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FIFTY YEARS OF RESEARCH IN SULFUR CHEMISTRY

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Marvin Carmack was born in 1913 near Dana, Vermillion County, Indiana, U.S.A., and attended public schools there. He graduated from the University of Illinois in 1937 with A.B. Honors in Chemistry. During 1937–40 he earned the M.S. and Ph.D. degrees at the University of Michigan, working with Professor Werner E. Bachmann on the synthesis of substituted benzopyrene compounds as potential carcinogens. At Michigan he carried out his first experiments with the Willgerodt Reaction, which remained one continuing subject of his interest for the next fifty years—an interest that broadened to include many aspects of sulfur chemistry.

A year of post-doctoral research with Professor Roger Adams at the University of Illinois dealt with the isolation and determination of structures of alkaloids of the *Crotalaria* and *Senecio* species. This research resulted in the revision of the structure of retronecine, the common subunit of most of these alkaloids.

In 1941 he joined the Faculty of Chemistry in the Towne Scientific School of the University of Pennsylvania in Philadelphia. At the beginning of World War II he became the Official Investigator of a contract between the University of Pennsylvania and the National Defense Research Committee of the Office of Scientific Research and Development. Its mission was the study of military high explosives. Later, under the Committee on Medical Research, his group investigated potentially antimalarial compounds.

After World War II, his academic program was divided between the isolation and structure determination of natural products and the study of sulfur chemistry. He served as consultant to several industries and the Los Alamos National Laboratory. He has been a member of many scientific societies.

During the academic year 1949–50, a Guggenheim Foundation Fellowship took him to the Swiss Eidgenössische Technische Hochschule in Zürich, where he worked with Professor Vladimir Prelog on the chemistry of the *Erythrina* alkaloids. A satisfying outcome that resulted from this research was a new spiro structure for the central ring system of the *Erythrina* alkaloids.

He attained the rank of Professor of Chemistry at the University of Pennsylvania in 1951. In 1953, he moved to Indiana University as Professor of Chemistry, teaching graduate and undergraduate courses in organic chemistry and continuing research in natural products and sulfur chemistry. In 1960, he married Joan M. Scully of LaGrange, Illinois, and with her spent most of 1960–61 in Melbourne, Australia, under a Fulbright Research Fellowship. He worked in the laboratory of natural products chemistry directed by Dr. J. R. Price of the Commonwealth Scientific and Industrial Organisation. At that time, Dr. Price was coordinating a large program involving collection and broad screening of many unique plant species of Australia and New Guinea for therapeutically useful compounds.

Carmack formally retired in 1978, with the rank of Professor Emeritus of Chemistry, but continued to be active within the Department of Chemistry at Indiana University. He worked informally with the research group under Rudy Professor of Analytical Chemistry, Dr. Milos Novotny. In addition to Dr. Novotny's main program of developing new and highly sensitive techniques in analytical chemistry, his group was also concerned with the application of their new technologies to the solution of problems in biology and medicine, among them the identification of mammalian pheromones. Working with Dr. Wesley K. Whitten and other noted biologists, the group studied pheromones of the red fox, the mouse, the wolf, and other species, and published a number of papers on the pheromones that were identified. Carmack's association with the Novotny group was concerned with the organic chemistry involved in the identification, structure determination, synthesis, and stereochemistry of specific mammalian pheromones.

Carmack has been active in community affairs, serving as Board Member and Treasurer of the Boys' Club of Bloomington and the Society of the Friends of Music of Indiana University. He is a member of the Board of the Bloomington Hospital Foundation, and the Hospital's Advisory Council. In 1993,

Carmack received the Indiana University President's Medal and Citation for Excellence in Teaching and Research.

Key words: Carmack, Marvin; Kindler reaction; pheromones; stereochemistry, thiadiazoles; thiirenes; Willgerodt reaction.

CONTENTS

1. INTRODUCTION

The richness of the chemistry of sulfur and its compounds is the result of a wide diversity of properties of the element, among which may be mentioned:

• Elemental sulfur can exist in an almost infinite number of forms.[1] The common form is the crystalline rhombic, consisting of crown rings of eight atoms, but elemental sulfur is known to form small, medium, and large rings with itself and other elements. These vary widely in reactivity. When elemental sulfur is heated at high temperature, monatomic sulfur is formed—a highly reactive species. Diatomic S_2 is formed and is stable at somewhat lower temperatures than monatomic S, but is still very reactive. Chains of sulfur atoms in the form of unbranched diradicals of four or more atoms have been characterized, as well as medium- to long-chain polymers. When long-chain polymers of sulfur, formed at temperatures well above the melting point, are quenched, the unstable polymeric forms are highly elastic but revert gradually to the stable ring forms. When the elastic forms of polymeric sulfur are stretched under proper conditions, a crystalline high polymeric form results in which the sulfur atoms form helices; this form also slowly reverts at room temperature to stable ring forms.

• Sulfur can form bonds with many other elements, such as halogens, oxygen, nitrogen, metals, etc. Bonds of sulfur with halogen or nitrogen are highly reactive polar bonds; combinations with other elements vary greatly in reactivity.

• A sulfur atom at the end of a chain, or in a ring, can bear a positive or negative charge, or an odd electron. Each of these types has a rich and varied chemistry.

• The sulfur atom may make use of higher orbitals with a valence shell of greater than eight, as in SF_6. The assumption that *d* orbitals are utilized in transient intermediates can be invoked to account for some of the unusual reactions of sulfur compounds.

• Sulfur functional groups occur in many natural products, of which a great number have important biological roles. In many enzymes the essential functionality involves sulfur, *e.g.* the thiol group (-SH). The -SH group is involved, for example in the process of cell division[2] and the mechanism of vision.[3] The -S-S- bridge is important as a chain-linking, or ring-closing bridge in numerous bioproteins and polypeptides; one can cite examples that include the immunoglobulins, many enzymes, structural proteins such as keratin and cyclic hormones such as oxytocin and vasopressin. The disulfide bridges serve to preserve the stereochemistry essential to the biofunctions.

• The vulcanization of natural rubber involves the formation of sulfur crosslinks[4] between isoprenoid polymer chains which serve to preserve the form and elasticity of the vulcanized rubber objects.

• Some volatile sulfur compounds contribute to, or constitute, the characteristic odors and flavors of food substances such as onion, garlic, mustard, coffee, pineapple, etc. Several mammalian pheromones have been characterized as sulfur compounds.

• Many therapeutic agents, both natural and synthetic, contain sulfur functions; the sulfur components generally play an essential role in contributing to the therapeutic roles.

• The -S- grouping can serve as a surrogate for the ethylenic grouping, -CH=CH-, in compounds, especially heterocyclic compounds, and the structures with the sulfur function show remarkable similarity to the ethylenic analogs. Thus, benzene compares in many of its properties closely with the five-ring thiophene; the thiazoles share analogous properties with the pyridine family. The sulfide group is said to be isoelectronic or "isosteric" with the ethylenic group. This principle has provided the rationale for the synthesis of numerous therapeutic agents.

2. FIRST ENCOUNTER WITH SULFUR CHEMISTRY

As a graduate student at the University of Michigan in the late 1930's, I was fortunate to be accepted as a candidate for the Ph.D. under the research direction of the late Professor Werner E. Bachmann.

During the late 1930's, Professor Bachmann served on the Editorial Board of the *Journal of the American Chemical Society.* One day, Professor Bachmann handed me a manuscript submitted for editorial consideration by Professor Louis Fieser[5] of Harvard University. He suggested that I read and comment on the paper. It described a new and greatly improved procedure for carrying out an old reaction first described by Conrad Willgerodt in 1887 at the University of Freiburg im Breisgau.

I read the paper with deep interest because Willgerodt's examples, extended by Fieser and Kilmer, at first seemed almost inexplicable. I decided at once to carry out some test examples to satisfy my curiosity and, as I shall presently relate, I happened to have, in connection with my dissertation research, a family of ketones ideal for such a test. The results of my experiments resulted in a lifelong fascination with the intricacies of sulfur chemistry.[6] The subsequent research of a number of my graduate students touched on many of the special features of sulfur chemistry mentioned in the Introduction.

The Willgerodt reaction involved heating an aryl alkyl ketone with aqueous ammonium polysulfide in a sealed glass tube at a temperature of approximately 300 °C. In a series of papers,[7] Willgerodt and his co-workers had shown that the aryl groups could be any one of the commonly known ones (*e.g.*, benzene, naphthalene, biphenyl, etc.). The ketones that reacted well consisted of *n*-alkyl aryl ketones with varying side-chain lengths (*e.g.*, acetyl-, propionyl-, *n*-butyryl-, *n*-valeryl-). Branching in the side chain (*e.g.*, isovalerylbenzene) did not completely block the reaction, but the yields were small, according to Willgerodt. A typical generalized Willgerodt reaction is illustrated in Equation 1.

$$\text{Aryl-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-(CH}_2\text{)}_n\text{CH}_3 \xrightarrow[\text{Heat ca. 300° C.}]{(\text{NH}_4)_2\text{S}_x} \text{Aryl-(CH}_2\text{)}_{n+1}\text{CONH}_2 \qquad (1)$$

Fieser's manuscript[8] reported an important variant of the original Willgerodt procedures in that by addition of dioxane to a typical Willgerodt reaction the required reaction temperature was lowered by as much as 140 °C and the yield and quality of product were improved. The obvious explanation was that dioxane improved the mutual miscibility of the aqueous reagent and the organic ketones.

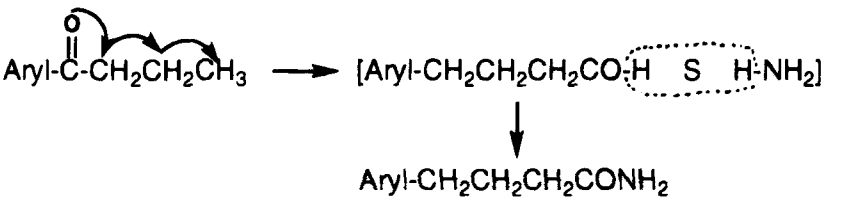
This account would be incomplete without a tribute to Professor Bachmann and the great influence by precept and example that he had on his students and other co-workers. He was himself constantly active in the organic synthetic laboratory and set a very high standard of experimental skill and excellence. He was a consummate master of the art of organic synthesis as it was practiced in the late 1930's, without the aid of the many non-destructive electronic instruments that only became widely available following World War II.

To some extent, Werner Bachmann discouraged speculation about the "course of reactions," or mechanisms, except as a guide to generate ideas for laboratory experiments. His attitude was to study each experiment and to repeat it with variations until it had yielded the best possible result. In this way an understanding of the underlying variables controlling the outcome of a synthesis could lead to a sounder understanding of the mechanism than much imaginative speculation. My orientation in his laboratory toward careful observation of the effects of small variations on the course of a synthetic procedure proved to be good preparation for my lifelong involvement with the complexities of sulfur chemistry. The literature of sulfur and its compounds up to World War II was filled with unsupported speculation based largely on imaginative theories.

3. THE WILLGERODT REACTION

3.1. *Confirming the Willgerodt Experiments*

Willgerodt had suggested[9] that the oxygen atom in the starting ketone moved along the chain of methylene groups to the terminal methyl group; the resulting isomeric aldehyde was pictured as reacting with one sulfur atom and one molecule of ammonia to form a carboxamide and hydrogen sulfide. Willgerodt's suggestion is illustrated in Equation 2.



(2)

I found the Willgerodt experiments irresistibly intriguing, and I was fortunate, as part of my doctoral dissertation problem, in having a series of ketones already previously prepared as intermediates in the synthesis of some substituted benzopyrene compounds. These were one segment of a larger program to relate carcinogenicity with structure. I lost no time in subjecting 1-acetylpyrene, 1-propionylpyrene, 1-*n*-butyrylpyrene, 1-*n*-valerylpyrene, 1-isobutyrylpyrene, and 1-isovalerylpyrene to conditions of the improved Willgerodt-Fieser reaction conditions.[10]

It was fortunate for me that pyrene compounds in general tend to crystallize readily and almost quantitatively, and my first attempts were probably further blessed by the fact that the very large bomb furnace then available to me needed many hours to cool to room temperature. The first reaction, carried out with 1-acetylpyrene, yielded 93% of large prisms of 1-pyreneacetamide, and these could be separated from the liquid reagent with forceps and rinsed clean. This dramatic result inspired me to go through all the available ketones mentioned above, with the result that good to fair yields of amides were produced with all the ketones **having unbranched chains,** whereas, only trace amounts of the

amides were produced from the branched chain ketones; I proved in these latter cases that the carbon side-chain had been retained without rearrangement.

These results, which were not part of my dissertation plan, could not be further investigated as part of my graduate program. But my interest in this strange reaction had been deeply aroused, and I placed it on my agenda for eventual study. As improbable as it at first seemed, it was difficult to think of an alternative explanation any more plausible than Willgerodt's suggestion that a carbonyl group is able, under proper conditions, to wander along an unbranched chain of methylene units to a terminal position (forming an aldehyde), where it becomes susceptible to irreversible oxidation. The conditions that bring about the Willgerodt transformation appear to cause both oxidation and reduction in the substrate. Obviously, if this process could be understood it could have many useful applications.

3.2. *Willgerodt Studies with DeLos F. DeTar*

It was necessary to defer action on this reaction until I became a faculty member at the University of Pennsyvania several years later and was fortunate that my first graduate student—DeLos F. DeTar—could be convinced that this very foul-smelling reagent offered promising possibilities for his strong and growing interest in elucidation of reaction mechanisms. The year, 1941, was the beginning of our involvement in World War II, when nonessential actvities were supposed to be subordinated to the war efforts. It was also the beginning of an upsurge of interest in the unravelling of reaction processes in a very fundamental way. Hammett's book had just appeared and schools of mechanistic studies were increasingly active, especially in the U.S.A. and England.

The need for improved aviation fuels, the search for synthetic substitutes for natural rubber, and other intensive war research efforts also stimulated the development of new electronic instruments that were easy to use: *e.g.*, infrared and ultraviolet spectrometers, mass spectrometers, electronic polarimeters and circular dichroism spectrometers—and, later on, nuclear magnetic resonance and other sophisticated and nondestructive technologies. Until the end of World War II, such instruments were mostly handmade and used in specialized physical-chemical research.

