34.

[50] M. H. Brodnitz, J. V. Pascale, *J. Agric. Food Chem.* **1971**, *19*, 269–272.

[51] J. L. Kice, *Adv. Phys. Org. Chem.* **1980**, *17*, 65–181.

[52] T. L. Moore, D. E. O'Connor, *J. Org. Chem.* **1964**, *31*, 3587–3592.

[53] a) R. W. Murray, R. D. Smetana, E. Block, *Tetrahedron Lett.* **1971**, 299–302; b) R. W. Murray, S. L. Jindal, *Photochem. Photobiol.* **1972**, *16*, 147–151; c) R. W. Murray, S. L. Jindal, *J. Org. Chem.* **1972**, *37*, 3516–3520.

[54] a) E. Block, *J. Am. Chem. Soc.* **1972**, *94*, 642–644; b) E. Block, *ibid.* **1972**, *94*, 644–645; c) E. Block, S. W. Weidman, *ibid.* **1973**, *95*, 5046–5048; d) E. Block, J. O'Connor, *ibid.* **1973**, *95*, 5048–5051; e) E. Block, J. O'Connor, *ibid.* **1974**, *96*, 3921–3929; f) E. Block, J. O'Connor, *ibid.* **1974**, *96*, 3929–3944.

[55] R. E. Penn, E. Block, L. K. Revelle, *J. Am. Chem. Soc.* **1978**, *100*, 3622–3624.

[56] The increasing bond length in the series ArSSAr, $ArSO_2SAr$, ArS(O)SAr (2.03 Å, 2.09 Å, and 2.108 Å, respectively) parallels the weakening of the S–S bond: C. T. Kiers, A. Vos, *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 166–170.

[57] J. B. F. N. Engberts, G. Zuidema, *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 1202.

[58] E. Block, *J. Org. Chem.* **1974**, *39*, 734–736.

[59] a) E. Block, E. R. Corey, R. E. Penn, T. L. Renken, P. F. Sherwin, *J. Am. Chem. Soc.* **1976**, *98*, 5715–5717; b) E. Block, E. R. Corey, R. E. Penn, T. L. Renken, P. F. Sherwin, H. Bock, T. Hirabayashi, S. Mohmand, B. Solouki, *ibid.* **1982**, *104*, 3119–3130.

[60] F. A. Davis, R. L. Billmers, L. A. Jenkins, *J. Org. Chem.* **1986**, *51*, 1033–1040.

