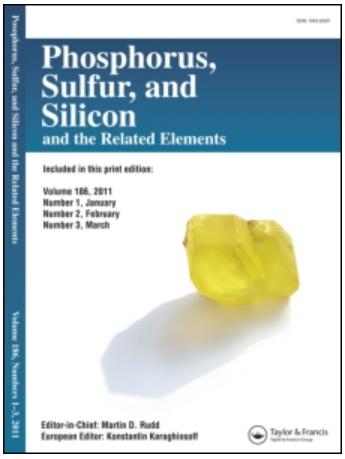

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The Organosulfur Chemistry of the Onion

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THE ORGANOSULFUR CHEMISTRY OF THE ONION

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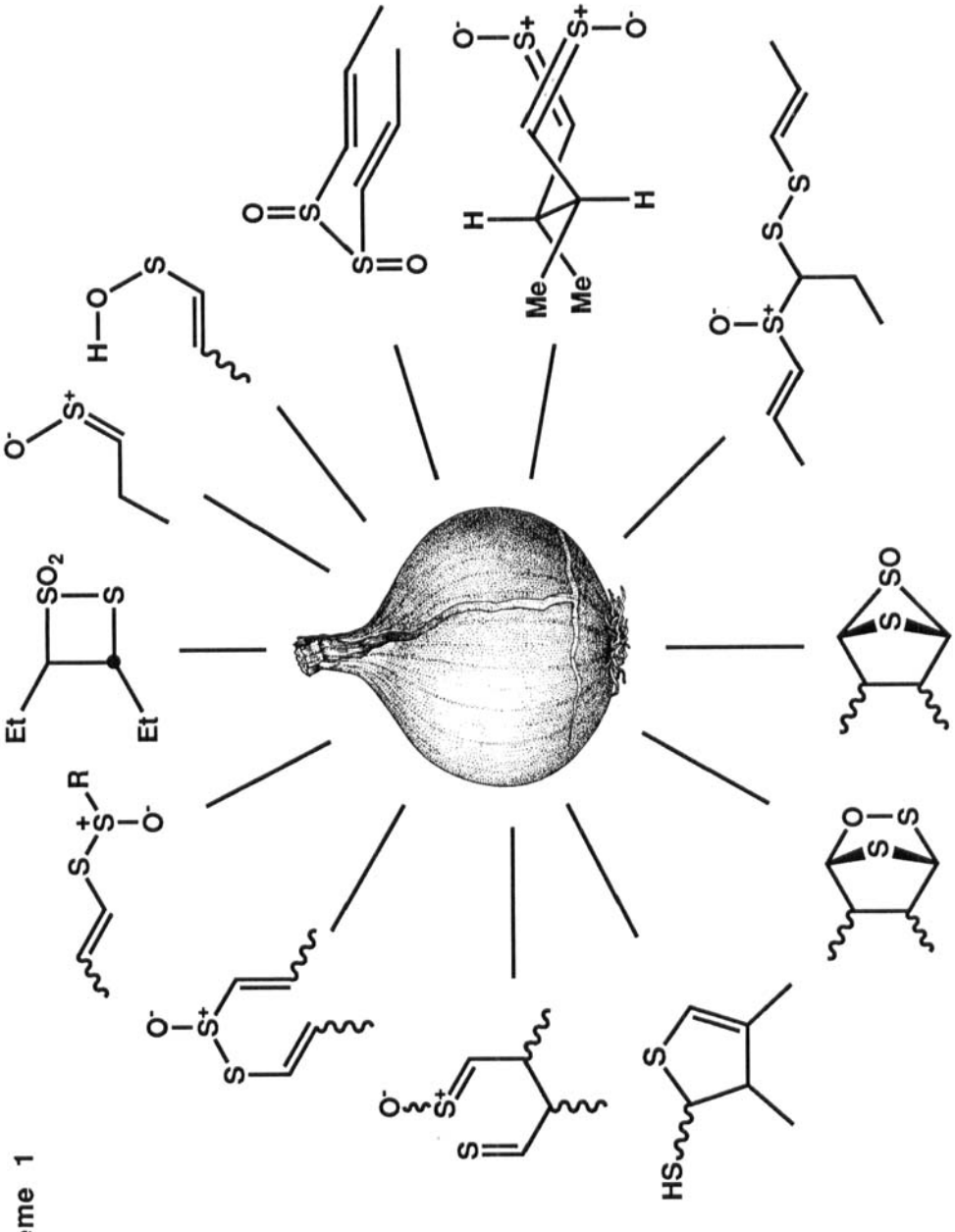
Abstract This review traces the transformation of S-alk(en)yl-L-cysteine sulfoxides, the onion aroma and flavor precursors, to a variety of remarkable cyclic and acyclic reactive organosulfur compounds, and their postulated intermediates, found in onion extracts and distillates. These compounds include sulfenic acids, mono and bis sulfines (thioaldehyde S-oxides), thioaldehydes, saturated and unsaturated thiosulfinate esters, 1,2-dithietanes 1,2-dioxides, 5,6-dithiabicyclo[2.1.1]hexanes ("zwiebelanes"), α-sulfinyldisulfides ("cepaenes"), dihydrothiophenes and thiophenes, among others.