The mass production of easy-to-use instruments produced a revolution in the way organic chemical research has been carried out after 1945. Moreover, the shift in the practices of organic chemical research from the use of rather large quantities of starting materials to smaller and smaller-scale quantitative procedures, aided by the manufacturers of ingenious new microchemical equipment, was a very significant change from the standard practices which had hardly changed during nearly one hundred years of organic chemical research. Moreover, these microchemical procedures have been enthusiastically adopted in many colleges and universities, where they have saved costly chemicals, greatly reduced laboratory hazards, are well matched to the use of the new electronic instruments, and are popular with students. They made possible the attack on challenging problems that would have been impossible with the use of the classical pre-World War II methods.

DeLos DeTar made a careful study[11] of the aqueous ammonium polysulfide reagent used in the Willgerodt reaction. The best results were obtained when elemental sulfur was suspended in concentrated aqueous ammonia, and just enough hydrogen sulfide was

introduced to take all of the sulfur into a deep red solution. The composition of such a reagent appeared to be approximately $(NH_4)_2S_5$. Use of more than this minimal amount of hydrogen sulfide appeared to lower the yields of amide and to promote the formation of by-products. Use of added dioxane in the reaction mixtures, as initiated by Fieser, was confirmed to be very advantageous. DeTar also found that pyridine could serve as a useful alternative, presumably to promote miscibility of the aqueous and organic phases.

Dexter Pattison and Liebe F. Cavalieri,[12] in their dissertation studies with me at the University of Pennsylvania, found that the aryl groups that had always been present in the examples by Willgerodt and others were not essential and seemed to play no roles in the mechanism. They found that unbranched alkanones readily yielded unbranched carboxamides with the same skeletons as the starting ketones.

In the late 1940's and early 1950's following World War II, a number of research groups investigated the Willgerodt reaction, in particular, M. Calvin and co-workers and J. A. King and F. H. Freeman.[13] With the use of acetophenone containing radio-labeled carbon in the carbonyl group, the Calvin group showed that no rearrangement of the carbon skeleton occurred during the Willgerodt formation of phenylacetamide. Their results were ambiguous with respect to the phenylacetate salt formed in the same reaction. This anomaly was later accounted for by a reexamination of the analytical procedures used, and the final conclusion was reached that no rearrangement had occurred, a conclusion subsequently confirmed by other workers.

King and McMillan performed numerous variants of the Willgerodt reaction and developed a theory that the labile function which moves along the chain is a thiol group, which "inchworms" its way to the terminal position by a series of additions and eliminations involving olefinic intermediates; the latter were thought to be formed *via* a thiocarbonyl group derived from the starting ketone.

E. V. Brown and co-workers published a series of significant papers,[14] in the first of which they demonstrated conclusively that no rearrangent of carbon skeletons occurs in several representative Willgerodt reactions. In their second paper, with the use of ^{14}C labeled *n*-alkanones (4-^{14}C-2-butanone, 1-^{14}C-2-pentanone, and 1-^{14}C-2-heptanone), they showed that the unidentified labile function can and does move in either direction along the chain. The amide function can be formed from either terminal methyl group, but that methyl closest to the starting carbonyl function is favored. In their third paper they made use of 2,2-dideuterio-4-decanone in the Willgerodt reaction to test several theories as to the nature of the labile peripatetic function. The olefin-thiol postulate of King and McMillan led Brown and co-workers to predict a 50 percent retention of the deuterium, while alternative theories would predict smaller retention values or complete loss of deuterium. The result was that only about five percent of the deuterium was retained, an observation that did not seem to fit any of the hypotheses thus far (1953) advanced. In fact, this retention factor would fit a picture in which there is complete mixing of the deuterium as D_2O into the aqueous ammoniacal reagent and reequilibration of the diluted deuterium back along the carbon chain. This latter interpretation will become clearer in view of the much later research described in Section 8 of this Review.

DeTar and I had noted that Willgerodt reported the formation of small amounts of styrene[15] in an experiment with acetophenone. A tentative hypothesis—later discarded—led us to consider that styrene might be an intermediate in the Willgerodt transformation of

acetophenone. An experiment with styrene under the Willgerodt-Fieser conditions did in fact yield phenylacetamide, although in somewhat lower yields than from acetophenone. Phenylacetylene, in contrast, produced a good yield of phenylacetamide—comparable to that from acetophenone. A number of olefins and acetylenes were then tried and found to yield amides containing the same carbon skeleton as the starting material. The idea that either olefins or acetylenes were in the direct reaction sequence of the Willgerodt reaction with ketones was discarded. The use of olefins and acetylenes was in fact a new reaction which offered a simple route to a great variety of carboxamides.

The Rohm and Haas Company saw possibilities for industrial applications to produce amides from olefins and acetylenes. With permission of the University of Pennsylvania, DeTar and I patented these new syntheses of amides,[16] with assignment to the Rohm and Haas Company. The latter studied many new examples of the reactions. A projected application at that time was for the synthesis of carboxamides to be incorporated in fermentations to produce new penicillin derivatives. At a later time, the DuPont Company seriously considered a new route to acrylonitrile from propene to propionamide, to propionitrile, to acrylonitrile, utilizing the polysulfide reagent for the conversion of propene to propionamide in the first step.

4. THE KINDLER REACTION

Some years after the series of papers by Willgerodt and co-workers, Karl Kindler,[17] a German pharmaceutical chemist, described a new reaction sharing some of the features of the Willgerodt reaction except that it was carried out in a secondary amine as solvent, with elemental sulfur as the reagent. Kindler carried out most of his examples in dimethylamine; its low boiling point required the reaction to be carried out in a vessel under pressure. Other investigators introduced the use of secondary amines with boiling points well above room temperature. A favorite proved to be morpholine,[18] whose boiling point permits the Kindler reaction to proceed at a convenient rate in refluxing morpholine.

$$\text{Aryl-CO-CH}_2\text{CH}_2\text{CH}_3 \xrightarrow[\text{Heat}]{S_8 + HNR_2} \text{Aryl-CH}_2\text{CH}_2\text{CH}_2\text{CS-NR}_2 \qquad (3)$$

The Kindler reaction is illustrated in the generalized Equation 3. The Kindler reaction shared with the Willgerodt reaction the remarkable ability to move a carbonyl function along a chain of methylene groups. It differed from the Willgerodt reaction in the fact that the terminal methyl group was converted into an *N,N*-disubstituted thioamide, rather than a carboxamide.

In an early review in *Organic Reactions,* written in collaboration with Marvin Spielman,[19] I suggested that an intermediate in the Kindler reaction could likely prove to be the enamine derived from the amine solvent and the starting ketone. In Footnote 23 of a paper with DeLos DeTar[20] in 1946, we had also suggested the possibility that a key intermediate in the Willgerodt reaction could be a thiirene ring, although at that time such

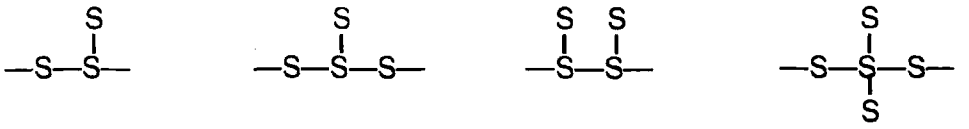


FIGURE 1 Early Interpretations of Polysulfide Structures.

a ring system had not yet been shown to exist. King and McMillan[21] had proposed a mechanism postulating thioketones, thiols, and olefins as intermediates. These speculative ideas were abandoned but they served to stimulate much later experimental work. A more plausible mechanism had to await years of advancement in the understanding of the chemistry of sulfur. Later experiments and a mechanism for the Kindler modification will be described in Section 8 of this review.

5. THE STRUCTURES OF POLYSULFIDES

5.1. *Synthesis of Polysulfides as Indicators of Structure*

The entry of the U.S.A. into World War II required us to turn our major attention to research directly related to the national security. I had just joined the Faculty of Chemistry in the Towne School of the University of Pennsylvania in 1941. Shortly after arriving I became the Official Investigator under a contract between the National Defense Research Committee (of the Office of Scientific Research and Development) and the University of Pennsylvania, with a full-time group of Ph.D. research chemists.

Our first assignment was the preparation of a review from the chemical literature on the nature of the so-called "Levinstein Mustard Gas," prepared by reaction of S_2Cl_2 and ethylene. It had been known that mustard gas prepared in this way contained a number of impurities, especially polysulfides, and it was desired to determine whether these could cause more serious casualties than pure mustard gas, bis-(2-chloroethyl) sulfide. Early work had claimed that the Levinstein product contained disulfides, trisulfides, tetrasulfides, and even pentasulfides. The older published literature gave fanciful structures for these polysulfides, frequently including branching in the sulfur clusters. Some of these proposed structures are illustrated in Fig. 1.

The possibility of branched polysulfur functions suggested to us that, if such exist, the sulfur atoms at the branches might be attached by branched, or coordinate covalent, bonds and represent more highly active forms of the element—possibly of significance in explaining the Willgerodt reaction. We therefore became interested in determining whether organic polysulfides in general can have unbranched or branched chains, and whether any special kind of sulfur-sulfur coordinate covalent bond exists. Our conclusions will be given below.

After the literature review on Levinstein Mustard Gas had been submitted to the N.D.R.C., our wartime research contract was redirected to work on the more urgent problems of new military explosives, and research on polysulfides was deferred until after World War II.

There was at that time no agreement on the structures of polysulfides: some chemists favored unbranched. Others favored branched sulfur chains with special pendant sulfur-sulfur bonds, analogous to the sulfoxide function. Such branched structures would be expected to show interesting physical and chemical properties. We undertook the synthesis of polysulfides, R-$(S)_n$-R, in which n could have values from 1 to 5, and R could be either alkyl or aryl.

To avoid the odor problem with volatile lower molecular weight alkyl sulfides and polysulfides, we chose R as *n*-hexadecyl, a selection which also yielded nicely crystalline derivatives that were soluble in organic solvents. Doctoral candidate Carroll C. Woodrow[22] prepared the series of crystalline *n*-hexadecyl sulfide, disulfide, trisulfide, and tetrasulfide, by procedures previously developed by John E. Baer.[23] My colleague at the University of Pennsylvania, Professor John G. Miller, determined the dipole moments of the four compounds in benzene at 30 ± 0.01 °C. The values of the dipole moments were, respectively, beginning with the monosulfide, 1.47, 2.00, 1.63, 2.16. He considered several models and made calculations which led him to conclude that these values were consistent with **unbranched polysulfide structures** in which rotation about each bond, while subject to some restriction, could result in equilibrium mixtures of rotational isomers in which the R-S-S- and -S-S-S- bonds would favor dihedral angles of approximately 105°. It was realized that some of the forms would be non-superimposable mirror images, and these might in principle be resolvable into enantiomeric pairs under some conditions. Our interest in the stereochemistry of disulfides was stimulated by this suggestion, but active work along these lines was not undertaken until much later after the end of World War II.

Alternative synthetic work with aryl polysulfides made use of *o*-nitrobenzenesulfenyl chloride, which had been the subject of earlier research in the University of Pennsylvania by Professor Ralph Connor and his students. Doctoral candidate and my co-worker, John F. Harris,[24] was able to prepare the nicely crystalline disulfide, (*o*-nitrophenyl)$_2S_2$, and the corresponding trisulfide, tetrasulfide, and pentasulfide.

A single disulfide resulted from reaction of the *o*-nitrobenzenesulfenyl chloride with the corresponding *o*-nitrobenzenethiol and was identical with the disulfide prepared by mild oxidation of the corresponding thiol. The reaction of sulfur monochloride with *o*-nitrobenzenethiol yielded *o*-nitrobenzene-S-S-Cl. The latter reacted with *o*-nitrobenzenethiol to produce the same crystalline trisulfide—*o*-nitrobenzene-S-S-S-*o*-nitrobenzene—as was produced by reaction of *o*-nitrobenzenesulfenyl chloride (2 molecular equivalents) with one equivalent of hydrogen sulfide. The two syntheses produced only one well-defined crystalline compound.

The tetrasulfide was prepared by reaction of S_2Cl_2 with *o*-nitrobenzenethiol, or alternatively by reaction of two moles of the *o*-nitrobenzenedithiochloride with potassium iodide. The product of both syntheses was the same tetrasulfide.

The pentasulfide could be assembled in two ways: (1) by reaction of the sulfenyl chloride with hydrogen trisulfide; (2) by reaction of the *o*-nitrobenzenesulfenyl chloride with one molecular equivalent of hydrogen sulfide to form *o*-nitrobenzene-S-S-H; then two molecular equivalents of the latter were coupled with one equivalent of sulfur dichloride, SCl_2.

Since the different methods of synthesis of each polysulfide led to the formation of a single product, it was concluded that in each case the chain of sulfur atoms was unbranched

(but not necessarily coplanar). Alternatively, if branched forms were formed in any of these procedures, they readily rearranged into the single unbranched product.

A great deal of work in other laboratories, including definitive X-ray crystallographic studies, has confirmed the generality of unbranched chains when a number of sulfur atoms are linked together in chains or rings.

5.2. *The Ultraviolet Spectra of Polysulfides*

The ultraviolet spectra of conjugated polyolefins have shown regularities and correlations with the number of unsaturated units and their stereochemical configurations.[25] We desired to see whether ultraviolet spectra would be useful in comparisons of polysulfides having varying numbers of adjoining sulfur atoms. Doctoral candidate John E. Baer[26] synthesized the series of *n*-hexadecyl sulfide, disulfide, trisulfide, and tetrasulfide mentioned above in connection with dipole moment studies. These compounds, as well as the *n*-hexadecanethiol and elemental rhombic sulfur (S_8 rings), were examined in purified hexane in the near ultraviolet region to approximately 200 nm. The spectra at room temperature were characterized by broad bands, which varied widely with the number of sulfur atoms. It became obvious that the correlations of spectra with structure among the polysulfides are complex and would require far more extensive and critical measurements than we were equipped to undertake at that time. It was clear that measurements would be sensitive to temperature. We realized that the stereochemistry of chains of sulfur atoms differs fundamentally from that of the conjugated polyenes. Nevertheless, these initial early studies showed that ultraviolet spectra could be empirically useful in characterizing clusters of sulfur atoms. We therefore conducted a survey of the ultraviolet spectra of a number of different sulfur functional groups, since only scattered data appeared in the literature at that time (1949).