[61] G. Winnewisser, M. Winnewisser, W. Gordy, *J. Chem. Phys.* **1968**, *51*, 3465.
[62] F. Turecek, L. Brabec, T. Vondrák, V. Hanus, J. Hájícek, Z. Havlas, *Collect. Czech. Chem. Commun.* **1988**, *53*, 2140–2158; F. Turecek, D. E. Drinkwater, F. W. McLafferty, *J. Am. Chem. Soc.* **1989**, *111*, 7696–7701.
[63] S. Besnainou, J. L. Whitten, *J. Am. Chem. Soc.* **1980**, *102*, 7444–7448.
[64] N. Nakamura, *J. Am. Chem. Soc.* **1983**, *105*, 7172–7173.
[65] J. L. Kice, L. Weclas-Henderson, A. Kewan, *J. Org. Chem.* **1989**, *54*, 4198–4203.
[66] E. Block, R. E. Penn, R. J. Olsen, P. F. Sherwin, *J. Am. Chem. Soc.* **1976**, *98*, 1264–1265.
[67] D. E. Powers, C. A. Arrington, W. C. Harris, E. Block, V. F. Kalasinsky, *J. Phys. Chem.* **1979**, *83*, 1890–1892.
[68] Y. Vallee, J.-L. Ripoll, C. Lafon, G. Pfister-Guillouzo, *Can. J. Chem.* **1987**, *65*, 290–291.
[69] E. Suzuki, R. Ishiguro, F. Watari, *J. Mol. Struct.* **1990**, *238*, 71–77.
[70] E. Block, A. Wall, *Tetrahedron Lett.* **1985**, *26*, 1425–1428.
[71] a) H. Kallio, L. Salorinne, *J. Agric. Food Chem.* **1989**, *38*, 1560–1564; b) H. Kallio, M. Leino, L. Salorinne, *J. High Resolut. Chromatogr.* **1989**, *12*, 174–177.
[72] E. Block, R. E. Penn, L. K. Revelle, *J. Am. Chem. Soc.* **1979**, *101*, 2200–2201.
[73] E. Block, A. Wall, *J. Org. Chem.* **1987**, *52*, 809–818.
[74] E. Block, M. Aslam, *Tetrahedron Lett.* **1982**, *23*, 4203–4206.
[75] C. R. Johnson, J. E. Keiser, J. C. Sharp, *J. Org. Chem.* **1969**, *34*, 860–864.
[76] G. A. Krafft, P. T. Meinke, *Tetrahedron Lett.* **1985**, *26*, 1947–1950.
[77] a) E. Block, A. Wall, J. Zubieta, *J. Am. Chem. Soc.* **1985**, *107*, 1783–1784; b) E. Block, A. A. Bazzi, L. K. Revelle, R. E. Penn, C. Saha, unpublished.
[78] W. Walter, K. Wohlers, *Justus Liebigs Ann. Chem.* **1971**, *752*, 115–135.
[79] a) Y. Makisumi, S. Takada, Y. Matsukara, *J. Chem. Soc. Chem. Commun.* **1974**, 850; b) G. A. Koppel, S. Kukolja, *ibid.* **1975**, 57–58; c) R. Bell, P. D. Cottam, J. Davies, D. N. Jones, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2106–2115; d) R. Bell, P. D. Cottam, J. Davies, D. N. Jones, N. A. Meanwell, *Tetrahedron Lett.* **1980**, *21*, 4379–4382; e) A. Heckel, W. Pfleiderer, *ibid.* **1983**, *24*, 5047–5050.
[80] F. Turecek, F. W. McLafferty, B. J. Smith, L. Radom, *Int. J. Mass Spectrom. Ion Processes* **1990**, *101*, 283–300.
[81] a) S. Tahara, H. Okamura, Y. Miura, J. Mizutani, *Agric. Biol. Chem.* **1979**, *43*, 2017–2020; b) S. Tahara, J. Mizutani, *ibid.* **1979**, *43*, 2021–2028.
[82] E. Block, R. E. Penn, A. A. Bazzi, D. Cremer, *Tetrahedron Lett.* **1981**, *22*, 29–32.
[83] R. Hoffman, R. A. Olofson, *J. Am. Chem. Soc.* **1966**, *88*, 943–946.
[84] H. Kameoka, Y. Demizu, *Phytochemistry* **1979**, *18*, 397–1398.
[85] A. M. Hamid, S. Trippett, *J. Chem. Soc. C* **1968**, 1612–1615.
[86] D. Barnard, E. R. Cole, *Anal. Chim. Acta* **1959**, *20*, 540–547.
[87] L. Field, R. B. Barbee, *J. Org. Chem.* **1969**, *34*, 36–41.
[88] a) E. Block, A. A. Bazzi, L. K. Revelle, *J. Am. Chem. Soc.* **1980**, *102*, 2490–2492; b) An example of *intermolecular* 1,3-dipolar addition of a sulfine to a thione has been described recently: G. Mloston, R. Huisgen, K. Polborn, *Abstracts, 15th International Symposium on the Organic Chemistry of Sulfur*, Caen, France, June 1992, 157.
[89] E. Block, A. Yencha, M. Aslam, V. Eswarakrishnan, J. Luo, A. Sano, *J. Am. Chem. Soc.* **1988**, *110*, 4748–4753.
[90] a) E. Block, A. A. Bazzi, *Tetrahedron Lett.* **1988**, *110*, 4569–4572; b) see also: F. Freeman, M. C. Keindl, *J. Org. Chem.* **1988**, *53*, 2026–2031.
[91] a) E. Block, A. Schwan, D. A. Dixon, *J. Am. Chem. Soc.* **1992**, *114*, 3492–3499.