INTRODUCTION

The onion (*Allium cepa*) was among the earliest of cultivated foods, easily identified by primitive food-seekers by its distinctive smell, now known to be associated with organosulfur compounds. The popularity of onions in folk medicine through the centuries for treatment of such varied disorders as dog bites, insect stings, earaches, burns and wounds, baldness, headaches, chest colds, respiratory ailments, asthma, pneumonia, diabetes, cardiovascular disorders, and rheumatism, among others, can be attributed to its pungent aroma, strong taste and lachrymatory effect. The American poet Carl Sandburg wrote: *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 finds a parallel in the large number of unusual organosulfur compounds produced on cutting or cooking onions (depicted schematically in Scheme 1). This review will briefly summarize the current state of affairs on the organic chemistry of onions, with emphasis on compounds containing sulfur and recent studies of these compounds in the author's laboratories.

Organosulfur compounds from onions[1] can be divided into three categories which will be discussed in turn: the stable derivatives of cysteine found in the intact bulb; the labile intermediates and reactive compounds having a fresh onion aroma formed upon cutting onions; the more stable odoriferous compounds found in the headspace above chopped onions or in the distilled essential oil of onion and typically having a characteristic aroma of cooked onions.



Scheme 1

ORGANOSULFUR COMPOUNDS OF INTACT ONION BULBS

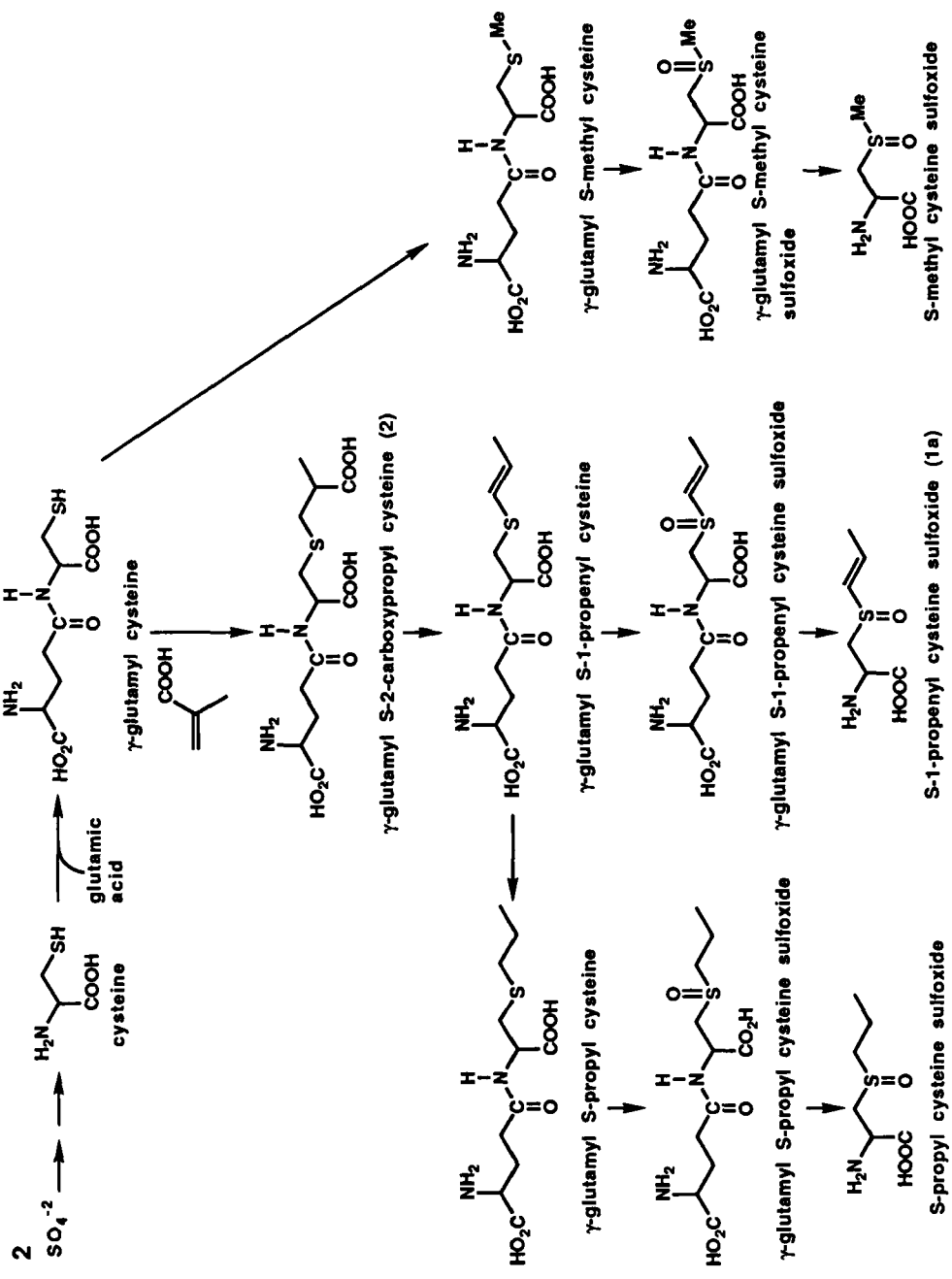
The earliest report (1892) concerning isolation of organic compounds from the onion identified di-*n*-propyl disulfide as the principal component of the distilled oil of onions.[2] In the 1940's it became apparent that this and other volatile sulfur compounds were secondary compounds formed by enzymatic action on precursors in the intact bulb.