6. ULTRAVIOLET SPECTRA OF SEVERAL SULFUR FUNCTIONAL GROUPS

6.1. *The Ultraviolet Spectra of Sulfides*

Edward A. Fehnel (American Chemical Society Postdoctoral Fellow) and I collaborated in a series of studies[27] of the ultraviolet spectra of the organic sulfide function alone[28] and in combination with various unsaturated functions.[29] The absorption of the lone sulfide is a strong, sharp band. When the sulfide is combined in a molecule with an olefinic function, a carbonyl function, an ester function, or an aromatic ring, there is no strong interaction of the functions if they are separated by two or more methylene carbons. When, however, the sulfide function shares the same carbon atom with an olefin, ketone, ester, or aryl group, very strong interactions are observed.

The sensitive variations in the ultraviolet spectra can prove useful in the determination of structure of certain sulfur-containing compounds; *e.g.*, the placement of a double bond, ketone, or ester function with respect to a sulfur function.[30]

Fehnel measured the ultraviolet spectra of a number of phenyl sulfides, substituted in varied ways. Of particular note was the strong interaction of sulfur and the hydroxyl group in 2-hydroxyphenyl methyl sulfide. The possibility of hydrogen bond formation may be significant in this instance. The influences of the amino and nitro substituent groups in various positions on aryl sulfides were also described.

6.2. *The Ultraviolet Spectra of Sulfones Combined with Other Functional Groups*

Simple aliphatic sulfones are transparent through the ultraviolet region down to about 210 nm. A single sulfone attached to an aromatic ring somewhat enhances the characteristic absorption of the aromatic chromophore without large shifts. When a sulfone group is separated by two or more carbon atoms from an aryl group, another sulfone, an olefinic group, a carbonyl function, or an ester, there is little change in the absorption of the unsaturated function, but when the sulfone shares the same carbon with the aryl, olefin, ketone, ester, or second sulfone, a strong interaction is observed in neutral solution, and intense interaction in alkaline solution.[31] In the latter case, the anion of the activated methylene group is involved. The strong effects noted in the ultraviolet absorption spectra of allyl sulfones, β-keto sulfones, and α-sulfonyl esters may be useful in structure assignments and the study of activation effects.

6.3. *Studies of 1,4-Thiapyrone 1,1-Dioxide and Comparison with* p*-Benzoquinone*

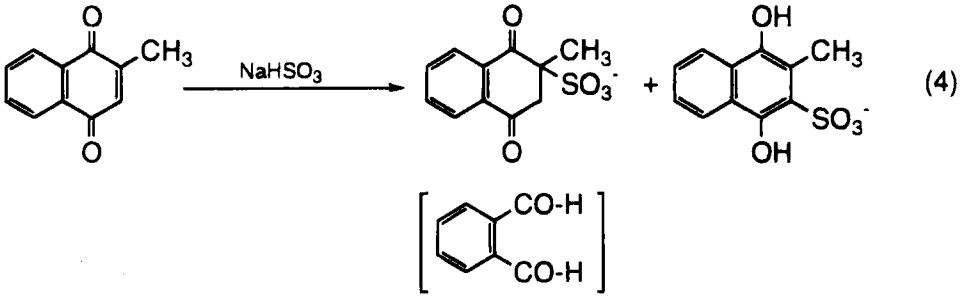
Fehnel[32] was interested to determine whether substitution of one of the carbonyl groups in *p*-benzoquinone with a sulfone function would greatly alter the typical quinone pattern of chemical and optical properties. He synthesized 1,4-thiapyrone 1,1-dioxide by oxidation of 1,4-thiapyrone and made parallel studies of *p*-benzoquinone with its mono-sulfone analog, including the ultraviolet absorption spectra of both compounds. He also investigated the chemistry of addition of bromine, hydrogen bromide, the dehydrobromination reactions, and the Diels-Alder addition reactions. The results were described in the cited publication.

6.4. *Steric Effects on the Ultraviolet Spectra in Mesityl Methyl Sulfone*

Ordinarily, the sulfone group has only a small intensifying effect upon the ultraviolet absorption when it is a substituent on a simply substituted benzene ring. An exception was found in the case of mesityl methyl sulfone, in which the steric crowding provided by two methyl groups flanking the bulky sulfone function produces a strong intensification of the absorption of the benzene ring, suggesting that the methyl groups flanking the sulfone function force the sulfone group into an untypical configuration that exerts an unusually strong polar influence on the benzene ring. This phenomenon suggests that if the *para* position were unsubstituted but the steric effect of two flanking *ortho* groups were retained—as, for example, in 2,6-dimethylphenyl methyl sulfone—it is possible that the *para* position would be activated for special substitution reactions. This would be an interesting idea to explore.

6.5. *The Structure of the Sodium Bisulfite Addition Product of 2-Methyl-1,4-naphthoquinone (Menadione)*

2-Methyl-1,4-naphthoquinone (the antihemorrhagic drug, Menadione) reacts readily in aqueous solution with sodium bisulfite to form two isomeric, water-soluble salts. Only one of these addition products has high antihemorrhagic properties and is a useful therapeutic agent.[33] Eq. 4 illustrates the formation of the two addition products, and their structures, which we confirmed. The first of these is the therapeutic product.



(4)

We were able to prove the structures of the two products[34] by the use of ultraviolet absorption spectra. The desirable antihemorrhagic salt is formed by addition of the bisulfite function on the 2-methyl carbon, thereby blocking the aromatization of the substituted ring and forming 2-methyl-2,3-**dihydro**naphthoquinone-2-sulfonate salt; this salt would have two ketone groups conjugated with the benzene nucleus, and the ultraviolet absorption spectrum would show this relationship clearly. In the biologically inactive addition product, the bisulfite adds in the opposite orientation to the 3-position. The resulting 3-sulfonate would undergo aromatization to 2-methyl-1,4-dihydroxy-3-naphthalenesulfonate salt.

The first addition product—the diketone—allows the ready β-elimination of HSO_3^- due to activation of the 3-methylene hydrogen by the 4-keto function. This reversal of the addition reaction with base regenerates the original Menadione as an active therapeutic agent. The water-soluble intermediate is more convenient for administration than the much less water-soluble Menadione itself.

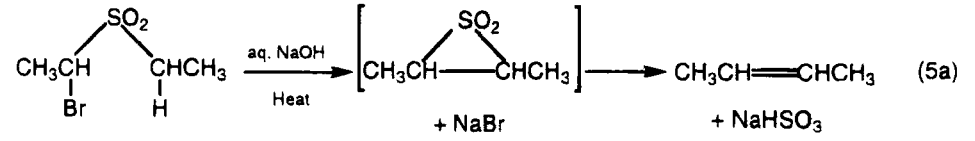
The structure proof was achieved by comparing the ultraviolet absorption spectra with *o*-phthalaldehyde. The medicinally active adduct with its two ortho keto groups showed very close resemblance to the model *o*-benzenedialdehyde. The determination of these structures was able to settle a question of patentability. A competing application had assumed the wrong structure for the active compound.

7. THIIRENE DIOXIDES: EXTENSIONS OF THE RAMBERG-BÄCKLUND REACTION

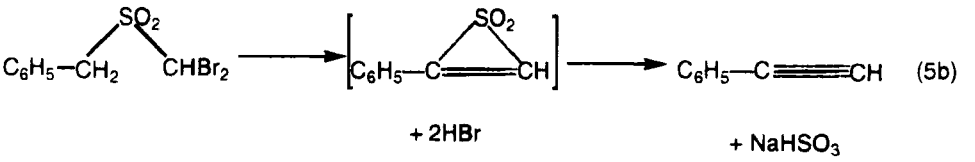
As mentioned previously, we speculated early on that the catalytic role played by sulfur in both the Willgerodt and Kindler reactions might involve a sulfur-bridged species—

perhaps a derivative of a thiirene, although no such structures were known until many years later.

As a possible route to thiirene compounds, we began to study the little known Ramberg-Bäcklund reaction[35] of α-bromoethyl ethyl sulfone. In that classic example, the bromo sulfone reacted in mild aqueous base to eliminate one mole of hydrogen bromide, with the joining of the two α carbon atoms. It has been shown that the intermediate is a **thiirane** intermediate, which in turn readily eliminates the sulfone function as bisulfite ion. The first example of this reaction in the literature is illustrated in Eq. 5a.



(5a)



(5b)

Doctoral candidate and co-worker, Frank Scholnick,[36] found that benzyl dibromomethyl sulfone readily eliminates *two moles* of hydrogen bromide in the presence of aqueous base to form phenylacetylene, in analogy with the Ramberg-Bäcklund reaction, as shown in Eq. 5b. Scholnick's doctoral dissertation of 1955 clearly stated the probability that the intermediate was 2-phenylthiirene dioxide. Subsequent research by others, as well as ourselves, proved this hypothesis to be correct. I regret that because I was in the process of transfer to Indiana University at that time, I was not able to follow up on this idea immediately. Several years later, Carpino and co-workers[37] isolated thiirene *S,S*-dioxides and *S*-monoxides and described their properties. Some are crystalline.

Thus the existence of derivatives of oxidized thiirenes, including also thiirene *S*-oxide as well as the thiirene *S,S*-dioxides, was demonstrated, and their relative chemical stabilities established. Strain in these three-atom rings makes the elimination of the sulfur functions rather easy under mild conditions.

The demonstration that thiirene compounds substituted by oxygen on sulfur can exist encouraged our pursuit of the early suggestion[38] concerning the bridging mechanism involved in the Willgerodt and Kindler reactions. If thiirenes are involved it seemed unlikely that they would be sulfur oxides but more likely the intermediates would be analogs of the thiirene *S*-oxides having nitrogen rather than oxygen on sulfur. The published literature of appropriately substituted sulfur-nitrogen compounds followed a long and sometimes baffling course. Ultimately, however, as the investigation of the chemistry of nitrogen-sulfur compounds accumulated, we found new reactions which suggested a

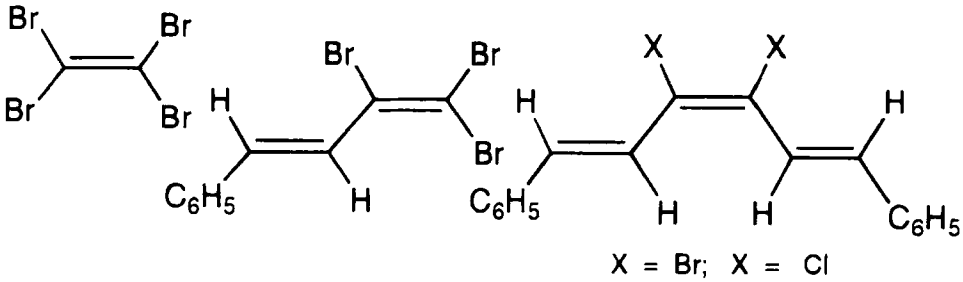


FIGURE 2 Kelley's Extensions of the Ramberg-Bäcklund Reaction.

plausible mechanism for the Kindler reaction. This mechanism will be discussed in Section 8 of this review.

Meanwhile, co-worker Charles J. Kelley[39] found extensions of the Ramberg-Bäcklund reaction to be useful in the synthesis of polyenes. A potentially useful synthon is bis(tribromomethyl) sulfone, produced by the bromination of dimethyl sulfoxide. Similarly, chlorination of dimethyl sulfoxide produces bis(trichloromethyl) sulfone.

The light-induced free radical addition of the bis(tribromomethyl) sulfone to olefins, specific examples being isobutylene and styrene, produces complex mixtures, among which major products are the addition products of two olefin units to one mole of the sulfone. In such products, triethylamine was found to remove bromine substituents adjacent to the sulfone function by reductive processes. Subsequent treatment of the reaction mixtures with LiH in DMF yielded, among others, the identified products shown in Fig. 2.

The intention was to return to the investigation of the hexabromo- and hexachlorodimethyl sulfones as useful reagents in the construction of polyunsaturated chain compounds. Unfortunately, we were never able to return to this promising area.

As the number of halogen substituents on the carbon adjacent to the sulfone function increases, the halogens appear to possess increased positive character. The use of precise modern electrochemical equipment should permit the controlled stepwise generation of potentially useful, reactive intermediates. These could be either radicals or carbanions capable of adding to olefins, acetylenes, or polyunsaturated compounds. The products should be variously halogen-substituted sulfones, some of which could react by elimination reactions proceeding *via* thiirane or thiirene intermediates. We believe that this could be an interesting field to explore.

8. FURTHER STUDIES OF THE KINDLER REACTION: THE ISOMERIZATION OF THE CARBONYL FUNCTION IN TERMINALLY BLOCKED ALKANONES

8.1. *Reactions of α,ω-Diarylalkanones*

In Section 3, the original proposal of Willgerodt[40] to explain his reaction with aryl *n*-alkyl ketones of varying chain length was mentioned briefly. He suggested that the ketone

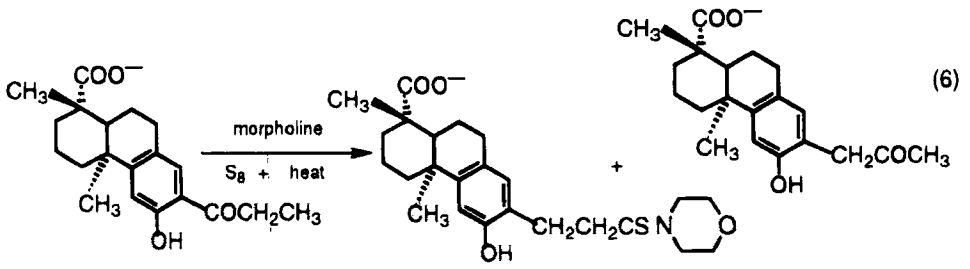
group "wanders" from carbon to carbon from an internal location to the terminal methyl group, thereby producing an isomeric ω-arylalkanal. In a final step, the reagent oxidizes the aldehyde to a carboxamide (refer to Eq. 2).

In Kindler's variant (Eq. 3) utilizing elemental sulfur and a secondary amine, his attempt to explain his process as involving a rearrangement of an aryl group on the carbon skeleton was discounted in early experiments. No mention or experimental evidence were presented in Kindler's publications to support the Willgerodt hypothesis of a wandering ketone function.

In our initial studies of the Willgerodt and Kindler reactions, as explained in the earlier Section 3, we assumed that the unsupported suggestion of Willgerodt may be correct, but the ketone function would necessarily first have to be activated by being converted into a labile function. A major research goal would be to explain how this activation could be achieved by the sulfur and basic nitrogen reagents used. The intermediate(s) would very likely be highly reactive and elusive. The literature at that time offered little help to confirm or modify our hypothesis that enamines and thiirene derivatives may be the reactive intermediates.