[92] a) E. M. Calvey, J. M. Betz, J. E. Matusik, K. D. White, E. Block, S. Naganathan, in press; b) N. K. Sinha, D. E. Guyer, D. A. Gage, C. T. Lira, *J. Agric. Food Chem.* **1992**, *40*, 368–372.
[93] J. F. Carson, F. F. Wong, *J. Agric. Food Chem.* **1961**, *9*, 140–143.
[94] For a related example of a steam distillation under reduced pressure see: N. S. A. Edwards, R. D. Gillard, P. W. Groundwater, *Chem. Ind. (London)* **1991**, 763.
[95] J. L.-P. Wu, C.-M. Wu, *J. Chromatogr.* **1981**, *214*, 234–236.
[96] H. Miething, *Dtsch. Apoth.-Ztg.* **1985**, *125*, 2049–2050; *Chem. Abstr.* **1985**, *103*, 187, 210.
[97] a) C. H. Wijaya, H. Nishimura, T. Tanaka, J. Mizutani, *J. Food Sci.* **1991**, *56*, 72–75; b) H. Nishimura, C. H. Wijaya, J. Mizutani, *J. Agric. Food Chem.* **1988**, *36*, 563–566; c) H. Nishimura, K. Fujiwara, J. Mizutani, Y. Obata, *ibid.* **1971**, *19*, 992–994.
[98] a) V. V. Talyzin, V. Y. Anisimova, O. I. Yakovleva, R. V. Golovnya, T. A. Misharina, S. V. Vitt, *Zh. Anal. Khim. (USSR)* **1988**, *43*, 911–916 (Engl. Transl. 718–722); b) T.-H. Yu, C.-M. Wu, Y.-C. Liou, *J. Agric. Food Chem.* **1989**, *37*, 725–730; c) G. Vernin, J. Metzger, D. Fraisse, C. Scharff, *Planta Med.* **1986**, 96–101; d) L. Schreyen, P. Dirinck, F. Van Wassenhove, N. Schamp, *J. Agric. Food Chem.* **1976**, *24*, 336–341.
[99] R. A. Bernhard, *Phytochemistry* **1977**, *9*, 2019–2027.
[100] G. G. Freeman, R. J. Whenham, *J. Sci. Food Agric.* **1975**, *26*, 1869–1886.
[101] H. Iida, S. Hashimoto, M. Miyazawa, H. Kameoka, *J. Food Sci.* **1983**, *48*, 660–661.
[102] I. A. Mackenzie, D. A. Ferns, *Phytochemistry* **1977**, *16*, 763–764.
[103] I. Sakai, *US-A 4933201*, **June 12, 1990**.
[104] B. H. Müller, *Dissertation*, Universität Erlangen-Nürnberg, **1991**.
[105] a) M. Mikolajczyk, J. Drabowicz, *J. Am. Chem. Soc.* **1978**, *108*, 2510–2515; b) Note that in the presence of chiral amines *t*-BuSOH gives chiral *t*BuS(O)S*t*Bu: J. Drabowicz, P. Lyzwa, M. Mikolajczyk, *Phosphorus Sulfur* **1983**, *16*, 267–270.
[106] a) R. Apitz-Castro, S. Cabrera, M. R. Cruz, E. Ledezma, M. K. Jain, *Thromb. Res.* **1983**, *32*, 155–169; b) R. Apitz-Castro, E. Ledezma, J. Escalante, F. M. Pinate, J. Moreno-Rea, G. Carrillo, O. Leal, M. K. Jain, *ibid.* **1986**, *42*, 303–311.
[107] a) E. Block, S. Ahmad, M. K. Jain, R. W. Crecely, R. Apitz-Castro, M. R. Cruz, *J. Am. Chem. Soc.* **1984**, *106*, 8295–8296; b) E. Block, S. Ahmad, J. Catalfamo, M. K. Jain, R. Apitz-Castro, *ibid.* **1986**, *108*, 7045–7055; c) E. Block, S. Ahmad, *US-A 4643994*, **February 17, 1987**; d) E. Block in *Folk Medicine: The Art and the Science* (Ed.: R. P. Steiner), American Chemical Society, Washington, D.C., **1986**, p. 125–137.
[108] a) A. J. Mura, Jr., D. A. Bennett, T. Cohen, *Tetrahedron Lett.* **1975**, 4433–4436; b) E. Vilsmaier, J. Schutz, S. Zimmerer, *Chem. Ber.* **1979**, *112*, 2231–2242.
[109] E. Vedejs, P. L. Fuchs, *J. Org. Chem.* **1971**, *36*, 366–367.
[110] E. Block, S. Ahmad, *J. Am. Chem. Soc.* **1985**, *107*, 6731–6732.
[111] H. Kwart, J. L. Schwartz, *J. Org. Chem.* **1974**, *39*, 1575–1583.
[112] C. J. Burrows, B. K. Carpenter, *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984.
[113] J. R. Hwu, D. A. Anderson, *Tetrahedron Lett.* **1986**, *27*, 4965–4968; J. R. Hwu, D. A. Anderson, *J. Chem. Soc. Perkins Trans. 1* **1991**, 3199–3206.
[114] J. B. Lambert, D. S. Bailey, C. Mixan, *J. Org. Chem.* **1972**, *37*, 377–382.
[115] A. Mukherjee, E. M. Schulman, W. J. le Noble, *J. Org. Chem.* **1992**, *57*, 3120–3126.
[116] a) B. Iberl, G. Winkler, K. Knobloch, *Planta Med.* **1990**, *56*, 202–211; b) with 2-propanol as solvent yields as high as 45% are claimed: B. Iberl, G. Winkler, B. Müller, K. Knobloch, *ibid.* **1990**, *56*, 320.