The onion and other members of the *Allium* spp. contain 1-5% dry weight of non-protein sulfur amino acid secondary metabolites. In the intact cell, the S-alk(en)yl-L-cysteine sulfoxides (aroma and flavor precursors) are located in the cytoplasm and the hydrolytic enzyme allinase in the vacuole.[3] Disruption of the cell results in release of allinase and subsequent hydrolysis of the sulfoxides to volatile and odorous low molecular weight organosulfur compounds. Onions contain S-(1-propenyl)-, S-methyl- and S-propyl L-cysteine sulfoxides (**1a**, **1b**, and **1c**, respectively).[4] Also present in the cell are a number of γ-glutamyl peptides of sulfur amino acids. These are considered to function as reserves of nitrogen and sulfur. Scheme 2 summarizes the proposed biosynthesis of the various onion peptides and aroma precursors based on the results of feeding onion plants $^{35}SO_4^{2-}$.[5] Sulfate is reduced and assimilated into cysteine in the chloroplasts[6] and then enters the glutathione cycle.[7] Michael addition of γ-glutamyl cysteine to methacrylic acid (from valine) can afford γ-glutamyl-S-2-carboxypropyl cysteine (**2**) which undergoes decarboxylation to give the γ-glutamyl-S-1-propenyl cysteine which is converted to γ-glutamyl-S-1-propenyl cysteine sulfoxide by an oxidase and is then cleaved by γ-glutamyl transpeptidase to **1a**.[8] Parallel processes (not shown) involve Michael addition of glutathione to methacrylic acid giving S-2-carboxypropyl glutathione followed by conversion of the latter to **2** and methylation of glutathione giving S-methyl glutathione followed by conversion of the latter to γ-glutamyl-S-methyl cysteine.