The experiments with variants and extensions of the Ramberg-Bäcklund reaction (Section 7 above) had provided evidence that thiirene derivatives can in fact exist. The known thiirene *S*-oxides and *S,S*-dioxides offered little promise of explaining the role of the basic nitrogen components of the mechanism. But the concept that sulfur plays a bridging role in causing the movement of the carbonyl function was, nevertheless, a guiding thought during a number of years of study of variations of these reactions. It was not until the body of known chemistry of sulfur functions had expanded enormously in recent years that a plausible mechanism was conceived.

A publication by Bible[41] had provided the first direct evidence that Willgerodt's idea of the moving ketone function is fundamentally sound—although incomplete. He showed that 7-propionylpodocarpate, under conditions of the Kindler reaction in morpholine, had yielded not only the expected γ-substituted propiothiomorpholide but also the 7-acetonylpodocarpate derivative (Eq. 6).



(6)

Shortly after the appearance of Bible's paper, doctoral candidate and co-worker Glenn Berchtold[42] observed the reaction of phenylacetone in the morpholine-sulfur reagent. He found that the reagent is sufficiently transparent in the region of the carbonyl absorption

bands that the Kindler mixtures could be directly observed in the infrared spectrometer. As the Kindler reaction proceeded, with the movement of the keto function, periodic samples showed the gradual decrease in the intensity of the unconjugated carbonyl function and a corresponding appearance and increase in a new band characteristic of aryl conjugated ketones. This direct optical evidence for the retro movement of the carbonyl group along the methylene chain to form phenyl ethyl ketone suggested that infrared observations could be a useful tool for the direct observance of the isomerization reaction.

Phenylacetone was obviously not well suited for separating the isomerization process from the terminal oxidative formation of amide. The strategy of blocking both ends of an unbranched alkanone with different aryl groups was conceived. The early model chosen was 1-*p*-chlorophenyl-4-phenyl-1-butanone. When that ketone was heated with the typical morpholine-sulfur reagent and the isolated ketonic reaction product was carefully chromatographed, Berchtold isolated three pure isomeric ketones: the starting 1-butanone isomer, the 2-butanone isomer, and the 4-butanone isomer. The yields were low and the 3-butanone isomer may have been present in undetectably small quantity. While this experiment demonstrated the "wandering ketone" hypothesis, it was obvious that it would not be a good model for quantitative experiments or rate measurements.

Dibenzyl ketone proved to be a good model for critical experiments. In the sulfur-morpholine reagent, we found that the reversible isomerization from 1,3-diphenyl-2-propanone (2-DPP) into 1,3-diphenyl-1-propanone (1-DPP) occurred in good yield. Berchtold isolated the mixture of ketonic isomers and determined the composition by observing the strong carbonyl infrared absorption bands. In the unconjugated 2-DPP, the carbonyl absorption appeared at 5.82 μm; in the isomer with the conjugated ketone, the band appeared at 5.91 μm. The difference is sufficient to permit analyses of the mixtures to be made.

In reaction mixtures which had been allowed enough time to reach a steady state, a purely statistical mixture would have contained 1-DPP/2-DPP in a 2/1 ratio. In some experiments the ratio was close to this value, but occasionally the conjugated isomer was somewhat favored. Prediction of the composition of the steady-state mixtures is not simple, since the extra stability of 1-DPP resulting from resonance would to some extent be opposed by the steric bulk of the phenyl group; later experiments revealed very marked steric inhibitory effects in isomerizations of the carbonyl group in other series.

When dry morpholine and elemental sulfur were heated with the ketone, the transparency of the medium in the region of the carbonyl absorption permitted direct observation of the typical, slightly separated, bands. By comparison with standard reference mixtures, the ratios of isomeric ketones could be determined. In experiments using dry morpholine, only about half the starting ketone could be accounted for as the total carbonyl recognizable in the sum of the two infrared absorption bands. But, upon addition of water to these mixtures, the total of the isomeric mixture of ketones almost equaled the mole quantity of the single starting ketone. We concluded from this that, in the dry morpholine, roughly half of the ketonic starting material had apparently become tied up in non-ketonic but readily hydrolyzable intermediates.

A study of the effect of increasing water content in the morpholine solvent showed that the rate of isomerization slowed progressively as the water percentage was increased from 0 to 20 percent. At the same time, the fraction of ketonic material not accounted

for fell to approximately 1–2 percent in a 20/80 solvent of water/morpholine. It was therefore advantageous for Berchtold to make rate studies in the 20/80 mixed solvent. The fact that the isomerization occurred readily, although more slowly, in the presence of water was an indication that the critical intermediate must be very reactive even though readily generated in the presence of substantial concentrations of water. This observation is probably also significant in the examples of the Willgerodt reaction, which is typically carried out in a mainly aqueous reagent.

When the 20/80 solvent mixture was used, the analytical procedure had to be modified. Aliquot samples of the reaction mixtures were removed at intervals, then worked up to isolate the ketonic mixture; finally, samples were dried and distilled before infrared analysis. Calibration standards were used.

With either ketone as starting material, the same steady-state mixture could be reached. The disappearance of one isomer and the appearance of the other could be followed through several half-life periods in apparent first order kinetics. The concentration of sulfur was expressed in terms of gram-atomic weights, with the realization that the state of that element in the reaction mixtures is always complex, constantly changing, and mostly polyatomic. It was established that less than one gram-atomic equivalent of elemental sulfur is capable of catalyzing the isomerization to the same steady state, although at a slower rate than when more than the gram-atomic equivalent is used. For example, in an experiment using one gram-atomic equivalent of sulfur to two molecular equivalents of ketone, the $t_{1/2}$ (h) at 99.59 °C was 10.8 h, compared with 3.1 h when the ratio of ketone:sulfur was in the reverse ratio of one molecular equivalent of ketone to two gram-atomic equivalents of sulfur. We interpret this as indicating that, whatever reactive sulfur-containing intermediates are formed, the sulfur is regenerated and is not used up. In the *preparative* Kindler reaction to produce thiocarboxymorpholide, one gram-atomic equivalent of sulfur is irreversibly used up in the formation of the thioamide.

A summarizing paper[43] details numerous experiments. From them some important generalizations could be drawn:

- Attempts to bring about isomerization with various sulfur forms but excluding all nitrogen bases failed completely. Alcoholic sodium hydroxide with sulfur, aqueous sodium tetrasulfide, and water-dioxane-sodium tetrasulfide were tried as catalysts but all failed.
- The amine must have at least one hydrogen atom; *i.e.*, tertiary amines, such as *N*-methylmorpholine, cannot induce the isomerization reaction. Various secondary amines may be used, with morpholine being favored because of its convenient boiling point and inability to aromatize. Kindler's original papers made use of dimethylamine that inconveniently required a vessel capable of containing elevated pressures. Piperidine and pyrrolidine can be used in open reaction flasks, but these bases can be dehydrogenated readily by sulfur to their aromatic equivalents, and react in other complex ways. Primary amines have been occasionally used, but sulfur can oxidize them to carboxylic acid derivatives.
- The form in which sulfur is introduced into the reaction is not critical, and many different sulfur-containing materials were found to generate catalytic activity. In addition to elemental sulfur (S_8 rings), sodium tetrasulfide, and 4,4′-dithio-bis-morpholine were also found to catalyze the isomerization. In sharp contrast, however, 4,4′-**mono**thio-bis-morpholine was totally unable to cause a trace of isomerization. We concluded that a

minimal requirement for catalytic activity is a cluster of >N-S-S—G (G may be a morpholine group of one or more additional sulfur atoms). Considering the relative polarity of nitrogen and sulfur, we view compounds containing the >N-S—bond as roughly equivalent to the sulfenyl halides in potential reactivity. Considering that the >N—S- is a high-energy bond may be the key to explaining the high reactivity of crucial intermediates in the ketone isomerization process.

• The obvious fact that rhombic sulfur reacts in a complex way with secondary amines makes it difficult to discuss the effects of the introduced sulfur compounds on the reaction rates. As noted, less than one gram-atomic equivalent of sulfur compared with the ketone can still catalyze the isomerization. Increasing the relative concentrations of introduced sulfur with respect to ketone increases the rates of isomerization but the increases are less than proportional.

8.2. *Isomerization of Cycloalkanones*

In a second strategy to elucidate the isomerization process—divorced from the irreversible terminal oxidation to thioamides typical of the Kindler reaction—we proceeded to the investigation of the movement of the ketone function around a cycloalkanone ring.

In fact, Horton and van den Berghe[44] had made the first of such studies. They found that when they heated 1-tetralone with sulfur and morpholine under typical Kindler preparative conditions, the product was 2-naphthalene-4′-morpholine. They did not show whether the morpholino group entered the equivalent 2- or 3-positions of the starting 1-tetralone, or both. Dauben, Ciula, and Rogen[45] showed that the product of heating 6-methoxy-1-tetralone with sulfur and morpholine is 6-methoxy-2-naphthalene-4′-morpholine. In our laboratory, experiments with 7-methyl-1-tetralone confirmed that the nitrogen appears on the carbon adjacent to the starting 1-ketone. We also found that 2-tetralone yields 2-naphthalene-4′-morpholine. From these examples it appears that, in general, the 2-position is the point of entry of the nitrogen of the morpholine, whether the ketone function is originally in the 1- or the 2-position.

The case of cyclohexanone in reaction with sulfur and morpholine under fairly vigorous conditions yielded a surprising result: 10 percent of 1,4-benzene-bis-4′-morpholine was isolated instead of the expected 4′-morpholinobenzene. It is possible that the latter is an intermediate and is further *p*-substituted by an as yet unknown mechanism. When 4-methylcyclohexanone was heated fairly vigorously with sulfur and morpholine, the aromatic product isolated was crystalline 2,5-di-(4′-morpholino)toluene. Migration of the ketone function must in this example have preceded the aromatization reaction. This reaction to produce **two** entering amino groups merits further investigation of its intriguing mechanism.

In general, however, we found that aromatization of cyclohexanone rings could be avoided by choice of suitably mild conditions. The choice of members of the methylcyclohexanone family provided, in the methyl group, a good marker for the extent and locus of isomerization. Starting with 4-methylcyclohexanone, doctoral candidate and coworker Mohammad Behforouz[46] found that isomerization of the ketone function could be observed to occur slowly even when reaction mixtures were allowed to stand at room temperature with the sulfur-morpholine reagent. Under these very mild conditions, the

ketone group moved only to the adjacent 3-carbon atom of the ring. With heating, at increasing temperatures and with longer reaction times, the isomerization moved further around the ring, forming mixtures of the three possible methylcyclohexanones. Several general observations were made in numerous experiments that started with each of the isomeric methylcyclohexanones in turn:

• In 4-methylcyclohexanone, movement of the ketone function from the 4-position to the adjacent 3-position (involving a single cycle of isomerization) occurred much more readily than to the 2-position (which would necessarily involve two cycles of isomerization).

• Movement of the ketone function away from the 2-position in 2-methylcyclohexanone required much longer reaction times than from the 4- or 3-positions. This observation and the preceding one indicate that the reaction intermediates, whatever their nature, are subject to marked steric inhibition. Movement of the ketone into or away from a position *ortho* to a branch in the chain is markedly inhibited but can be forced. If the isomerization could occur with relative ease to any other ring position, one would expect it would be easy to end up with the statistical distribution of 4-:3-:2-methylcyclohexanone of 20:40:40, but in fact this result was never quite realized, and even a close approach to this ratio was rarely achieved. In general, the 3-methylcyclohexanone was the favored product.

• Elemental sulfur as the catalytic agent could be effectively replaced with dithio-bis-4,4′-morpholine, but no trace of isomerization occurred when the sulfur-containing reagent was **mono**thio-bis-4′-morpholine. We concluded that a minimum of **two connected sulfur atoms linked to nitrogen** must be present in the sulfur catalyst.

• Our early hypothesis that enamines are intermediates in the first stages of the isomerization of ketones was finally demonstrated experimentally by Behforouz[47] in his doctoral research. 4-Methyl-1-cyclohexenyl-4′-morpholine was heated with one gram-atomic equivalent of elemental sulfur and one molar equivalent of dry morpholine at 100–110 °C. After one hour, the cooled mixture was treated with water to hydrolyze the enamine product, and a mixture of isomeric ketones was isolated and purified. The isomer ratio of 4-:3-:2-methylcyclohexanone was 44:54:2. When a very similar experiment was carried out with a slight molar excess of dry morpholine (1.25 molar equivalents), the isomerization was facilitated: in one hour of heating the resulting ratio of ketonic isomers was 31:65:4. After two hours of reaction time, the ratio of ketones became 35:58:6. A comparison experiment was carried out with 4-methylcyclohexanone and the same proportions of sulfur and morpholine for one hour at 100–110 °C; the isomer ratio of products was 16:50:34. This single experiment produced the closest approach to the statistical ratio of 20:40:40. Although the experiment started with dry reagents, the initial enamine formation would release a small amount of water into the reaction mixture. Isomerization of pure enamine in anhydrous medium is apparently more subject to steric inhibition than is the reaction of ketones in which a substantial concentration of water is present.

• The process of formation of an enamine from a mixture of a ketone and a secondary amine was investigated by co-worker Samuel Berkowitz.[48] An equimolar mixture of cyclohexanone and morpholine at room temperature begins to form the enamine slowly and the progress of the reversible reaction can be observed easily in an infrared spectrometer, since the characteristic absorption of the enamine at 6.08 μm is well separated from the carbonyl absorption band. In this case, a steady state is reached at approximately

20–30 percent enamine. When cyclopentanone is mixed at room temperature with an equimolar quantity of pyrrolidine, reaction occurs more rapidly. Immediately upon mixing, the clear solution becomes turbid and two layers separate—one apparently consisting largely of enamine and water and the other of ketone with water.

• Experiments with 3-methylcyclopentanone[49] in the morpholine-sulfur reagent demonstrated that isomerization occurs more rapidly than in parallel experiments with 4-methylcyclohexanone. This is the expected result in view of the results described in the foregoing paragraph. When 3-methylcyclopentanone was heated with ketone:morpholine:sulfur (equivalent weights in the ratio of 1:2:1) for only ten minutes at 50–70 °C, the mixture of isolated ketones contained the 3- and 2-isomers in 75:25 ratio.

