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E. Campaigne[a]
[a] Department of Chemistry, Indiana University, Bloomington, Indiana, U.S.A.

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ADVENTURES IN ORGANIC SULFUR CHEMISTRY

E. CAMPAIGNE
Department of Chemistry, Indiana University, Bloomington, Indiana 47405, U.S.A.

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On several occasions, SULFUR REPORTS has invited persons who have done outstanding work in sulfur chemistry to summarize highlights of their research career in a semiautobiographical review. The present account is from a distinguished chemist who has contributed importantly for nearly 50 years to medicinal and organic aspects of sulfur chemistry. Ernest E. Campaigne (who prefers simply E. Campaigne) was born in Chicago, Illinois, in 1914. He received the B.S. and M.S. degrees in chemistry and the Ph.D. degree in biochemistry at Northwestern University. After a short stretch of teaching at Bowdoin College, he spent a postdoctoral year with the well-known sulfur chemist C.M. Suter in the Department of Chemistry at Northwestern University and a year in research at the M.D. Anderson Hospital for Cancer Research in Texas. In 1943, he joined the faculty of Indiana University, where he rose to the rank of Professor of Chemistry in 1953 and from which he became Professor Emeritus in 1979. Over the years he has spent time at the Oak Ridge National Laboratory, the Universities of California at Los Angeles and San Francisco, University College (London), Cambridge University, and many of the universities in Australia. He has been a consultant for many years to major industrial companies, as well as to the National Institutes of Health, the Office of the Surgeon General of the U.S. Army, and the Cancer Chemotherapy National Service Center. For the American Chemical Society, Professor Campaigne not only has had many important general responsibilities but has served in many ways in the Divisions of Medicinal and Organic Chemistry; he also has played a role in the affairs of IUPAC. He has served on several editorial boards, has his name on four textbooks, and has authored nearly 300 publications in medicinal and organic chemistry, particularly in relevance to sulfur chemistry and heterocycles. The table of contents below shows the breadth of his interests and the areas highlighted in his article. Included are interesting ideas others may wish to carry forward.

Key words: Thiones, thials, thiophenes, cyclizations, benzothiophenes, dithiolium salts, thiourea derivatives.

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CONTENTS

1. SULFONATION AND SULFONIC ACIDS

I first became involved with Organic Sulfur Chemistry as a postdoctoral research associate in the laboratories of Professor C.M. Suter, at Northwestern University. At that time he was actively pressing forward with his studies on the use of dioxane sulfotrioxide (DSO, Scheme 1) as a sulfonating agent.[1] I arrived in Evanston in the fall of 1941, and shared a laboratory with another new postdoctoral fellow, Frederick G. Bordwell. The advanced graduate students at this time included William Truce and Norman Kharasch, so study and discussion of organic sulfur chemistry, especially the tetracovalent forms of sulfur, was intense. I was quickly plunged into the whole field by being asked to assist Professor Suter in the final stages of completion of a manuscript for his landmark monograph on "Organic Chemistry of Sulfur."[2]

In his first paper on the sulfonation of isobutylene,[3] Suter pointed out that Bistrzycki[4] had obtained an unsaturated disulfonic acid by sulfonation of trimethylacetic acid. I was asked to repeat this work and identify the disulfonic acid. Since Bistrzycki had also reported another unidentified sulfonic acid from the decarbonylation of dimethylphenylacetic acid in concentrated sulfuric acid,[4] I also undertook to identify that product.

The disulfonic acid from trimethylacetic acid was easily identified. Repetition of Bistrzycki's experiment gave the disulfonic acid sodium salt in 50% yield,[4] and it was converted to the *S*-benzylisothiuronium salt, the disulfonyl chloride and the disulfonanilide. These three compounds were shown to be identical with the same derivatives prepared from the dioxane salt of 2-methylpropene-1,3-disulfonic acid (**6**). Sulfonation of isobutylene with dioxane sulfotrioxide had been carefully examined by Suter and co-workers and is shown in Scheme 1.[3,5] Carbyl sulfates, such as **2** and **4** are intermediate, and the reaction terminates with formation of the stable disulfonic anhydride **5**. Hydrolytic work-up produced 2-methylpropene-1,3-disulfonic acid (**6**).

We postulated a similar cyclic mechanism for the formation of **6** from trimethylacetic acid in concentrated sulfuric acid (Scheme 1).[6] The penultimate step in this sequence was assumed to be the formation of the disulfonic acid **9**, which undergoes decarbonylation, and loss of water to form **6**. Formation of the anhydride **5** may play a role here also.