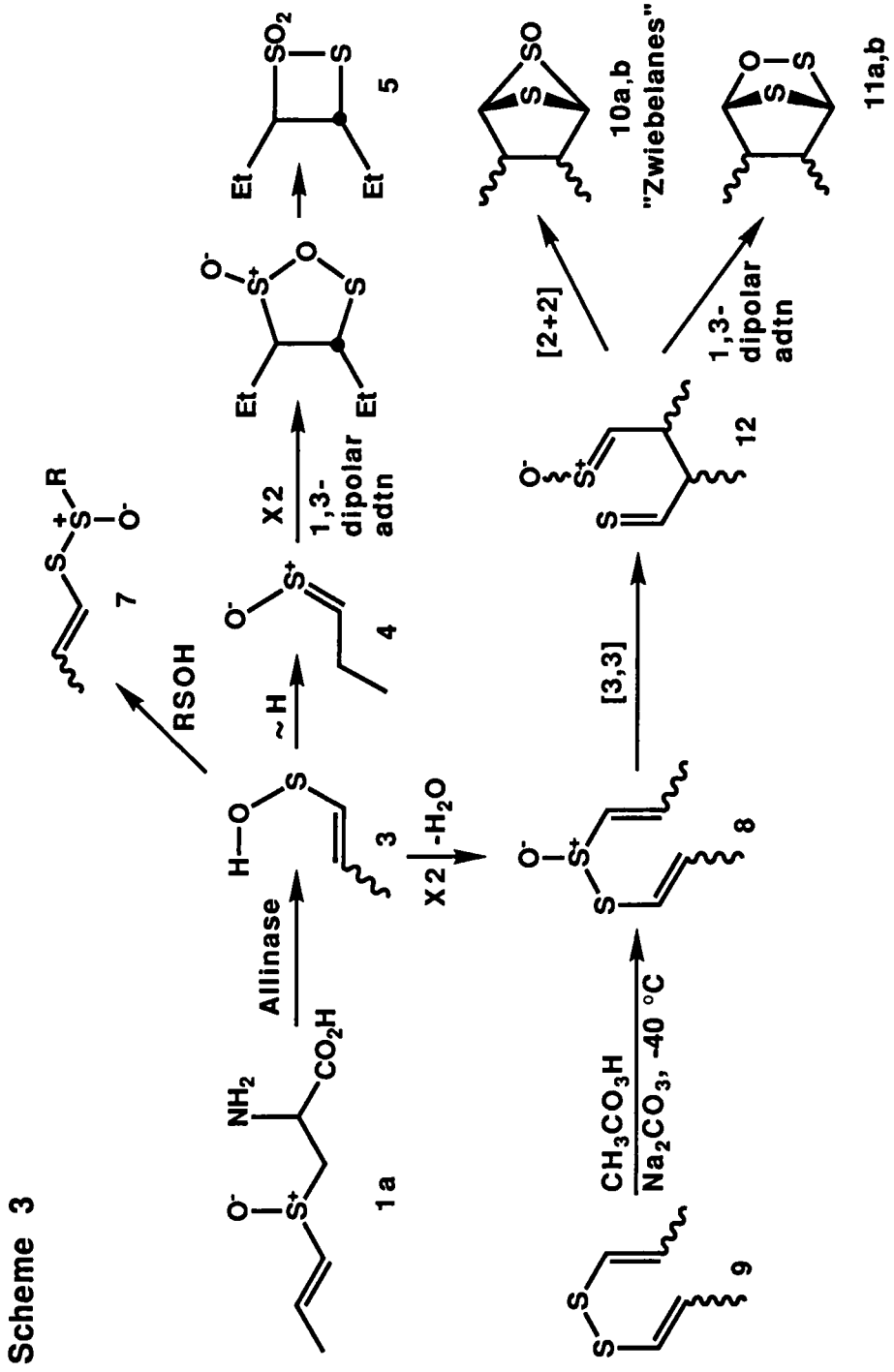
ORGANOSULFUR INTERMEDIATES AND REACTIVE COMPOUNDS OF CUT ONIONS

Hydrolysis of **1a-c** is thought to first afford *trans*-1-propenesulfenic acid (**3**), methanesulfenic acid, and propanesulfenic acid, respectively (Scheme 3). Based on our microwave spectroscopic characterization of methanesulfenic acid as MeS-O-H,[9] I suggest that all of these sulfenic acids exist in the form RS-O-H rather than RS(O)H.

One of the most remarkable of the reactive compounds of cut onions is propanethial S-oxide (**4**), the isolable form of the lachrymatory factor of the onion, and the first naturally occuring representative of a class of compounds known as sulfines (S-oxides of thioaldehydes and thioketones).[10] This compound which exists as a mixture of (Z)- and (E)-isomers with the former predominating, has been characterized by GC-MS,[11a] IR,[11a]



Scheme 3



microwave spectroscopy[11b] and ^{1}H,[11c] ^{13}C[10a] and ^{17}O[10a] NMR spectroscopy and can be trapped as a group of isomeric cyclopentadiene Diels-Alder adducts.[12] We have suggested that **4** is formed by 1,4-prototropic rearrangement of sulfenic acid **3**.[11b] On standing **4** is converted into the interesting dimer *trans*-3,4-diethyl-1,2-dithietane 1,1-dioxide (**5**, Scheme 3).[13] Compound **4** is not the only sulfine from onions. Recently we have reported the isolation from onion extracts of an unusual bis-sulfine, (Z,Z)-d,l-2,3-dimethyl-1,4-butanedithial S,S'-dioxide (**6**; O=S=CHCHMeCHMeCH=S=O).[14] Compound **6** will be discussed below.

Another significant group of odorous compounds detected in fresh onion extracts are the thiosulfinates MeS(O)SMe, (E,Z)-MeCH=CHSS(O)Me (**7a**), (E,Z)-MeCH=CHSS(O)Pr (**7b**), and PrS(O)SPr, which most likely are formed by condensation of the several sulfenic acids.[15a] It is notable that the thiosulfinates exert antiasthmatic activity in vivo and are dual inhibitors of cyclooxygenase and 5-lipoxygenase in vitro.[15] Authentic samples of these thiosulfinates can be regioselectively prepared by oxidation of the respective unsymmetrical disulfides with MCPBA.[16] Apparently the sulfur attached to the sp^2 carbon is substantially less nucleophilic toward MCPBA than the sulfur attached to the saturated carbon.

In view of the detection of thiosulfinates MeS(O)SMe and PrS(O)SPr from the minor sulfenic acids MeSOH and PrSOH along with major amounts of thiosulfinates **7a/b** apparently derived from MeCH=CHSOH it is surprising that the thiosulfinate MeCH=CHS(O)SCH=CHMe (**8**) is not detected. The reason for the absence of **8** became apparent during attempts to prepare this compound by MCPBA oxidation of isomers of bis(1-propenyl) disulfide (**9**). Thus, while (Z,Z)-MeCH=CHS(O)SCH=CHMe could indeed be detected and characterized at -40 °C by low temperature NMR techniques,[16] upon warming TO -15 °C it rapidly rearranged to a compound found in onion extracts and termed a zwiebelane (**10a**)(see Scheme 3; trans isomer **10a** is more precisely named (±)-(1α, 2α, 3β, 4α, 5α)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide).[17]