• 4-Heptanone was studied in a number of experiments,[50] and the movement of the ketone function along the chain could be readily observed in the isolated and purified mixtures; heptanal was also formed. The latter would be the substrate for the classic Kindler reaction and would be irreversibly converted into heptanothiomorpholide if the reaction time were prolonged. The terminal oxidation would remove the catalytic sulfur from the mixture gradually and diminish the rates of isomerization. It was interesting to observe that when one started an isomerization reaction with heptanal, reverse isomerization to mixtures of ketones occurred. Apparently isomerization can compete favorably with the Kindler conversion to thioamide. The reactions of isotopically labeled pentanone and heptanone were studied by E. V. Brown and co-workers.[51] Their experiments were designed to decide among several then current hypotheses regarding mechanisms, but did not agree with the predicted outcomes. The reasons for the observed results will be referred to later in the light of more recent interpretations.

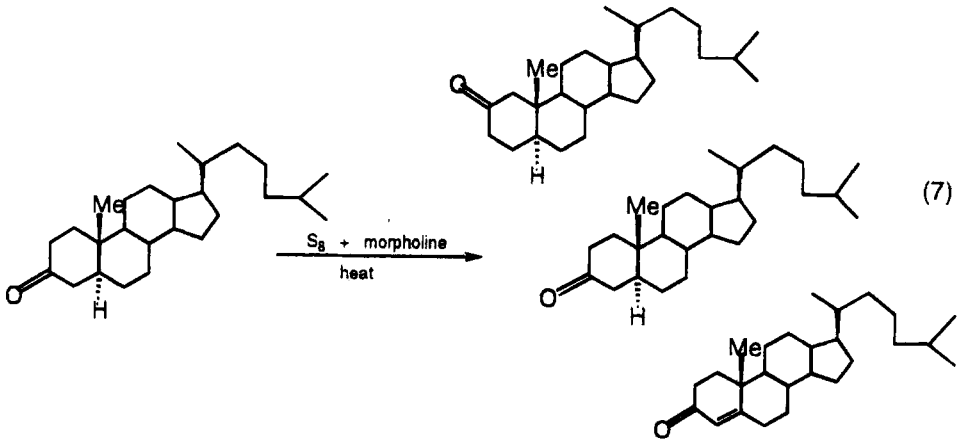
• Other variously substituted ketones were studied by Behforouz.[52] 2,6-Dimethyl-4-heptanone (diisobutyl ketone) isomerized into 2,6-dimethyl-3-heptanone but the process was slow. The ratio of 4-:3-isomer after 22 hours of heating at 120–125 °C was only 70:30 rather than a statistical ratio of 1:2. The experiment illustrates the strong inhibiting influence of branching methyl groups.

• A few experiments with 6,10-dimethyl-2-undecanone (hexahydropseudoionone) yielded two isomeric ketones considered likely to be the 3- and 4-isomers. No peak in the GC was noted that would correspond to the 5-isomer. Isomerization to the aldehyde was not observed; presumably it would be subject to the Kindler transformation to thiomorpholide, and any aldehyde formed may thus have been irreversibly oxidized.

• 4-*tert*-Butylcyclohexanone was heated at 120 °C for eight hours. No 2-isomer was found in the resulting ketonic mixture. The ratio of 4- to 3-isomer was 76:24. Steric effects are apparent.

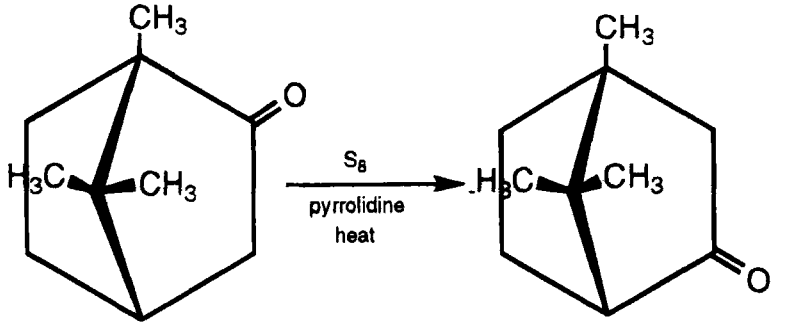
• The isomerization reaction could prove useful when applied to keto steroids and other natural and synthetic ketones. It could provide simple routes from readily available ketones to isomers otherwise hard to obtain.

We had limited success with 3-cholestanone. Under conditions of heating four hours at 130–135 °C (designed to offset expected steric inhibition), the ketonic product was purified by liquid column chromatography to yield 19.7 percent of the starting 3-cholestanone, 19.7 percent of isomeric 2-cholestanone, and 4.4 percent of $\Delta^{4,5}$-3-cholestenone. The reactions are shown in Eq. 7. In spite of the evident steric inhibition in this one example, we believe that further investigations of keto steroids can be fruitful.



(7)

• As a further example of the conversion of a readily available natural ketone to a less available isomer, we investigated the conversion of natural (+)-camphor into (−)-epicamphor. The structures are illustrated in Eq. 8. While the movement of the carbonyl to its adjacent carbon proved to be possible, it proved also to be strongly subject to steric inhibition and required long heating at higher than usual temperatures. Even under these forcing conditions, the conversion was incomplete. Efforts to force the isomerization by use of even more drastic conditions led to reductive formation of bornyl thiols. In view of the greater ease of formation of enamines with pyrrolidine than with morpholine, pyrrolidine was used with sulfur at 95–97 °C for 25 hours and the purified ketonic product showed the resulting ratio of camphor:epicamphor to be 84:16.



(8)

(−)-Epicamphor is very nearly a mirror image of (+)-camphor except for the location of the bridgehead methyl. Not surprisingly, separation was almost as difficult as the resolution of a racemate, and was achieved only by repeated recrystallization and liquid-column chromatography applied to the 2,4-dinitrophenylhydrazones, from whose purified

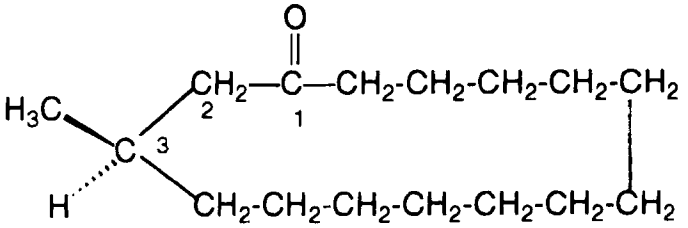


FIGURE 3 Natural (−)-Muscone (3-Methylcyclopentadecanone).

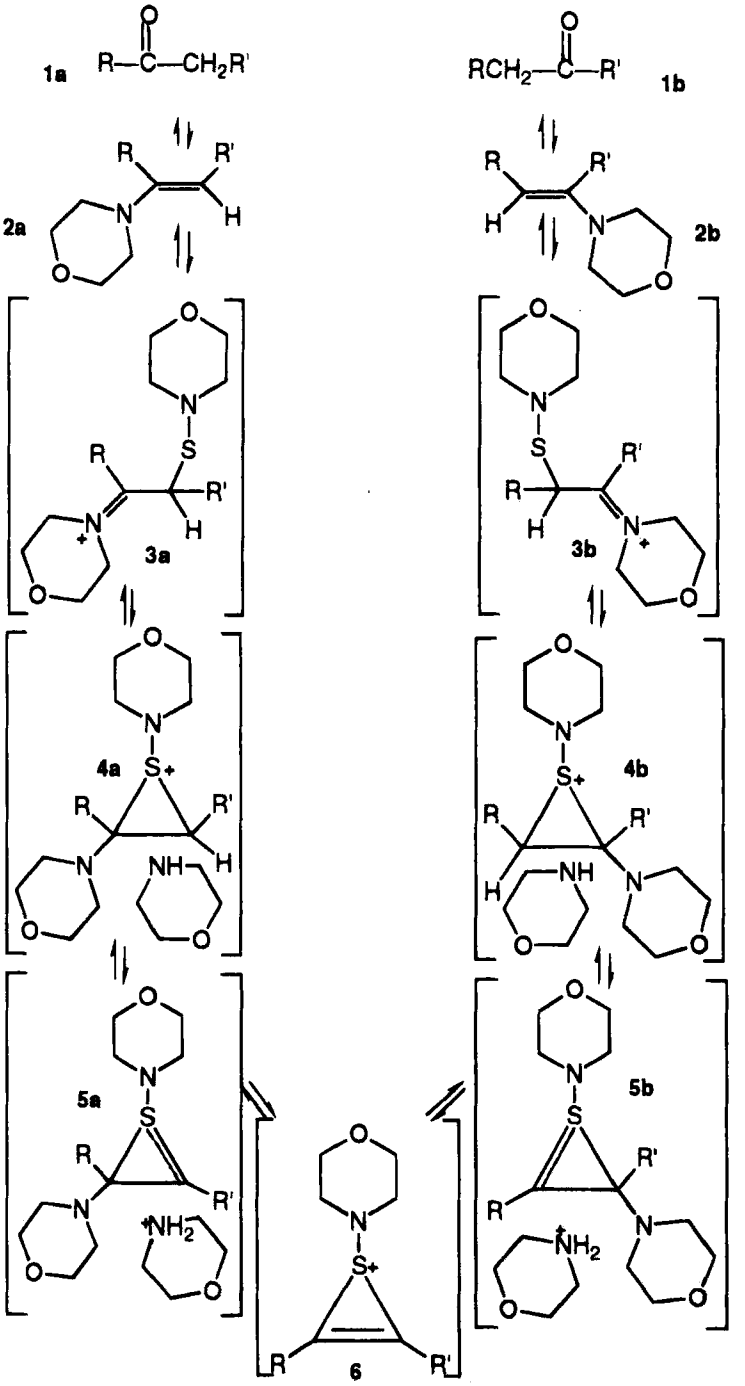
forms the ketones were recovered. The circular dichroism spectra of the two ketones are nearly mirror images; CD measurements could be used to analyze mixtures of the two.

• Natural muscone [(−)-3-methylcyclopentadecanone] (Fig. 3) would offer a uniquely interesting subject for studies of the isomerization. If isomerization of the carbonyl to form the 2-isomer were to occur, facile racemization could occur. But the foregoing examples suggest that the carbonyl group would be much more likely **to move away from the asymmetric C-methyl** and optical activity could be retained through the formation of the 4-, 5-, 6-, 7-, and 8-isomers. If the ketone function moved further on around the ring to form the 9-isomer (a mirror image of the 8-isomer), generation of mirror image forms would occur from there onward around the ring. This would be a possible, but still theoretical, example of a novel kind of racemization. If all isomers could be separated in pure form, they would provide materials for an interesting experiment in the correlations of six different optically active muscone stereoisomers with their odors.

8.3. *Mechanism of Carbonyl Isomerization with Sulfur and* sec*-Amines*

The original papers[53] must be consulted for other examples and details of the many experiments. We were finally able to put together the facts we had observed with our early suggestions of involvement of enamines and thiirene-type intermediates. The excellent monograph by Oae and Furukawa[54] reviewing the growing body of knowledge of sulfur-nitrogen chemistry provided hints at the possible nature of the higher reactive sulfur-nitrogen catalytic intermediates in the carbon isomerization reaction.

We propose that the long-sought symmetrical intermediate in the passage of a carbonyl group to a location on its adjacent carbon atom may be a thiirene-SN-*sec*-amine. In view of the relative stability of thiirene *S*-oxides, there appears to be a good possibility that compounds analogous to the thiirene *S*-oxides may also be capable of existence with nitrogen replacing oxygen. The stability of the thiirene *S*-oxides encourages the hope that the nitrogen analogs may be capable of being isolated and may be crystalline entities. This objective seems worthy of special research attention, which we unfortunately did not have the opportunity to explore in the laboratory.



SCHEME 1

The lengthy discussion of details of the proposed mechanism that has been published[55] will not be repeated in this review. The important first step in the Kindler-type isomerization is postulated to be the attack of the nitrogen of the secondary amine on the S_8 ring to open it and to form a sulfenamide $R_2N\text{-}S(S_x)H$ or its anion. The polar nature of the >N-S bond is considered to provide the high reactivity necessary to drive the isomerization. At least two sulfur atoms must be present to provide for the postulated attack of an enamine, with displacement of sulfur on sulfur.

Beyond these minimal requirements the catalytically active species may vary widely. Sulfur atoms may be split off during the catalytic processes but would be expected to catenate rapidly into chains or rings and become available for further reaction with amine. Thus, it is unnecessary to postulate that sulfur is used up in the isomerization itself; this conclusion is consistent with the fact that less then one gramatomic equivalent of sulfur is still enough to bring about one cycle of isomerization in the methylcyclohexanones. The chemical details we suggest for the completion of one cycle of movement of a carbonyl function from one carbon to its adjacent carbon are shown in Scheme 1. This Scheme 1 applies to the Kindler type of transformation. Willgerodt's aqueous procedure probably has unique features in the light of the numerous possibilities for reactions between elemental sulfur or polysulfides and ammonia.

9. THE STEREOCHEMISTRY OF SULFUR-SULFUR BONDS

Skewed, or non-planar, preferred configurations were predicted for compounds containing atoms—Ä—B̈—with two pairs of unshared electrons on each atom (Penney and Sutherland, 1934[56]). If the pair of joined atoms for various reasons could not rotate around the uniting bond, enantiomeric pairs could exist. This generalization would apply to the ubiquitous disulfide bond. The barrier to free rotation about the sulfur-sulfur bond has been estimated over a wide range,[57] but in general the energy barrier is not considered great enough to support a prediction that simple disulfides can exist as stable, isolable enantiomers at ambient temperatures.

The situation is different if a disulfide bond is present in a molecule which contains a fixed center of asymmetry besides the disulfide function. In such a situation, more or less labile diastereoisomeric forms can exist through steric induction, and the fixed asymmetric center could induce an excess of one diastereomeric form of the disulfide over the other. The disulfide bond in its usual skewed configuration prefers a dihedral angle (Φ) of about 90° and exhibits a strong absorption band centered at about 250 nm in simple non-cyclic disulfides. If there is an excess of one dissymmetric form of the disulfide, induced by the presence in the molecule of a fixed asymmetric center, positive or negative circular dichroism should be observable in the disulfide absorption band, and enhanced optical rotation values may be observed even in the visible region of the spectrum.

Fredga[58] published a list of compounds fitting these criteria, and noted that they tend to show large optical rotations in the visible region. Fieser[59] has called attention to the large and variable optical rotations observed for cystine—a striking exception among the natural amino acids. In view of the frequent occurrence of disulfides in proteins, it is important to keep in mind that each disulfide in a peptide or protein represents a potential

asymmetric center. The right- or left-handed helicity inherent in each disulfide bond could increase the total number of *potential* diastereoisomeric forms, even though many would be labile or incapable of forming. This possibility might be especially significant in proteins containing many disulfide bonds, such as the immunoproteins.