[117] a) H. Bock, S. Mohmand, T. Hirabayashi, A. Semkow, *Chem. Ber.* **1982**, *115*, 1339–1348; b) E. Vedejs, T. H. Eberlein, D. L. Varie, *J. Am. Chem. Soc.* **1982**, *104*, 1445–1447; c) P. Beslin, *J. Heterocycl. Chem.* **1983**, *20*, 1753–1754.
[118] E. Block, R. Iyer, S. Grisoni, C. Saha, S. Belman, F. P. Lossing, *J. Am. Chem. Soc.* **1988**, *110*, 7813–7827.
[119] a) Lawson finds that **1** from garlic homogenized in water decomposes to the extent of 9% after 24 h at room temperature affording **4c** and **4b** in a 2:1 molar ratio [119b]. He also finds that the half-life of **1** at room temperature is 10 days in 1 mM citric acid (pH 3), 4 days in water, 48 h in MeOH or $CHCl_3$, 3 h in ether, 2 h in hexane and 16 h in the absence of solvent [119b]. On the other hand, Brodnitz reports that *neat* **1** decomposes nearly completely in 20 h at 20 °C giving **4c** and **4b** in a 0.14:1 molar ratio [35a]; b) L. D. Lawson in *Human Medicinal Agents from Plants* (Eds: A. D. Kinghorn and M. Balandarin), American Chemical Society, Washington, D. C., in press; c) E. J. Corey, T. A. Engler, *Tetrahedron Lett.* **1984**, *25*, 149–152; d) recent work indicates that as much as 10% of **79** may in fact be formed from decomposition of **1** (L. D. Lawson, personal communication).
[120] M. A. Belous, I. Y. Postovsskii, *Zh. Obshch. Khim.* **1950**, *20*, 1701–1710; *Chem. Abstr.* **1951**, *45*, 2391.
[121] a) L. D. Lawson, B. G. Hughes, paper presented at the International Joint Symposium, Bonn (FRG), July, 1990; b) L. D. Lawson, S. G. Wood, B. G. Hughes, *Planta Med.* **1991**, *57*, 263–270.
[122] a) L. D. Lawson, B. G. Hughes, *Planta Med.* **1992**, *58*, 345–350; b) B. G. Hughes, L. D. Lawson, *Phytotherapy Research* **1991**, *5*, 154–158.
[123] A. Sendl, H. Wagner, *Planta Med.* **1991**, *57*, 361–362.
[124] R. E. Hermes, *US-A 4917921*, **April 17, 1990**.
[125] a) W. Dorsch, E. Schneider, T. Bayer, W. Breu, H. Wagner, *Int. Arch. Allergy Appl. Immunol.* **1990**, *92*, 39–42; b) H. Wagner, W. Dorsch, T. Bayer, W. Breu, F. Willer, *Prostaglandins, Leukotrienes Essential Fatty Acids* **1990**, *39*, 59–62; c) T. Bayer, H. Wagner, V. Wray, W. Dorsch, *Lancet* **1988**, 906; d) W. Dorsch, H. Wagner, T. Bayer, B. Fessler, G. Hein, J. Ring, P. Scheftner, W. Sieber, T. Strasser, E. Weiss, *Biochem. Pharmacol.* **1988**, *37*, 4479–4485; e) W. Dorsch, B. Adelmann-Grill, T. Bayer, M. Ettl, G. Hein, H. Jaggy, J. Ring, P. Scheftner, H. Wagner, *Allergologie* **1987**, *10*, 316–324; f) W. Dorsch, M. Ettl, G. Hein, P. Scheftner, J. Weber, T. Bayer, H. Wagner, *Int. Arch. Allergy Appl. Immunol.* **1987**, *82*, 535–536; g) W. Dorsch, H. Wagner, T. Bayer, *Allergologie* **1989**, *12*, 388–396; h) W. Dorsch in *Late Phase Allergic Reactions* (Ed.: W. Dorsch), CRC Press, Boca Raton, **1990**, Ch. 32, pp. 325–332.
[126] H. Nishimura, A. Mizuguchi, J. Mizutani, *Tetrahedron Lett.* **1975**, 3201–3202.
[127] P. Vermeer, J. Meijer, C. Eylander, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1976**, *51*, 25–27.
[128] T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, M. Kumada, *J. Org. Chem.* **1986**, *51*, 3772–3781.
[129] C. E. Fuller, D. G. Walker, *J. Org. Chem.* **1991**, *56*, 4066–4067.
[130] F. Freeman, C. S. Lee, *Magn. Reson. Chem.* **1988**, *26*, 813–816.
[131] J. E. Baldwin, G. Höfle, S. Choi, *J. Am. Chem. Soc.* **1971**, *93*, 2810–2812.
[132] M. Tada, Y. Hiroe, S. Kiyohara, S. Suzuki, *Agric. Biol. Chem.* **1988**, *52*, 2383–2385.
[133] Y. H. Kim, T. Takata, S. Oae, *Tetrahedron Lett.* **1978**, *26*, 2305–2308.
[134] J. A. Ross, R. P. Seiders, D. M. Lemal, *J. Am. Chem. Soc.* **1976**, *98*, 4325–4327.