The chemistry associated with the oxidation of isomers of **9** is actually rather complex: Monooxidation of (E,E)-**9** affords 5-*exo*-6-*endo*-dimethyl-2,7-dithia-3-oxabicyclo[2.2.1]heptane (**11a**), monoxidation of (Z,Z)-**9** gives **10a** (along with a trace of trans-**11a**) as already noted, and monooxidation of (E,Z)-**9** yields a mixture of the cis-dimethyl isomer **10b** (major product) and **11b** (minor product) via two isomeric thiosulfinates.[16] These processes must involve stereospecific [3,3]-sigmatropic rearrangements since carbon stereochemistry is conserved. In each case ^{13}C and ^{1}H NMR spectroscopy indicates that the corresponding thiosulfinates (E,E)-, (Z,Z)-, and (E,Z)-**8**, respectively, are the sole products at -40 °C. At -15 °C (E,E)-**8** has a half life of 20 minutes; the ratio

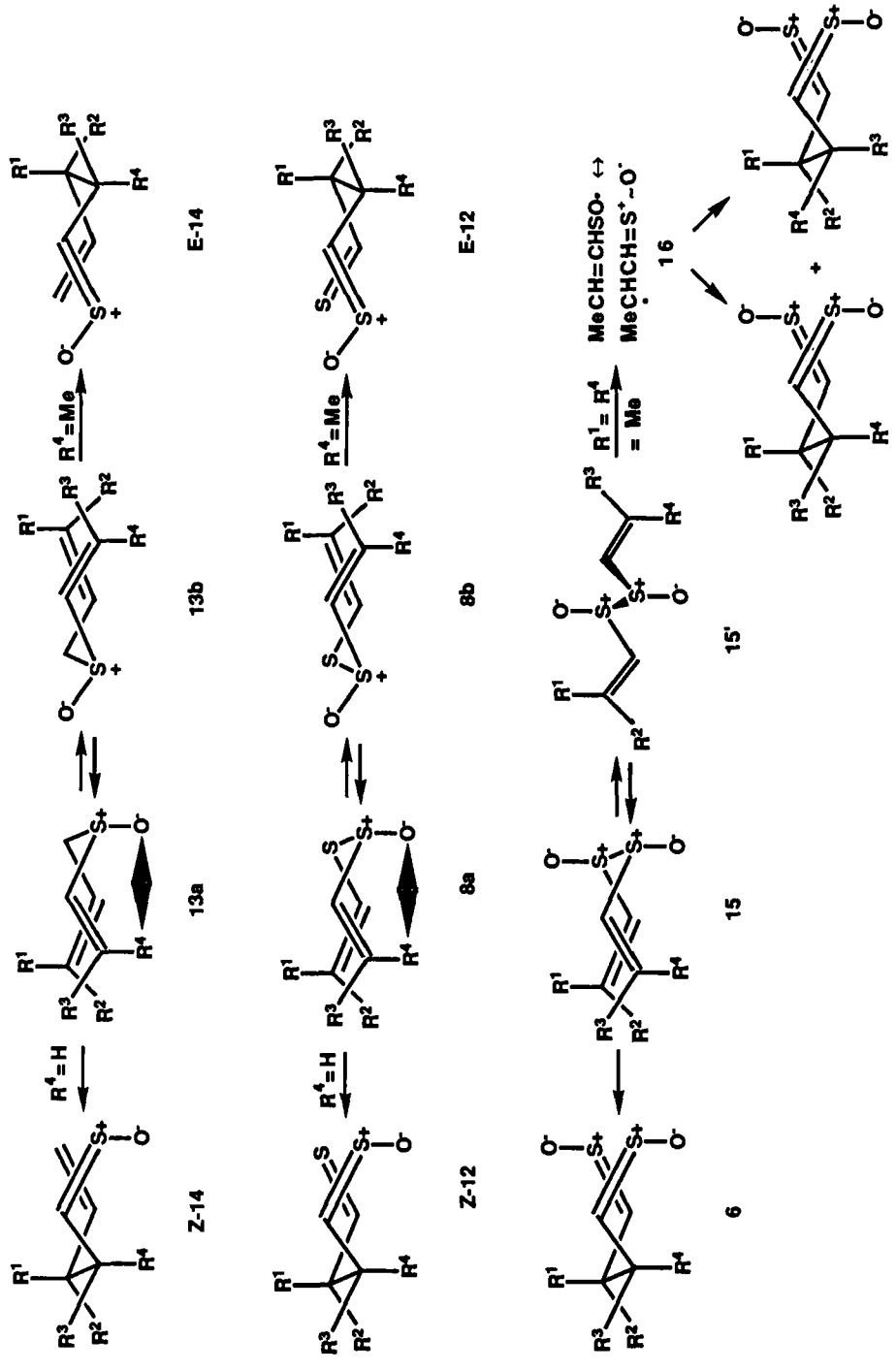
of rearrangement rate constants (E,E)-**8**:(E,Z)-**8**:(Z,Z)-**8** is 2.7:1.4:1 which is similiar to values for Claisen rearrangement of 1-alkenyl 2-alkenyl ethers.[18] I suggest that the difference in products is due to differences in stereochemistry at sulfur in the pseudocyclic transition state (e.g. pseudoaxial or pseudoequatorial orientation of sulfoxide oxygen) leading to Z and E isomers of 2,3-dimethyl-1,4-butanedithial S-oxide ((Z)-**12** and (E)-**12**).