We had long been interested in this phenomenon of potential inherent dissymmetry in the disulfide, and some of its consequences. We saw the opportunity to study this question in connection with the *racemic* dithiothreitol (Cleland's reagent), widely used in biochemical research as a reagent for reducing disulfides to thiols under mild conditions. With co-worker Charles J. Kelley,[60] we developed synthetic routes to the pure enantiomers of dithiothreitol, starting with the commercially available (+)- and (−)-enantiomers of tartaric acid. The ethyl esters were converted to the acetone ketals, from which the ester functions could be converted into sulfhydryl groups in four synthetic steps; hydrolysis of the acetals yielded the pure optical enantiomers of dithiothreitol.

Mild oxidation of the dithiothreitol acetals closed the rings by converting the thiol groups to disulfides in cyclic dithianes. Subsequent hydrolysis of the acetals yielded dihydroxydithianes of known absolute configuration related to tartaric acid. It was only necessary to assume that the dithiane rings would prefer the chair conformations to assign absolute configurations to the disulfide groups in each enantiomer. From observations of the circular dichroism spectra (CD), the generalization was made[61] that "*in simple 1,2-dithiane systems a positive CD band corresponding to the lowest frequency ultraviolet absorption band of the disulfide group (in the case of 1,2-dithianes in the range of 280–290 nm) is associated with a right-handed (P) screw sense of the helix containing the atoms C-S-S-C and a negative CD band is associated with a left-handed (M) screw sense of the helix.*" This parallels the rule developed for skewed dienes.[62] The dihedral angle, Φ, of the 6-ring disulfides would necessarily have a smaller value than 90°. We noted that the optically active dithianes had their CD bands shifted to longer wavelengths and the band was somewhat weaker than in open disulfides that are free to assume a larger angle of about 90°. The size of the shift to longer wavelengths if the dihedral angle is forced to assume a smaller value than 90° can be used as a fairly accurate measure of the dihedral angle.

D. W. Urry and co-workers[63] have made use of this rule in assigning configurations of cyclic neurohypophyseal hormones (*e.g.*, oxytocin and related hormones) in solution. They made comparable studies with related cyclic peptide hormones in which the disulfide ring-closing function had been replaced with a diselenide function. The same rule relating helicity with circular dichroism in the disulfides[61] applied also to the diselenides.

The interesting case of the unusual CD absorption of optically active lipoic acid reported by Djerassi, Wolf, and Bunnenberg[64] attracted our attention. The dihedral angle of the disulfide contained in the dithiolane ring is quite small and gives rise to two weak bands of opposite sign, slightly separated, in the vicinity of 360 nm. The absorption region extends a little way into the visible violet, with the result that the compound has a light yellow color. In this situation, the five-membered ring readily reverses its -S-S- conformation. The fixed asymmetric carbon center induces a slight preference of the disulfide dihedral angle for one form over the other, while a slight difference in the dihedral angles causes the two oppositely-signed CD bands to be slightly separated in

wavelength, so that they partially overlap and largely cancel each other. The result has the appearance of a small sine wave, with positive and negative lobes.

Co-worker Leonard A. Neubert[65] observed that these bands are temperature-sensitive, and made use of their changes with temperature to calculate equilibrium constants for the two forms. CD spectra of several other optically active dithiolanes were measured. In addition, Neubert[66] determined the circular dichroism spectra of a series of cyclic disulfides having dihedral angles ranging from 0° to 60° in the 400-185 nm spectral region and noted the systematic variations of the absorption bands with variations in the dihedral angles.

racemic-Dithiothreitol was reported (Falconi, Scotto, and DeFranciscis, 1968, 1970[67]) to be moderately effective as a protective agent against radiation damage in mice. Although not outstanding in this respect, it is interesting because it was reported by the same authors to reduce the mortality in mice even if administered as much as *24 hours after exposure* to X-radiation. We were participating at the time in the U.S. Army's search for such protective agents, and it occurred to us that it would be interesting to determine whether the two pure enantiomers of dithiothreitol, which we had synthesized but which had not yet at that time been reported in the literature, would exhibit differing radiation protective activities and toxicities in mice. The results were interesting and suggestive.

The two pure enantiomers of dithiothreitol were submitted to Professor Kenneth P. DuBois of the University of Chicago for evaluation as protective agents against radiation damage, with mice as the test animals. Professor DuBois[68] reported that the enantiomeric dithiothreitol derived by synthesis from the common natural tartaric acid was *not effective as a radiation protective agent* and was also more toxic than the enantiomer derived from the uncommon tartaric acid. [The LD_{50} was 169 mg/kg for the *racemic*-DTT as compared with 255 mg/kg for the (+)-DTT derived from unnatural tartaric acid and 179 mg/kg for the (—)-DTT derived from natural fermentation tartaric acid.] Protection from radiation damage afforded by (—)-DTT at a dosage of 150 mg/kg, with mice exposed for 10 minutes to 625 R of radiation, was totally ineffective, showing 100 percent mortality. The (+)-DTT (from unnatural tartaric acid) showed a mortality of only 20 percent when mice were exposed 10 minutes to 600 R after having received 200 mg/kg of the agent. With radiation up to 750 R and other conditions the same, there was still only 60 percent mortality. While these data do not indicate high protective activity, they suggest that stereochemistry should be taken into account in the investigation of protective agents.

The observation that the reported radiation protective action of *racemic*-dithiothreitol is due to only one of the enantiomers, and that this form is also less toxic was not investigated further by us, but suggests that further investigation of the synthetic (+)-DTT might be worthwhile, either as a therapeutic acid or a useful special reagent in protein chemistry.

For example, it has been found[69] that compounds that can reduce disulfide bonds under very mild conditions (*e.g.*, cysteamine and *rac*-DTT) can alleviate the rare condition known as cystinosis (a disease in which a defect in the lisosomal cystine transporter allows cystine to accumulate in cells). The condition can be debilitating or lethal.

The 98 percent pure *levo* enantiomer of dithiothreitol derived from L_g-(+)-tartaric acic (fermentation) has been offered by the Sigma Chemical Co. of St. Louis, MO, under their Catalog No. D9760 at a price approximately four times that of the racemic Cleland's reagent.

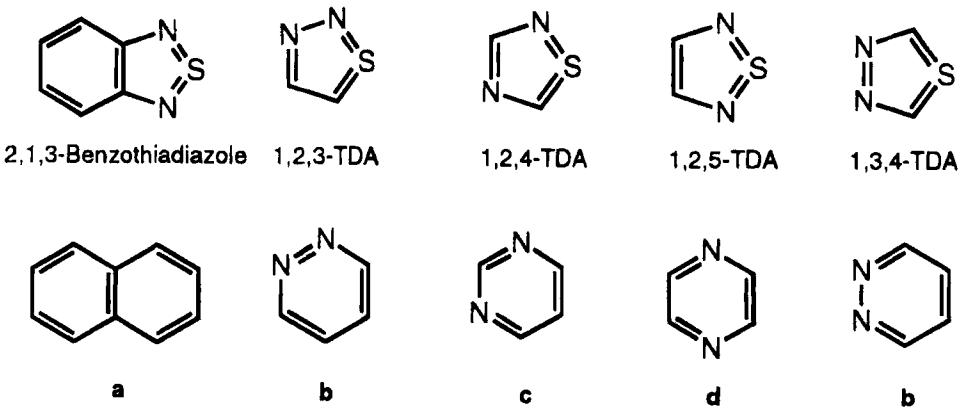


FIGURE 4 Thiadiazoles Compared with Diazine Analogs.

An idea that we were not able to investigate was the possibility that the individual optically active forms might have a degree of selectivity, and differing reactivity, in cleaving the disulfide bonds in some peptides and proteins. If this idea were confirmed, the availability of pure enantiomers of dithiothreitol could enhance the usefulness of the Cleland reagent.

10. 1,2,5-THIADIAZOLES

10.1. *Synthetic Studies of the 1,2,5-Thiadiazoles and Related Compounds*

In 1953, an undergraduate student showed me a test tube in which he had dissolved some rhombic sulfur in ethylenediamine. He asked me if I could explain the chemistry that produced the bright green color of the solution. I had to admit that the answer would take some thought and probably a fair amount of research, for I knew that the reaction of amines with sulfur had not been extensively studied and would almost certainly prove complex.

This query, however, set in motion a train of thought that suggested a new field of research and opened up a virtually untapped area of heterocyclic chemistry. It led to several doctoral dissertations and eventually several new medicinal agents.

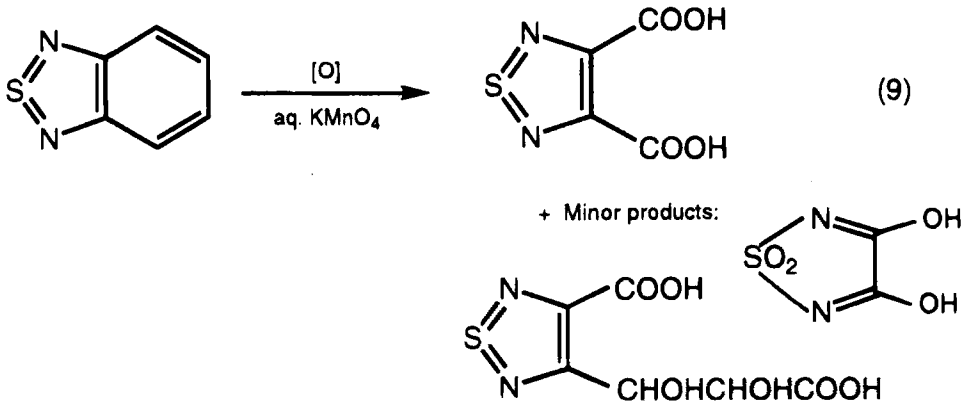
It was known that amines open up the S_8 ring and form polythiosulfenamides. In the case of ethylenediamine in reaction with sulfur, the possibility of facile ring closure in such a sulfenamide to form a five-membered heterocyclic ring seemed a logical step. It would contain two carbon atoms, two nitrogens, and one sulfur, with the nitrogens flanking the sulfur atom. Elemental sulfur could also in principle dehydrogenate and aromatize such a hydroaromatic ring.

This line of thought led to the possibility that 1,2,5-thiadiazole might be formed from ethylenediamine and sulfur, and might be a stable, aromatic sompound. A search revealed that little was known of the 1,2,5-thiadiazole **monocyclic** ring system. A number of **polycyclic** fused-ring systems containing the 1,2,5-thiadiazole nucleus were known, and the heterocyclic portion in general showed strong aromatic characteristics. The literature then existing was also meager on the other three isomeric monocyclic systems: 1,2,3-, 1,2,4, and 1,3,4-thiadiazoles, as illustrated in Fig. 4.

The ability of -S- to simulate a $-C=C-$ grouping in heteroaromatic systems: *e.g.*, thiophene and benzene and likewise the thiazoles and pyridines, has long been known. The thia and the olefinic groups have a so-called "isosteric" or isoelectronic relationship, and in numerous cases may be interchanged in aromatic compounds with remarkably small changes in physical and chemical properties. This line of reasoning would predict that 1,2,5-thiadiazole should be aromatic and have a close relationship to pyrazine. By the same line of reasoning, the 1,2,4-thiadiazole system should resemble pyrimidine, while 1,2,3- and 1,3,4-thiadiazoles should have close relationships to the 1,2-diazines. The existing literature of polycyclic fused-ring systems, such as 2,1,3-benzothiadiazole, which contain the 1,2,5-thiadiazole nucleus and are aromatic, supported the prediction that the monocyclic ring system would also have aromatic properties.

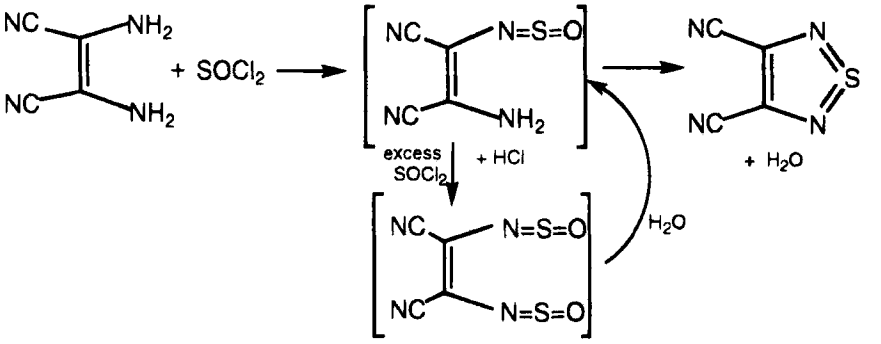
Doctoral candidates and co-workers, Leonard Weinstock[70] and Daniel Shew,[71] took on the problem of developing synthetic routes to the monocyclic 1,2,5-thiadiazole system, both the simple ring without substituents and derivatives that could be interconverted readily into other functionalities. Both were successful in finding alternative routes to the mono- and dicarboxylic acids, which could in turn become starting materials for producing many mono- and disubstituted derivatives.

Weinstock's approach was the oxidation of the benzene half of benzo[*c*]-1,2,5-thiadiazole (Eq. 9). The permanganate oxidation attacked principally the carbocyclic moiety—an indication that the 1,2,5-thiadiazole ring is very resistant to oxidation and a strong indication that it would prove to be aromatic. The monoammonium salt of the 3,4-dicarboxylic acid was nicely crystalline and useful in the separation and purification of this acid. A small amount of by-product in the oxidation was a 1,2,5-thiadiazoledicarboxylic acid retaining all of the carbon atoms of the carbocyclic half of the starting benzothiadiazole with one carboxyl on one carbon of the ring and a dihydroxypropionic acid group on the other carbon. This acid was isolated as the silver salt. Another by-product of the potassium permanganate oxidation was the potassium salt of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide, as illustrated in Eq. 9.



Shew's approach was the ring closure of hydrogen cyanide tetramer (2,3-diaminomaleonitrile or a tautomer of it); it is illustrated in Eq. 10. Hydrogen cyanide tetramer can be

prepared by controlled polymerization of hydrogen cyanide; at that time (*ca.* 1956–57) the tetramer was a rather rare chemical in spite of the fact that patented routes existed for its preparation. It later became commercially available, and also figured as a key postulated intermediate in the primordial biogenesis of early life forms. The cyclization of hydrogen cyanide tetramer was achieved with thionyl chloride. 3,4-Dicyano-1,2,5-thiadiazole, formed as a crystalline product, could be converted by hydrolysis to the dicarboxylic acid or directly into other derivatives.