[135] a) E. Block, S. Naganathan, T. Bayer, unpublished; b) E. Block, S. Naganathan, T. Bayer, unpublished; c) E. Block, D. Putman, H. Gulati, S.-H. Zhao, J. Catalfamo, unpublished; d) E. Block, S.-H. Zhao, *J. Org. Chem.* **1992**, in press.
[136] T. Bayer, *Dissertation*, Universität München, **1988**.
[137] T. Bayer, H. Wagner, E. Block, S. Grisoni, S. H. Zhao, A. Neszmelyi, *J. Am. Chem. Soc.* **1989**, *111*, 3085–3086.
[138] A. Ishii, J. Nakayama, M. Ding, N. Kotaka, M. Hoshino, *J. Org. Chem.* **1990**, *55*, 2421.
[139] P. Vittorelli, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1975**, *58*, 1293–1309.
[140] M. G. Matturro, R. P. Reynolds, *Tetrahedron Lett.* **1987**, *28*, 4981–4984 and references cited therein.
[141] a) M.-C. Kuo, M. Chien, C.-T. Ho, *J. Agric. Food Chem.* **1990**, *38*, 1378–1381; b) M.-C. Kuo, C. T. Ho, *ibid.* **1992**, *40*, 111–117.
[142] R. Huisgen, E. Langhals, *Tetrahedron Lett.* **1989**, *30*, 5369–5372.
[143] a) W. C. Lumma, *J. Am. Chem. Soc.* **1969**, *91*, 2820–2821; b) J. R. Hwu, J. A. Robl, *J. Chem. Soc. Chem. Commun.* **1986**, 704.
[144] E. Block, T. Bayer, *J. Am. Chem. Soc.* **1990**, *112*, 4584–4585.
[145] B. Zwanenburg, A. Wagenaar, L. Thijs, J. Strating, *J. Chem. Soc. Perkin Trans. 1* **1973**, 73–75.
[146] F. Freeman, C. N. Angeletakis, W. J. Pietro, W. J. Hehre, *J. Am. Chem. Soc.* **1982**, *104*, 1161–1165.
[147] P. L. Folkins, D. N. Harpp, *J. Am. Chem. Soc.* **1991**, *113*, 8998–9000.
[148] a) F. Freeman, C. N. Angeletakis, *J. Am. Chem. Soc.* **1981**, *103*, 6232–6235; **1982**, *104*, 5766–6774; **1983**, *105*, 4039–4044; b) F. Freeman, C. Lee, *J. Org. Chem.* **1988**, *53*, 1263–1266; c) F. Freeman, *Chem. Rev.* **1984**, *84*, 117.
[149] a) S. Kawakishi, Y. Morimitsu, *Lancet* **1988**, 330; b) Y. Morimitsu, S. Kawakishi, *Phytochemistry* **1990**, *29*, 3435–3439; c) Y. Morimitsu, S. Kawakishi, *Agric. Biol. Chem.* **1991**, *55*, 889–890; d) Y. Morimitsu, Y. Morioka, S. Kawakishi, *J. Agric. Food Chem.* **1992**, *40*, 368–372.
[150] T. Bayer, W. Breu, O. Seligmann, V. Wray, H. Wagner, *Phytochemistry* **1989**, *28*, 2373–2377.
[151] M. Yagami, S. Kawakishi, M. Namiki, *Agric. Biol. Chem.* **1980**, *44*, 2533–2538.
[152] E. Block, M. Aslam, *Tetrahedron Lett.* **1985**, *26*, 2259–2262.
[153] J. W. Chen, C.-M. Wu, paper presented at the 9th Int. Congr. of Essential Oils, Singapore, **1983**.
[154] H. Naimie, Z. Samek, L. Doleis, Z. ReHacek, *Collect. Czech. Chem. Commun.* **1972**, *37*, 1166–1177.
[155] a) P. Dubs, R. Stüssi, *Helv. Chim. Acta* **1978**, *61*, 2351–2359; b) for related syntheses, see: P. Dubs, M. Joho, *ibid.* **1978**, *61*, 2809–2812.
[156] J. Meijer, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 242.
[157] E. Block, L. K. Revelle, A. A. Bazzi, *Tetrahedron Lett.* **1980**, *21*, 1277–1280.
[158] a) G. J. Karabatsos, R. A. Taller, *J. Am. Chem. Soc.* **1964**, *86*, 4373–4378; b) G. J. Karabatsos, N. Hsi, *Tetrahedron* **1967**, *23*, 1079; c) G. J. Karabatsos, K. L. Krumel, *ibid.* **1967**, *23*, 1097; d) G. J. Karabatsos, R. A. Taller, *ibid.* **1968**, *24*, 3347; e) G. J. Karabatsos, C. E. Osborne, *ibid.* **1968**, *24*, 3361.
[159] R. R. Fraser, T. Durst, M. R. McClory, R. Viau, Y. Y. Wigfield, *Int. J. Sulfur Chem. Part A* **1971**, *1*, 133–142.
[160] E. Vedejs, D. A. Perry, R. G. Wilde, *J. Am. Chem. Soc.* **1986**, *108*, 2985–2989.
[161] W. G. Klemperer, *Angew. Chem.* **1978**, *90*, 258–271; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 246–254.
[162] T. Takata, Y. H. Kim, S. Oae, K. T. Suzuki, *Tetrahedron Lett.* **1978**, 4303–4306.
[163] D. F. Ewing, K. A. Holbrook, R. A. Scott, *Org. Magn. Reson.* **1975**, *7*, 554–556.
[164] a) E. Block, A. A. Bazzi, J. B. Lambert, S. M. Wharry, K. K. Andersen, D. C. Dittmer, B. H. Patwardhan, D. J. H. Smith, *J. Org. Chem.* **1980**, *45*, 4807–4810; b) J. B. Lambert, S. M. Wharry, E. Block, A. A. Bazzi, *ibid.* **1983**, *48*, 3928–3985.
[165] a) T. A. Powers, S. A. Evans, K. Pandiarajan, J. C. N. Benny, *J. Org. Chem.* **1991**, *56*, 5589–5594; b) T. A. Powers, L. G. Pedersen, S. A. Evans, *Phosphorus, Sulfur, Silicon Relat. Elements.* **1991**, *58*, 499–504.
[166] E. Block, S. Naganathan, *Heteroat. Chem.*, in press.
[167] M. Barfield, E. W. Della, P. E. Pigou, *J. Am. Chem. Soc.* **1984**, *106*, 5051–5054.
[168] F. Challenger, D. Greenwood, *Biochem. J.* **1949**, *44*, 87–91.
[169] S. Belman, G. Barany, private communication.
[170] a) Boiling chopped/crushed garlic in water for 20 min in a closed container completely converts **1** into **4b** and **4c**, while in an open container 7% of thiosulfinates are retained but most **4b** and **4c** are evaporated. [119b] Cysteine sulfoxides and γ-glutamylcysteines (see Scheme 2) are the exlusive sulfur compounds found when whole cloves of garlic are cooked under similar conditions. [119b] Stir-frying chopped garlic cloves in hot soybean oil for 1 min retains 16% of **4b** and **4c** in the oil, but no **1**. [119b]; b) L. D. Lawson, Z.-Y. J. Wang, B. G. Hughes, *Planta Med.* **1991**, *57*, 363–370.
[171] E. Block, S.-H. Zhao, *Tetrahedron Lett.* **1990**, *31*, 5003–5006.
[172] R. D. Baechler, J. P. Hummel, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 4442–4444.
[173] E. Block, S.-H. Zhao, *Tetrahedron Lett.* **1990**, *31*, 4999–5002.
[174] H. Boelens, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 141–145.