To rationalize the results it is useful to recall our analysis of the stereochemical effects seen in the related sulfoxide accelerated thio-Claisen rearrangement (Scheme 4).[19a] Assuming a chairlike transition state for rearrangement of 1-alkenyl 2-alkenyl sulfoxides **13** to sulfine **14** then pseudoaxial or pseudoequatorial orientations become possible for the sulfoxide oxygen. In the case of thiane S-oxides an axial orientation for oxygen 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.[19b] Similar effects prevail in the sulfoxide thio-Claisen, e.g. favoring **13a** → (Z)-**14** when R^4 = H but favoring **13b** → (E)-**14** when R^4 = Me.[19a]

By the same analysis a pseudoaxial conformation for oxygen (e.g. **8**, $R^1 = R^4$ = H, $R^2 = R^3$ = Me from (E,E)-**9** or $R^2 = R^4$ = H, $R^1 = R^3$ = Me, one regioisomeric oxidation product from (E,Z)-**9**) should represent the lowest energy geometry for thiosulfinate dithio-Claisen rearrangements except in the case of a Z C=C double bond (e.g. **8**, $R^1 = R^4$ = Me, $R^2 = R^3$ = H from (Z,Z)-**9** or $R^2 = R^4$ = Me, $R^1 = R^3$ = H, a second regioisomeric oxidation product from (E,Z)-**9**). Pseudoaxial sulfoxide transition state geometry correlates with the geometry of (Z)-**12** while pseudoequatorial sulfoxide geometry correlates with the geometry of (E)-**12**. While (Z)-**12** can readily undergo intramolecular 1,3-dipolar cycloaddition of the C=S-O dipole to the C=S group affording **11a** (arrow with (Z)-**12** in Scheme 4), geometric restraints prevent (E)-**12** from undergoing an analogous process thereby favoring an alternative 2+2 process leading to **10**.

In the case of further oxidation of **8** to bis(1-propenyl) vic-disulfoxides (**15**), theoretical studies predict[20] that an anti (diaxial) arrangement of the oxygens should be favored. This correlates with Z,Z-bissulfine geometry in **6**. With (E,E)-**9** the second oxidation procedes cleanly via the diaxial vic-disulfoxides which in turn undergoes concerted [3,3] rearrangement at -25 °C to the d,l bis-sulfine whose geometry was unequivocally established both by spectroscopic means and by degradation to the dimethyl ester of d,l-2,3-dimethylsuccinic acid.[14] In these studies **6** is prepared by oxidation of E,E-**9** with two equivalents of MCPBA or treatment of (E)-1-propenyl (E)-1-propenethiosulfinate E,E-**8** at-40 °C with one equivalent of oxidant. Compound **15** cannot be detected using low-temperature NMR methods. Apparently the rate of rearrangement of **15** is faster than the rate of oxidation of thiosulfinate **8** so the former never