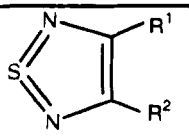
(10)

The cyclization of *ortho*-diamines with thionyl chloride is an interesting reaction (Eq. 10). In most cases, the reaction proceeds spontaneously with the closure of the new thiadiazole ring. In one case in which an excess of thionyl chloride was used, a red, crystalline compound was isolated which had a pair of *ortho* $-N=S=O$ groups. This compound reacted almost explosively with small amounts of water to produce the thiadiazole derivative. We interpret the usual pathway as proceding through the *mono*-NH_2-*mono*-$N=S=O$ intermediate; the hydrogen chloride generated probably catalyzes the elimination of water to form the 1,2,5-thiadiazole. This *ortho*-bis-$N=S=O$ derivative may only be formed when sufficient thionyl chloride is used to scavenge the water formed in ring closure; it in turn is very sensitive to catalytic amounts of water.

It was found that the 1,2,5-thiadiazole ring system is strongly electron-withdrawing and activates the carboxyl groups so that one is readily decarboxylated by heating in a high-boiling solvent such as phenetole at 160–180 °C to produce the monocarboxylic acid. The second carboxyl of the mono acid can be decarboxylated at higher temperatures of *ca* 200 °C, either in a high-boiling solvent or in a sealed tube, producing the liquid parent 1,2,5-thiadiazole. If the mono- and dicarboxylic acids are equilibrated in deuterium oxide, then decarboxylated, the resulting mono- and dideutero-1,2,5-thiadiazoles can be produced, and were useful in physical studies.

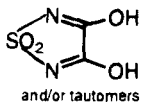
1,2,5-Thiadiazole is a colorless liquid, boiling at 94.1 °C. Its odor is reminiscent of a mixture of pyridine and acetone. The ultraviolet absorption spectrum has a strong band centered at 254 nm (log ϵ 3.90). The structure of the compound was determined by electron diffraction by Bonham and Momany.[72] Dobyns and Pierce[73] have published a microwave study. Early examination of the infrared spectrum was done by Weinstock and

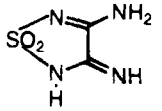
TABLE 1 Mono- and Polycyclic 1,2,5-Thiadiazoles Prepared

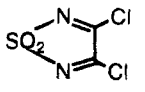


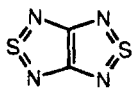
R^1 = H	D	COOH	$COOR^3$	COCl	CHO	COOH	$COOR^3$
R^2 = H	H	H	H	H	H	COOH	$COOR^3$

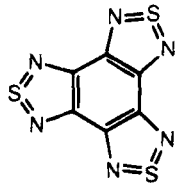
R^1 =	$CONHR^3$	CHO	COOH	Cl	NH_2	OH	OR^3
R^2 =	$CONHR^3$	COOH	NH_2	Cl	NH_2	OH	OR^3

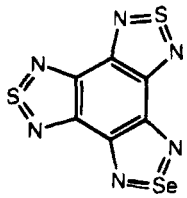












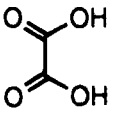
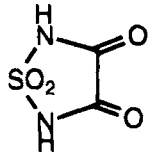
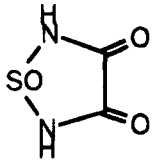
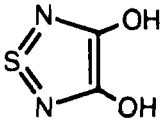
Shew, elaborated further by Marquardt,[74] and a definitive analysis of the infrared and Raman spectra has been published by Šoptrajanov and Ewing.[75]

A derivative of the ring system having the sulfur oxidized to $-SO_2-$ was synthesized by the reaction of sulfamide with oxalyl chloride to form the 3,4-dihydroxy-1,2,5-thiadiazole *S,S*-dioxide, or a mixture of its tautomeric forms. This compound has the properties of a rather strongly acidic non-aromatic compound.

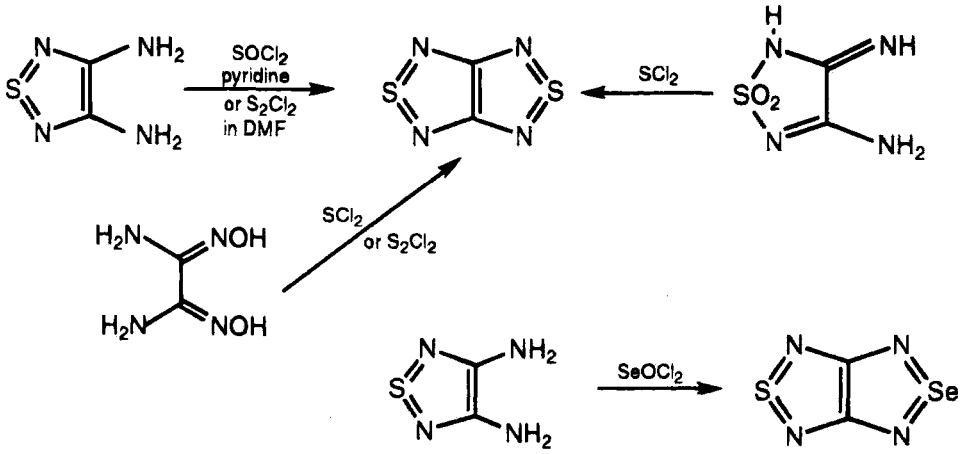
In a series of studies by my graduate students[76]—Fritz-Hans Marquardt, Leonard Weinstock, Daniel Shew, Richard Y. Wen, Ian W. Stapleton,[77] Robert Street, and Andrew P. Komin[78]—a considerable number of mono- and disubstituted derivatives of 1,2,5-thiadiazole and also its *S,S*-dioxide derivatives were prepared, and their properties investigated. The original papers should be consulted for details of these syntheses, which laid the groundwork for a great expansion of the chemistry of the 1,2,5-thiadiazole ring system. Table 1 shows many of the important monocyclic derivatives that were prepared—most for the first time—and some by several alternative routes.

It is interesting to compare the acidic ionization constants of a group of disubstituted 1,2,5-thiadiazole derivatives with oxalic acid in Table 2.

TABLE 2 Ionization Constants of Diacids Related to 1,2,5-Thiadiazole Derivatives

Compound	pK_{a1}	pK_{a2}
	1.23	4.10
	2.20	5.55
Note: the second and third compounds probably exist as tautomers		
	2.62	6.56
	4.68	7.50

The acidities of the acids indicate that the 1,2,5-thiadiazole itself is strongly electron-withdrawing. This is consistent with the relative resistance to oxidation of the 1,2,5-thiadiazole half of benzo[*c*]-1,2,5-thiadiazole. It was found that the methyl group of 3-methyl-1,2,5-thiadiazole is sufficiently activated by the ring nucleus so that base-catalyzed condensations can be carried out on it with relative ease.



SCHEME 2

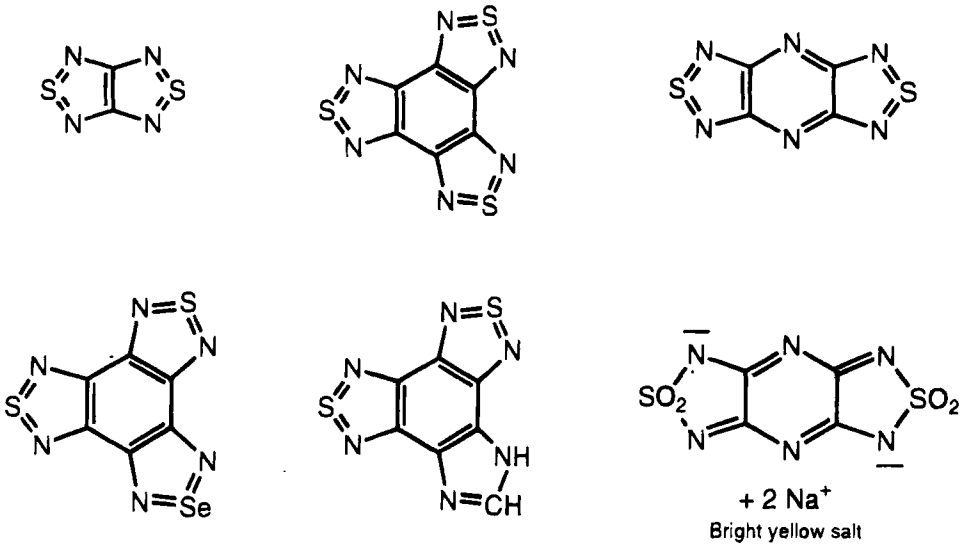


FIGURE 5 Polycyclic 1,2,5-Thiadiazole Derivatives Having No Substituents Other Than Electron Pairs.

We synthesized a group of polycyclic derivatives of 1,2,5-thiadiazole that have no external substituents except unshared electron pairs. These are shown in Fig. 5.

The compound thiadiazolo[1,2,5][3,4-*c*][1,2,5]thiadiazole (referred to for convenience as TDA/TDA) is of special interest because of its relationship to thieno[3,4-*c*]thiophene. The latter compound has been sought in various studies, but only heavily substituted derivatives have been isolable. The questions regarding the resonance forms and possible aromaticity of the thienothiophene have been much discussed. Our synthesis of the thiadiazolothiadiazole turned out to be surprisingly easy. Several alternative routes are shown in Scheme 2.

Its first synthesis was planned as a multistep process starting from 3,4-diamino-1,2,5-thiadiazole *S*,*S*-dioxide (top right); it had been anticipated that several separate steps would be required to replace the sulfonyl. Surprisingly, the starting material reacted with sulfur dichloride to produce the desired TDA/TDA in a single step. Evidently several anticipated intermediates spontaneously reacted in the next step of the planned sequence. Hydrolysis of the TDA/TDA yielded 3,4-diamino-1,2,5-thiadiazole, which could be readily reconverted to the bicyclic parent with thionyl chloride. Still another route started with the diamino-dioxime shown in the lower left of Scheme 2.

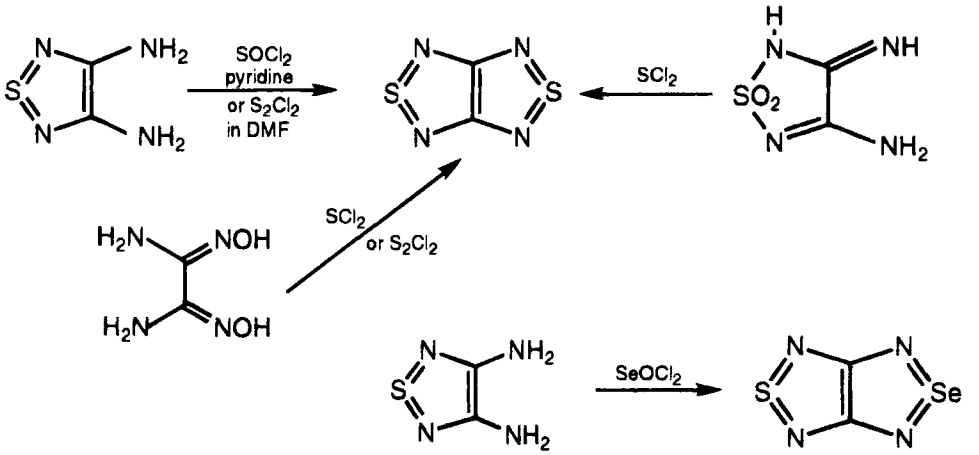
The bicyclic TDA/TDA formed colorless prisms, m.p. 115.7–116 °C. It could be purified by column chromatography on silica gel (a small amount of elemental sulfur preceded the bicyclic product) or by sublimation (which occurred readily in analogy with naphthalene) or by recrystallization from methanol. The compound could not be steam distilled, as is possible with benzo[*c*-1,2,5]thiadiazole, because in hot water at 75 °C it hydrolyzes into 3,4-diamino-1,2,5-thiadiazole, oxamide, sulfur dioxide, and elemental sulfur. Although some of the bicyclic compound must hydrolyze to oxamide *via* the diaminothiadiazole in this example, the latter compound is not hydrolyzed to oxamide in hot water unless sulfur

dioxide is present. Sulfur dioxide would of course be generated in the first step of hydrolysis of the TDA/TDA.

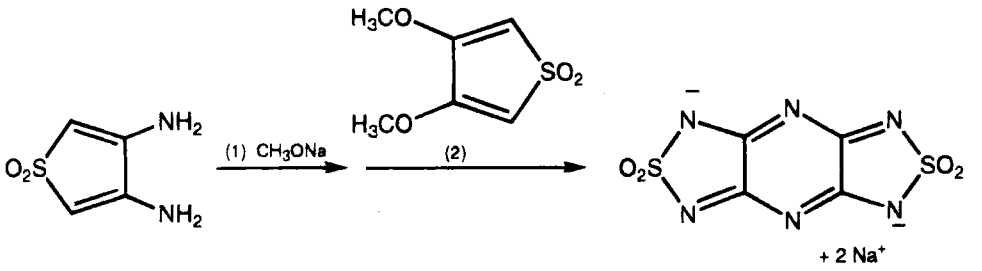
J. C. Huffman[79] made an X-ray crystallographic study of 1,2,5-thiadiazolo-1,2,5-thiadiazole and found it to be planar, with the bond angle NSN 103.08°, the angle SNC 104.36° and angle NCC 114.08°. The bond lengths were determined to be NS 1.62 Å, NC 1.35 Å, and CC 1.44 Å.