[175] a) M. M. Campbell, D. M. Evgenios, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2866; b) F. C. V. Larsson, L. Brandsma, S.-O. Lawesson, *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 258.
[176] M. Boelens, P.J. de Valois, H. J. Wobben, A. van der Gen, *J. Agric. Food Chem.* **1971**, *19*, 984–991.
[177] a) This is said to be a Rabelaisan verse from the Medical School of Salerno translated by Harington; b) Dr. Simon, *Med. Klin.* **1932**, *3*, 86–87.
[178] L. Pasteur, *Ann. Chim. Phys. Ser. 3* **1858**, *52*, 404–418.
[179] A. I. Virtanen, E. J. Matikkala, *Acta Chem. Scand.* **1959**, *13*, 1898–1900.
[180] N. Didry, M. Pinkas, L. Dubreuil, *Pharmazie* **1987**, *42*, 687–688.
[181] F. Barone, M. Tansey, *Mycologia* **1977**, *69*, 713–824.
[182] L. E. Davis, J.-K. Shen, Y. Cai, *Antimicrob. Agents Chemother.* **1990**, *34*, 651–653.
[183] M. A. Ghannoum, *J. Gen. Microbiol.* **1988**, *134*, 2917–2924.
[184] a) V.-N. Tariq, A. C. Magee, *Mycol. Res.* **1990**, *94*, 617–620; b) R. D. Durbin, T. F. Uchytil, *Phytopathol. Mediterr.* **1971**, *10*, 227–230.
[185] Y. Cai in *Cardiol. Practice* **1991**, June Suppl., p. 11.
[186] A. S. Weisberger, J. Pensky, *Science (Washington, D.C.)* **1957**, *126*, 1112–1115.
[187] a) B. H. S. Lau, P. P. Tadi, J. M. Tosk, *Nutr. Res. (N.Y.)* **1990**, *10*, 937–948; b) J. G. Dausch, D. W. Nixon, *Prev. Med.* **1990**, *19*, 346–361.
[188] a) W. C. You, W. J. Blot, Y. S. Chang, A. Ershow, Z. T. Yang, Q. An, B. E. Henderson, J. F. Fraumeni, Jr., T. G. Wang, *J. Natl. Cancer Inst.* **1989**, *81*, 162–164; b) W. J. Blot in *Accomplishments in Cancer Research 1987* (Eds.: J. G. Fortner, J. E. Rhoads), J. B. Lippincott, Philadelphia, **1987**, pp. 231–239; c) E. Buiatti, W. Blot et al., *Int. J. Cancer* **1989**, *44*, 611–616.
[189] a) M. Xing, W. Mei-ling, X. Hai-xiu, P. Xi-pu, G. Chun-yi, H. Na, F. Mei-yun, *Yingyang Xuebao (Acta Nutr. Sin.)* **1982**, *4*, 53–58; b) C. S. Yang, *Cancer Res.* **1991**, *51*, 1509–1514.
[190] a) S. Belman, J. Solomon, A. Segal, E. Block, G. Barany, *J. Biochem. Toxicol.* **1989**, *4*, 151–160; b) J. P. Perchellet, E. M. Perchellet, S. Belman, *Nutr. Cancer* **1990**, *14*, 183–193.
[191] a) M. Wargovich, *Carcinogenesis (London)* **1987**, *8*, 487–489; b) M. Wargovich, J. C. Woods, L. V. Eng, L. C. Stephens, K. Gray, *Cancer Res.* **1988**, *48*, 6872–6875; c) M. A. Hayes, M. T. Goldbert, T. H. Rushmore, *Carcinogenesis* **1987**, *8*, 1155–1157; d) J. F. Brady, H. Ishizaki, D. Li, C. S. Yang, *Cancer Res.* **1988**, *48*, 5937–5940; e) H. Sumiyoshi, M. Wargovich, *ibid.* **1990**, *50*, 5084–5087.
[192] V. L. Sparnins, G. Barany, L. W. Wattenberg, *Carcinogenesis* **1988**, *9*, 131–134.
[193] L. W. Wattenberg, *Proc. Nutr. Soc.* **1990**, *49*, 173–183.
[194] a) V. A. Gudi, S. V. Singh, *Biochem. Pharmacol.* **1991**, *42*, 1261–1265; A. K. Maurya, S. V. Singh, *Cancer Lett.* **1991**, *57*, 121–129; b) H. J. Prochaska, A. B. Santamaria, P. Talalay, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 2394–2398; c) P. P. Tadi, *Nutr. Cancer* **1991**, *15*, 87–95.
[195] S. Belman, A. Seilakumar, M. C. Bosland, K. Savarese, R. D. Estensen, *Nutr. Cancer* **1990**, *14*, 141–148.
[196] a) A. Bordia, H. C. Bansal, *Lancet* **1973**, *2*, 1491–1492; A. Bordia, *Am. J. Clin. Nutr.* **1981**, *34*, 2100–2103; b) A. Bordia, *Dtsch. Apoth. Ztg.* **1989**, *129* (Suppl. 15), 16–17; A. Bordia, *Cardiol. Prac.* **1989**, *7* (Suppl. 10), 14; c) K. T. Augusti, P. T. Mathew, *Experientia* **1974**, *30*, 468–470; d) M. F. Kerekes, T. Feszt, *Artery* **1975**, *1*, 325–326; e) R.C. Jain, *Am. J. Clin. Nutr.* **1977**, *30*, 1380–1381; f) Second International Garlic Symposium, in *Die Medizinische Welt* **1991**, Suppl. 7a, pp. 1–50; *Cardiol. Practice* **1991**, June Suppl., pp. 2–19; *Dtsch. Apoth.-Ztg.* **1991**, *131*, Suppl. 24, pp. 1–24.
[197] a) M. Focke, A. Feld, H. K. Lichtenthaler, *FEBS-Lett.* **1990** (14), 106–108; b) R. V. O. Kumar, A. Banerji, C. K. R. Kurup, T. Ramasarma, *Biochim. Biophys. Acta* **1991**, *1078*, 219–225.
[198] a) P. R. Mayeux, K. C. Agrawal, J.-S. H. Tou, B. T. King, H. L. Lippton, A. L. Hyman, P. J. Kadowitz, D. B. McNamara, *Agents Actions* **1988**, *25*, 182–190; b) A. Bordia, *Atherosclerosis (Shannon, Irel.)* **1978**, *30*, 355–360; c) D. J. Boullin, *Lancet* **1981**, 776–777; d) A. N. Makheja, J. Y. Vanderhoek, R. W. Bryant, J. M. Bailey, *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 309–312; e) J. Y. Vanderhoek, A. N. Makheja, J. M. Bailey, *Biochem. Pharmacol.* **1980**, *29*, 3169–3173; f) H. Weisenberger, H. Grube, E. Koenig, H. Pelzer, *FEBS-Lett.* **1972** (26), 105–108; g) M. Ali, M. Thomson, M. A. Alnaqeeb, J. M. Al-Hassan, S. H. Khater, S. A. Gomes, *Prostaglandin Leukotriene Essential Fatty Acids* **1990**, *41*, 95–99.
[199] a) E. D. Wills, *Biochem. J.* **1956**, *63*, 514–520; b) J. D. Gaffen, I. A. Tavares, A. Bennett, *J. Pharm. Pharmacol.* **1984**, *36*, 272–274.
[200] K. Scharfenberg, R. Wagner, K. G. Wagner, *Cancer Lett.* **1990**, *53*, 103–108.
[201] a) A. Sendl, G. Elbl, B. Steinke, K. Redl, W. Breu, H. Wagner, *Planta Med.* **1992**, *58*, 1–7; b) H. Wagner, M. Wierer, B. Fessler, *Planta Med.* **1987**, *53*, 305–306.
[202] a) R. Apitz-Castro, E. Ledezma, J. Escalante, F. M. Pinate, J. Moreno-Rea, G. Carrillo, O. Leal, M. K. Jain, *Drug Res.* **1988**, *38*, 901–904; b) F. Rendu, M. K. Jain, D. Daveloose, J. C. Debouzy, R. Apitz-Castro, N.