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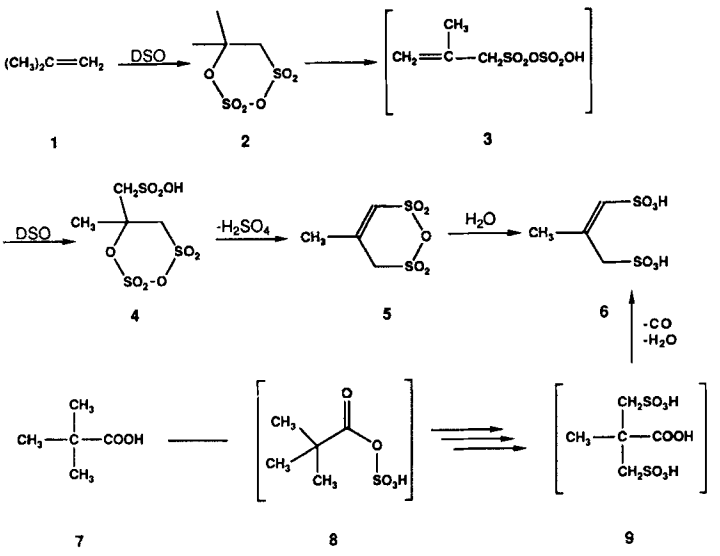
Scheme 1



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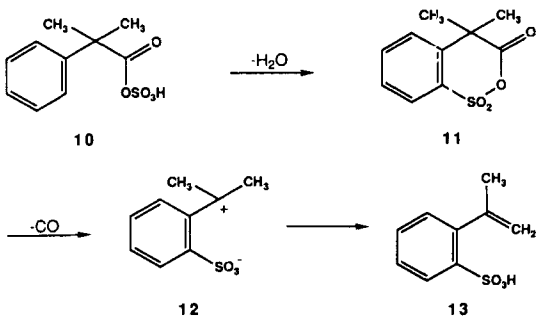
Some support for the mixed sulfuric carboxylic anhydride intermediate was found in study of dimethylphenylacetic acid (Scheme 2). Bistryzcki had obtained a sulfonic acid, $C_9H_9SO_3H$, in good yield which we proved to be **13**.[4] Repetition of this experiment gave a glassy solid in 67% yield. Oxidation of this polymer gave *o*-sulfobenzoic acid.[6] Sulfonation of α-methylstyrene under similar conditions gave a mixture of *p*- and *m*-sulfonated products, as shown by oxidation to the benzoic acid derivatives. Therefore decarbonylation did not precede sulfonation, and a cyclic mechanism was proposed to explain the difference (Scheme 2).[6] It was necessary to identify these sulfobenzoic acids, and we developed a convenient procedure, based on the characteristics of the *S*-benzylisothiuronium salts.[7]

Scheme 2

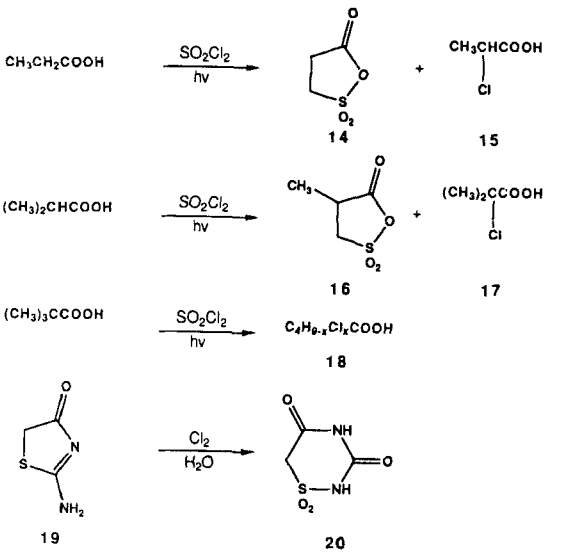


During this period a paper appeared, by Morris Kharasch and co-workers,[8] on the sulfonation of aliphatic acids with sulfuryl chloride in the presence of activating light,

and the absence of peroxide. Propionic acid gave a 52% yield of the 3-sulfocarboxylic anhydride **14** (Scheme 3) and a 45% yield of 2-chloropropionic acid (**15**). The material balance was less satisfactory for the sulfonation of isobutyric acid. In this case only 42% of 2-methyl-2-sulfopropionic anhydride (**16**) was obtained, along with 28% of the α-chlorination product, **17**.

It seemed obvious that trimethylacetic acid would be the ideal substrate for this reaction — all methyl groups available for sulfonation, no α-hydrogens for chlorination! Could I produce compounds **9** or **6** (Scheme 1) by this reaction ? It seemed strange that Kharasch hadn't thought of that, and here I learned a lesson I never forgot. When a well-known scientist leaves an obvious experiment unreported, be skeptical. There must be a good reason.

Scheme 3



Reaction of equimolar amounts of trimethylacetic acid and sulfuryl chloride proceeded smoothly at 50–60° when irradiated with a 300 W lamp, with evolution of hydrogen chloride. When gas evolution ceased, the product was worked up from an aqueous wash, to leave an oil which did not contain any sulfur, and seemed to be a mixture of isomeric chlorinated 5-carbon acids (**18**, Scheme 3)! Fractional distillation of these high-boiling oils proved difficult, and on Suter's advice, I returned to my proper work. However, the development of GLC analysis provides a technique to easily solve this problem, and someone should rerun this experiment. It seemed to me that some rearrangement of the carbon skeleton may have occurred. Identification of the products formed should cast some light on the mechanism of the sulfuryl chloride reaction with aliphatic acids.