Scheme 4

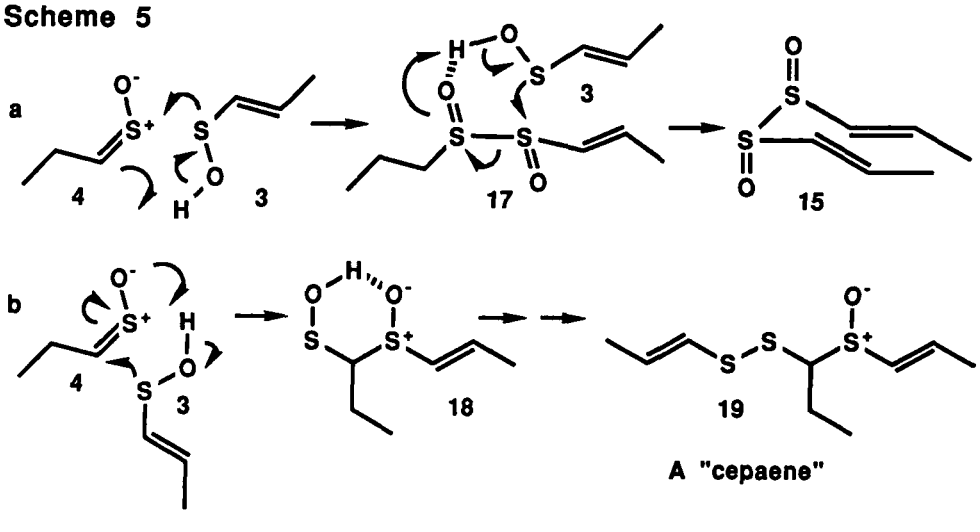


accumulates. When the cis C=C geometry unduly increases the energy of the chairlike transition state with pseudodiaxial bis-sulfoxide geometry (e.g. **15**, $R^1 = R^4 = Me$), the favored open form of vic-disulfoxide (**15'**) cannot assume a chair geometry necessary for concerted rearrangement so it undergoes homolytic cleavage to a pair of 1-propenylsulfinyl radicals **16** which randomly combine giving both d,l and meso bis sulfines **6** and **6'**.

How is **15** formed? We have suggested[14] that thiophilic addition of **3** to **4** gives n-propyl 1-propenyl *vic*-disulfoxide (**17**) which reacts further with a second molecule of **3** giving **15** (Scheme 5).[14] If reaction of **3** with **4** occurs instead through carbophilic addition an α-(1-propenesulfinyl)propanesulfenic acid (**18**) results. These intermediates are believed to be the precursors of another class of unusual biologically active organosulfur compounds from onion, the cepaenes, α-sulfinyl disulfides such as (E,E)-MeCH=CHS(O)CHEtSSCH=CHMe (**19**), (E)-MeCH=CHS(O)CHEtSSCH$_2$CH$_2$Me, MeS(O)CHEtSSMe (Scheme 5).[15a,21] The cepaenes are also potent dual inhibitors of cyclooxygenase and 5-lipoxygenase in vitro.[15]

What other compounds remain to be identified in fresh onion extracts? Application of field desorption mass spectroscopy, a method particularly suitable for thermally unstable organic compounds, to the analysis of onion extracts indicates that the heaviest compounds present have masses of 325-326 and 298-301,[16] corresponding respectively to molecular formulas $C_{12}H_{20}S_4O_2/C_{12}H_{22}S_4O_2$ and $C_{10}H_{18}S_4O_2/C_{10}H_{20}S_4O_2$. Efforts to identify these compounds are underway.