Bourdeau, S. Levy-Toledano, *Biochem. Pharmacol.* **1989**, *38*, 1321–1328; c) J. C. Debouzy, D. Daveloose, J. M. Neumann, J. Viret, M. Herve, R. Apitz-Castro, *Eur. Biophys. J.* **1989**, *17*, 211–216; d) R. Apitz-Castro, M. K. Jain, F. Bartoli, E. Ledezma, M.-C. Ruiz, R. Salas, *Biochim. Biophys. Acta* **1991**, *1094*, 269–280.

[203] a) M. P. Jamaluddin, L. K. Krishnan, A. Thomas, *Biochem. Biophys. Res. Commun.* **1988**, *153*, 479–486; b) G. F. Sud'ina, A. V. Tatarintsev, A. A. Koshkin, S. V. Zaitsev, N. A. Fedorov, S. D. Varfolomeev, *Biochim. Biophys. Acta* **1991**, *1091*, 257–260.

[204] a) S. Yoshida, S. Kasuga, N. Hayashi, T. Ushiroguchi, H. Matsuura, S. Nakagawa, *Appl. Environ. Microbiol.* **1987**, *53*, 615–617; b) U. P. Singh, V. N. Pandey, K. G. Wagner, K. P. Singh, *Can. J. Bot.* **1990**, *68*, 1354–1356; c) G. Sanblas, F. Sanblas, F. Gil, L. Marino, R. Apitz-Castro, *Antimicrob. Agents Chemother.* **1989**, *33*, 1641–1644.