The TDA/TDA can be reduced to a radical anion. The electron spin resonance spectra of the radical anion and similar forms of related heterocyclic compounds have been reported by Kwan, Carmack, and Kochi.[80]

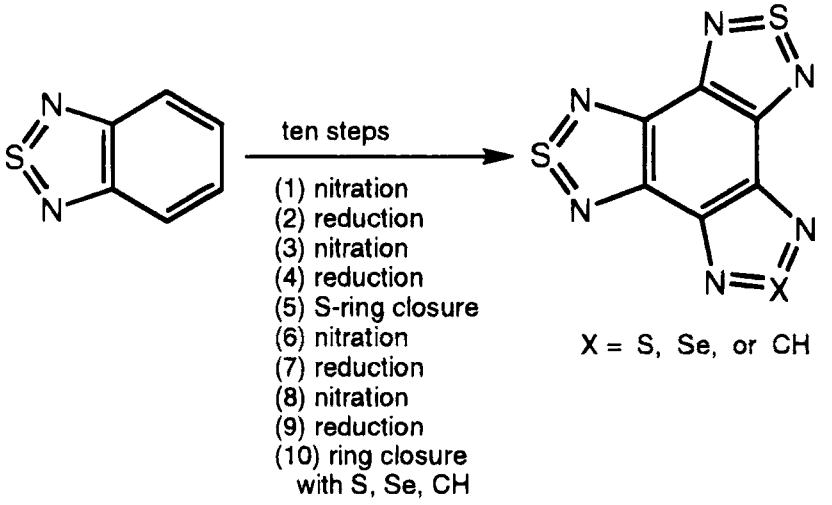
The unusual feature of TDA/TDA of having no substituent groups—only electrons on both faces and all edges—suggested that such compounds might have unique electrical properties. This idea prompted us to synthesize a series of bicyclic, tricyclic, and tetracyclic heterocyclic systems containing nitrogen and sulfur and having no atomic substituents—only electrons—on their external surfaces. (*cf.* Fig. 5 and Schemes 2-4.)



SCHEME 2



SCHEME 3



SCHEME 4

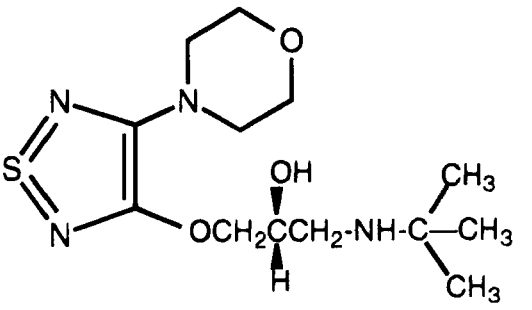


FIGURE 6 Timolol™.

10.2. *Medicinals from 1,2,5-thiadiazole derivatives*

Leonard M. Weinstock and Daniel Shew, after completion of their doctoral work with me, were employed by Merck and Co. By arrangement with the Indiana University Foundation, the Merck research group continued studies of 1,2,5-thiadiazole chemistry and prepared many new derivatives. A number of these derivatives showed biological activities and therapeutic possibilities. One in particular, named **timolol** (Fig. 6), was ultimately the active ingredient in three commercial pharmaceuticals: Timoptic™, Blocadren™, and Timolide™. Timoptic, a solution containing timolol, has been a very successful drug for a number of years in the treatment of glaucoma.

11. MAMMALIAN PHEROMONES CONTAINING SULFUR

A pheromone is a natural signal chemical transmitted from one animal to another of the same species to convey specific information. Two types are recognized: those which

trigger an immediate behavioral response, and those which trigger a deep-seated biochemical response. Pheromones were first extensively investigated in insects, and have proved invaluable in the study of their behavior and control.

More recently, mammalian pheromones have been the subjects of expanding investigations. It is recognized that the semiotic systems of higher animals are complex[81] and methodologies for their study require the use of every forefront analytical technique available. In fact, progress in this field moves in step with the advances in analytical and organic chemistry.

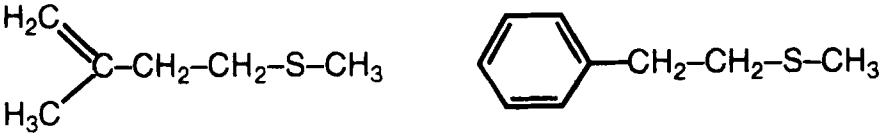
Animals often have a series of specialized glands that secrete different pheromones to carry different messages.[82] The pheromones generally become airborne and are detected by sensitive receptors of the olfactory and vomeronasal centers. (The vomeronasal organ is present in the nasal passage of most animals and gives them the capability of detecting non-volatile substances such as salts, peptides, etc. that are inhaled as aerosols. Its occurrence in humans has been denied and is controversial, but recent claims maintain that it is not only present in humans but may play important, heretofore unrecognized, roles in human detection of semiochemicals). Specific behavioral patterns of individual species permit the synthesis, excretion, and dissemination of the signal chemicals at appropriate times. This field of study requires close collaboration among biologists, analytical chemists, and organic chemists.

It became possible to develop a research program in mammalian pheromones at Indiana University when Professor Milos Novotny (now Rudy Professor of Analytical Chemistry) joined the faculty of the Chemistry Department. As a specialist in analytical research, he brought to the Department his forefront program of devising new and highly sensitive methods of separating small quantities of complex mixtures into their individual components. Because of the very small quantities of the separated individual compounds, a major new and challenging field of research is the development of new ways of obtaining structural data in order to assign chemical structures and to determine their stereochemistry.

I had long been interested in pheromonal phenomena and had reviewed the subject periodically for my graduate course in the chemistry of natural products. When Professor Novotny joined our Chemistry Faculty I realized that the analytical skills required for serious work in this field were close at hand. Professor Novotny was especially interested in applying the new analytical techniques to the solution of problems of medical and biochemical significance. He saw the possibilities of making significant contributions to the field of mammalian pheromones. Just prior to my formal retirement, and continuing afterward, I was associated with Professor Novotny's group as consultant in organic chemistry.

It turned out that several, although not the majority, of pheromones that came to the attention of the group at Indiana University have been sulfur compounds. Species that make use of sulfur-containing pheronones are usually easily recognizable by the typically strong and obnoxious smells. These include, among many others, the skunk, the mouse, and the fox. The red fox and the mouse were the first two species to which the group associated with Professor Novotny turned early attention.

The mouse is an especially important experimental animal because of the availability of many pure-bred strains and the large body of existing genetic knowledge relating to



Δ^3-Isopentenyl methyl Sulfide 2-Phenethyl methyl Sulfide

FIGURE 7 Pheromones of the Male Red Fox.

mouse species. The mouse has been the experimental animal of choice in the study of many medical and biological problems.

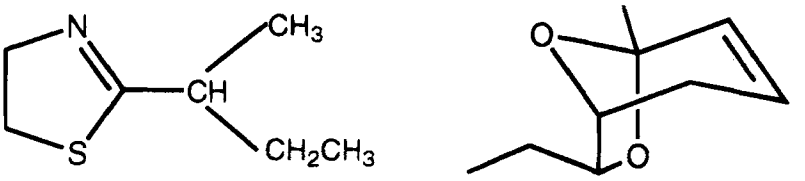
We were fortunate to enlist the interest and the active collaboration of Dr. Wesley K. Whitten, a widely recognized Australian biologist and mouse geneticist. While a co-worker with Professor Sir Alan Parkes at Cambridge University, Whitten identified the first mammalian pheromone, a classic in physiology textbooks known as the Whitten effect[83] in mice. After years of research at the Roscoe B. Jackson Laboratory in Bar Harbor, Maine, Dr. Whitten retired to Australia but was called back into a new career in the field of human *in vitro* fertilization, based upon his earliest publications describing the detailed conditions for *in vitro* fertilization in mice.

The first publication from the Novotny group in the field of pheromone chemistry, however, concerned the identification of constituents in the urine of the male red fox (*Vulpes vulpes* L.) during the winter mating season. In this first pheromone project at Indiana University, we received invaluable help from Dr. and Mrs. Whitten, who collected fresh frozen specimens of male and female urines[84] in the cold winter snows of Maine. The frozen samples were transported in the frozen condition to Indiana University to minimize chemical changes.

Novotny and his co-workers applied advanced techniques of gas-liquid chromatography to separate the large number of volatile products in both the male and female urines. Then close comparison of the chromatographs revealed the small number of compounds distinctive of either the male or the female. Among the compounds identified in male urine (absent or in very low concentration in female) were two sulfur compounds,[85] together with several additional terpenoid compounds. The two sulfur compounds are shown in Fig. 7.

These significant sulfur compounds were synthesized in the Novotny laboratory. It was subsequently shown that synthetic duplicates of the natural male red fox scent constituents (one being the isopentenyl methyl sulfide described above) seem to simulate the effects of the natural pheromones produced by the fox. It was demonstrated[86] that the male red foxes are stimulated to increase their marking behavior during courtship when they detect the presence of the synthetic analogs of their male pheromones described above. It is believed that the sulfur compounds are attractants to the female red fox during the mating season. The female excretes a pleasant-smelling chemical from a gland above the base of the tail (the supracaudal gland). Its structure and synthesis have been studied elsewhere.

English workers have shown[87] that the biologically active sulfur compounds begin to be excreted by the male red fox at the beginning of the courtship season in midwinter and are deposited in the snow or on the ground in the male urine. These sulfur compounds gradually increase in quantity to reach a maximum at the time of mating some weeks



2-*sec*-Butyl-4,5-dihydro-1,3-thiazole (R,R)–Dehydro-*exo*-brevicomin

FIGURE 8 Mouse Pheromones Responsible for the Whitten Effect.

later; the excretion of the sulfur compounds decreases rapidly after mating. Thus, the close connection with the period of courtship and mating of the red fox and the excretion of the sulfur compounds during this period suggest that the latter play an important role in the reproductive behavior. Red foxes are not a highly social species like the wolf, but tend to be lone animals except during the weeks of winter courtship, when the male fox selects a vixen and runs with her for several weeks before mating. After mating, the male fox again becomes a loner.

The synthesis of identified pheromonal compounds makes available to biologists key compounds for the study of animal behavior. Practical applications of synthetic pheromones lie in the possibility of human control of specific animal populations—either to enhance their propagation (in the case of endangered species), or to reduce selectively the populations of pest species without harm to other species.

For example, the English scientists referred to above have studied the red fox pheromones as a possible way of protecting England from invasions of rabid foxes from the Continent where rabies is still a problem. In Australia, much attention has been given to pheromones of the rabbit, which was introduced by early settlers but has proliferated in plague numbers in Australia, where they do not have the natural predators found elsewhere. The pheromonal communication system of the rabbit is especially complex.

The Novotny group has also given intense and continuing attention to the pheromones of the mouse. Various species and pure-bred genetic strains of mice have been bred in laboratories such as the Roscoe B. Jackson Laboratories of Bar Harbor, Maine, and the Sloan Kettering Institute for Cancer Research in New York City. These mouse colonies provide important subjects for investigations of cancer and other diseases. Wild mice are a nuisance species because they consume food and because they are known to carry human diseases. Studies to date show that mice make extensive use of pheromones in their interactions—a complex chemical language which can provide insight into animal physiology and behavior. One important application lies in the development of species-specific population control methods.

In the collaborative studies of mice with Whitten and the Novotny group, we have identified several key pheromones of the mouse. Two important ones are shown in Fig. 8: 2-*sec*-butyl-4,5-dihydro-1,3-thiazole and (R,R)-dehydro-*exo*-brevicomin.

It has been demonstrated[88] that the sulfur compound identified above, in combination with the bicyclic oxygen-containing compound (possibly derived from a fatty acid) can induce in female mice the phenomenon known as the Whitten effect. This effect is the reversal of the condition of anestrus in a colony of female mice closely grouped together.

The induction of regular, synchronized estrus in such a female colony by male mouse urine was discovered by Whitten. It can be induced either by the introduction of an adult male mouse into a closely caged anestrous female colony or by the chemicals identified and synthesized by the Indiana University research group. The agents responsible are volatile compounds excreted in the male mouse urine, and perceived by the females through their olfactory senses.

A number of other mouse pheromones have been identified in Novotny's laboratory. They reveal a complex chemical "language," with specific signals being exchanged between adult and immature animals of both sexes and in all combinations. The availability of synthetic copies of the natural pheromonal chemicals provides biologists with materials for research on the roles and mechanisms of perception of pheromones.

The mechanism of the biosynthesis of *sec*-butyl-4,5-dihydro-1,3-thiazole in the animal has been of some interest. A plausible hypothesis suggests that the compound may be derived from cystine and isoleucine. The *in vivo* synthesis of this compound in the mouse is on the agenda for future detailed study.

There is an asymmetric carbon in the *sec*-butyl side chain. It has proved difficult to establish whether the mice release this compound in a preferred enantiomeric form, which would be reasonable if the compound is derived from natural isoleucine. Synthetic efforts have produced both pure enantiomers with known absolute configurations, but the procedure for isolation of the animal-generated pheromone, involving heating during liquid-gas chromatography, can apparently result in racemization. The unsaturation in the ring's 2,3-positions provides a mechanism for facile racemization by activating the asymmetric center in the side chain. If, as has been postulated, this molecule is loosely covalently bound to proteins that act as carriers in the mouse urine, the addition of an amino, thiol, or hydroxyl group in a carrier protein to the 2-position in the ring could easily be stereoselective, thus fixing the new side chain in a preferred configuration. Under physiological conditions, the dihydrothiazole, bound as suggested to a carrier protein by a labile covalent bond, could in principle be released under physiological conditions in optically active form.

These studies are ongoing. Sulfur-containing compounds are important in some animals, as in the foregoing examples, but research in pheromonal chemistry has not been confined to sulfur compounds.

Work is in progress to identify the specific receptor sites of pheromones and the genes that control their formation, as well as the neural networks that generate the responses to the semiochemicals. Knowledge of the structures of the pheromones is a key step in these basic genetic studies. Synthetic analogs containing specific isotopic markers would assist in the identification of receptor sites, and could serve also to elucidate the biosynthetic pathways.

ACKNOWLEDGMENTS

It is a pleasure to give credit and thanks to the students, both undergraduate and graduate and also the post-doctoral associates, who have worked with me on sulfur chemistry during these many years—enduring the odors, the occasional social ostracism because of

the evil smells, and the complexity of sulfur reactions. I have tried to include the names of all who contributed research results, either in the text or the references. I thank Distinguished Research Professor Raymond N. Castle for his permission to use Scheme 1, previously published in his *Journal of Heterocyclic Chemistry.* Gratefully recognized and thanked for financial support are the following: The National Science Foundation, the National Institutes of Health, the Army Medical Institute, Abbott Laboratories, Merck, Rohm and Haas Company, Sharp & Dohme, Indiana University, and Indiana University Foundation. I appreciate the helpful suggestions of my colleage, Professor Emeritus Ernest E. Campaigne, who read the manuscript and made many helpful suggestions. Especially grateful acknowledgment goes to the Associate Editor of this series, Professor Emeritus Lamar Field of Vanderbilt University, whose strong encouraging words kept me going on this project and whose detailed suggestions did much to improve the presentation.

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