Scheme 5



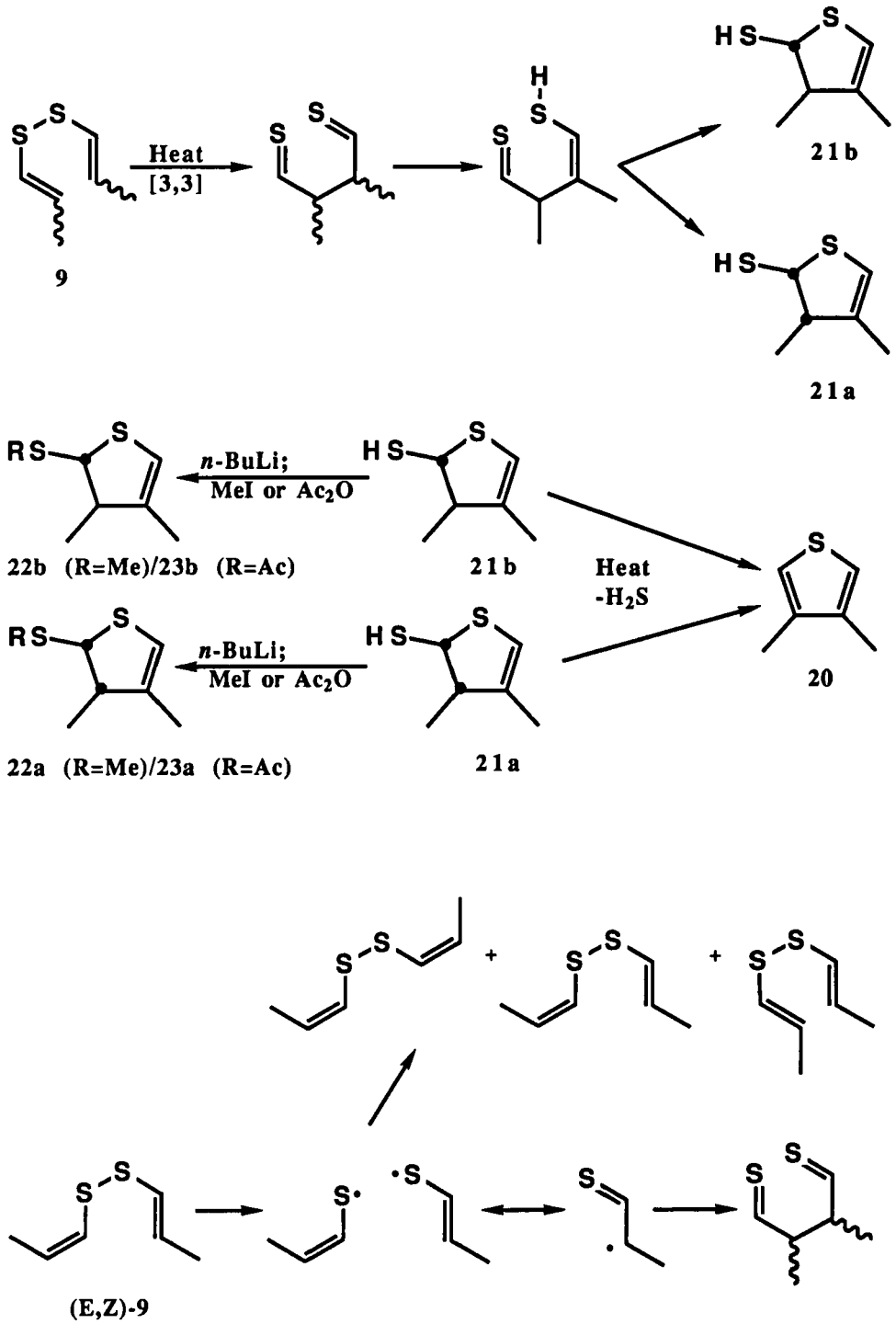
ORGANOSULFUR COMPOUNDS IN ONION ESSENTIAL OIL AND HEADSPACE VOLATILES

Modern analytical methods such as GC-MS now reveal the presence of over 100 different organosulfur compounds in the essential oil of onion.[22] Of course many of these compounds are thermal decomposition products, formed during the steam distillation process, of more labile compounds produced by slicing or chopping fresh onions. One recent GC-MS study of the composition of the diethyl ether-water distillate of ground onions claims the appearance of the following acyclic organosulfur compounds: MeS_nMe (n = 2-5), *i*-PrSSR (R = Me, Et, *n*-Bu), *n*-PrSSR (R = Bu, Et), MeS_nPr-*n* (n = 2-5), *n*-PrS_nPr-*n*, (n = 2,3,4), $CH_2{=}CHCH_2S_nR$ (R = Me, *n*-Pr, $CH_2{=}CHCH_2$-; n = 2,3), (E,Z)-$CH_3CH{=}CH_2S_nR$ (R = Me, Pr; n =2,3,4), (E,Z)-$(CH_3CH{=}CH_2)_2S_n$ (n = 2,3,4).[22] These polysulfides presumably originate by thermal decomposition and disproportionation of precursors such as thiosulfinates. A limitation of GC-MS in both qualitative and quantitative analysis of higher polysulfides in onion distillates is that these compounds can be unstable under the conditions of analysis.[23] Analysis by the recently developed techniques of LC-MS and SCFC (supercritical fluid chromatography) should minimize the problems due to thermal decomposition of unstable onion components.

Curiously the major component of onion oil, *n*-PrSSPr-*n*, is present to a far greater extent than is reflected in the relative amount of the propyl cysteine derivative **1c** in fresh onions (**1a**:**1c** = 85:12). To explain this fact we suggest that *n*-PrSSPr-*n* arises by sequential reduction of lachrymator **4** to propanesulfenic acid and then propanethiol; the latter two compounds combine forming the disulfide.[16] A natural reducing system approximately equal to sodium borohydride in reducing power, is known to be present in onion juice.[24]

One of the significant cyclic sulfur compounds found in onion distillates is 3,4-dimethylthiophene (**20**)[25]. Compound **20** is one of the significant contributors to the aroma of cooked or fried onions and long known to be a component of the headspace above chopped onions.[25] We find that heating a 1% solution of the isomers of bis(1-propenyl) disulfide (**9**) in benzene at 85 °C for 3 h affords a 1:1 mixture of *cis*- and *trans*-2-mercapto-3,4-dimethyl-2,3-dihydrothiophene (**21a/b**)(Scheme 6).[26] When individual isomers of **9** are subjected to heating in benzene each affords the same mixture of **21a/b**. Furthermore no isomerization from one isomer of **9** to another occurs under the thermolysis condition. We suggest that compounds **21a/b** are formed from **9** via dithio-Claisen [3,3]-sigmatropic rearrangement followed by thioenolization and intramolecular addition of SH to CH=S. The absence of interconversion of isomers **9** under the reaction conditions precludes a homolytic route to **21a/b**.[28] While **21a/b** are rather unstable they can be converted into stable derivatives by treatment with methyl iodide or acetyl

Scheme 6



chloride.[26] Prolonged heating at higher temperatures results in the conversion of **4a/b** into **20**.[26] We believe that thiophene **20** is formed in onions via **21a/b** by loss of H_2S.

CONCLUSION

From what has been presented in this review it is apparent that from a chemical standpoint "to know one's onions" is a highly challenging task affording a fascinating insight into a host of unusual, reactive, and physiologically potent organosulfur compounds.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the major contributions of my many coworkers and colleagues, whose names are indicated in the references, in our continuing investigation of the organosulfur chemisty of onion and garlic. Our work was funded by NSF, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, NATO, and the McCormick Company.

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