[205] Y. Gargouri, H. Moreau, M. K. Jain, G. H. de Haas, R. Verger, *Biochem. Biophys. Acta* **1989**, *1006*, 137–139.

[206] a) S. A. Barrie, J. V. Wright, J. E. Pizzorno, *J. Orthomol. Med.* **1987**, *2*, 15–21; b) Lawson suggests that the garlic oil used by Bordia in his extensive clinical studies of lowering of blood lipids [196a] is also rich in **9**, **74**, and **75** [119b].

[207] M. L. Allen, M. H. Mellow, M. G. Robinson, W. C. Orr, *Am. J. Gastroenterol.* **1990**, *85*, 377–380.

[208] E. Block, P. F. Purcell, S. R. Yolen, *Am. J. Gastroenterol.* **1992**, *87*, 679.

[209] K. Wallenfels, W. Ertel, A. Hockendorf, J. Rieser, K. H. Uberschar, *Naturwissenschaften* **1975**, *65*, 459–467.

[210] a) I. Laakso, T. Seppanen-Laakso, R. Hiltunen, B. Mueller, H. Jansen, K. Knobloch, *Planta Med.* **1989**, *55*, 257–261; b) T. Minami, T. Boku, K. Inada, M. Morita, Y. Okazaki, *J. Food Sci.* **1989**, *54*, 763–765; c) T. G. Hartman, J. Lech, R. T. Rosen, *Abstracts, Society of Mass Spectrometrists*, **Mai 1991**, Nashville, TN.

[211] a) A patient who made reproduction antique china dolls complained that whereever she touched the dolls' heads when painting them, black speckles appeared after firing, requiring that those dolls' heads be rejected [211b]. It was determined that the clay was high in iron, the speckles consisted of iron sulfides, and the doll maker ate a great deal of garlic and sweated in her job. Analysis of sweat samples showed the presence of diallyl disulfide, allyl methyl disulfide and dimethyl disulfide. Thus, the mystery was solved and simple solutions, abstinence from garlic or use of latex gloves, proposed. b) C. M. Harris, R. H. Waring, S. C. Mitchell, G. L. Hendry, *Lancet* **1986**, 492–493.

[212] M. A. Blankenhorn, C. E. Richards, *J. Am. Med. Assoc.* **1936**, *107*, 409–410.

[213] a) P. Noether, *Münch. Med. Wochenschr.* **1925**, *72*, 1641–1642; b) L. Lawson, private communication (1992).

[214] J. A. Mennella, G. K. Beauchamp, *Pediatrics* **1991**, *88*, 737–744.

[215] a) J. W. Burks, *Ann. Allergy* **1954**, *12*, 592–596; b) C. Papageorgiou, J. P. Corbet, F. Menezes-Brandao, M. Pecegueiro, C. Benezra, *Arch. Dermatol. Res.* **1983**, *275*, 229–234; c) A. E. Falleroni, C.4R. Zeiss, D. Levitz, *J. Allergy Clin. Immunol.* **1981**, *68*, 156–160.

[216] a) B. Kaplan, M. Schewach-Millet, S. Yorav, *Int. J. Dermatol.* **1990**, *29*, 75–76; b) T. Y. Lee, T. H. Lam, *Contact Dermatitis* **1991**, *24*, 193–196; c) G. Lembo, N. Balato, C. Patruno, L. Auricchio, F. Ayala, *ibid.* **1991**, *25*, 330–331.

[217] K. D. Rose, P. D. Croissant, C. F. Parliament, M. B. Levin, *Neurosurgery* **1990**, *29*, 880–882.

[218] a) S. V. Amonkar, A. Banerji, *Science (Washington, D.C.)* **1971**, *174*, 1343–1344; b) S. V. Amonkar, E. L. Reeves, *J. Econ. Entomol.* **1970**, *63*, 1172–1175.

[219] G. Catar, *Bratisl. Lek. Listy* **1954**, *34*, 1004–1010; *Chem. Abstr.* **1955**, *49*, 2002.