Interest in the oxidation of organic sulfur compounds by chlorine and water led us to investigate the product obtained by Kramps by oxidation of 2-amino-4-thiazolidone (**19**) with chlorine in dilute hydrochloric acid.[9] Kramps gave the empirical formula of his product as $C_3H_6N_2O_3S$, but recalculation of his values fitted better to $C_3H_4N_2O_4S$, the

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formula of trimethylene-1,2,4-thiadiazine-3,5-dione 1,1-dioxide (**20**, Scheme 3) which may be considered a sulfur analog of barbituric acid. Repetition of Kramps' work produced an unstable crystalline solid whose structure was shown to be **20** by comparison of degradation products to those of known compounds.[10] This interesting oxidative rearrangement unfortunately seemed limited to **19** and its 4-methyl homolog, and was not explored further.

2. THIOCARBONYL CHEMISTRY

2.1. Thioketones

In the summer of 1942 I accepted an appointment as a biochemist at the newly formed M.D. Anderson Hospital for Cancer Research, which had established laboratories in the John Sealy Hospital in Galveston, Texas. The laboratories were the responsibility of Dr. J.K. Cline, who, with R.R. Williams, had obtained fame by the synthesis of thiamine.[11] The new dean, Dr. John W. Spies, was interested in buccal cancer, prevalent in India, which seemed to be associated with the chewing of betel nut. An important constituent of betel nut is anethole, and Cline reasoned that this might dimerize under the conditions of the betel nut chew to produce potentially carcinogenic analogs of diethylstilbestrol. We needed some *p,p'*-dimethoxy-α,α'-diethylstilbene, and Cline suggested I take a look at the coupling reaction of thioketones, as suggested by Linnell and Sharma for the synthesis of the desired compound.[12]

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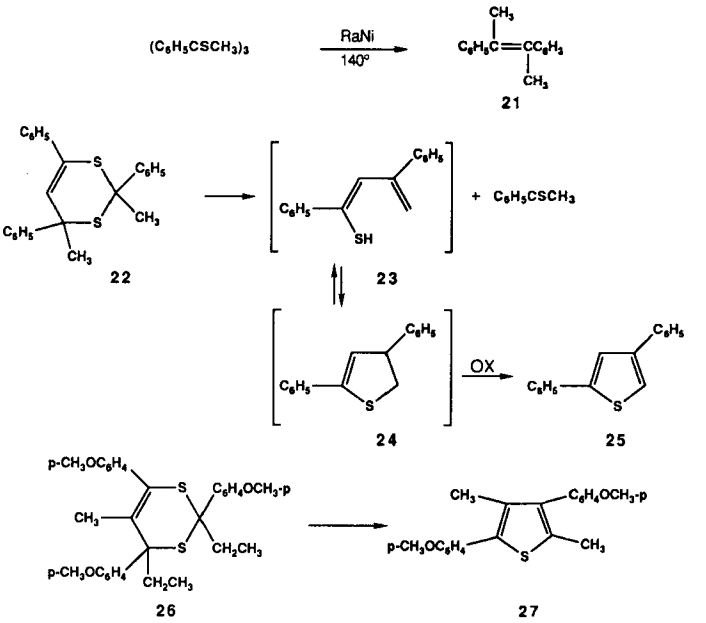
Treatment of *p*-methoxypropiophenone with hydrogen sulfide and hydrogen chloride in cold alcohol failed to produce the expected trimer of the thioketone, instead giving large white needles melting sharply to a red liquid at 158–159°, but having the empirical formula $C_{30}H_{34}O_3S_2$, a compound we showed belonged to a larger class of phenone derivatives (see later). In order to examine the feasibility of the coupling reaction, I decided to first try the reaction with a known trithioketone, trithioacetophenone. This compound had been readily obtained from acetophenone by Baumann and Fromm,[13] and was known to dissociate to bright violet monomeric thioacetophenone above its melting point of 121–122°. The usual conditions for coupling thiocarbonyl compounds involved heating with freshly reduced copper powder or copper-bronze powder.[14] However, I was not able to get coupled products on refluxing trithioacetophenone in xylene with copper powder. I therefore tried a more reactive metal, Raney nickel, and obtained an 18% yield of the desired *trans*-α,α'-dimethylstilbene **21** (Scheme 4).[15] The reaction was complicated by a large amount of reduction by the usual Raney nickel reaction to give ethylbenzene. Later, in unpublished work with W.B. Reid, we found that by degassing the Raney nickel to remove adsorbed hydrogen, yields were much improved. Other metals also could be used. Finely divided bismuth, prepared by reduction of bismuth oxide, gave yields of α,α'-dimethylstilbene in the range of 40–50%.

During the preparation of trithioacetophenone, Baumann and Fromm[13] had obtained a second compound from the mother liquors after recrystallization of the trithioacetophenone. This compound had the formula $C_{24}H_{22}S_2$, melted at about 107–108°, and was given the name "anhydrotriacetophenone disulfide," later shown to have structure **22**. On one occasion I neglected to keep the reaction mixture at 0° while treating acetophenone with hydrogen sulfide in strongly acidic alcohol, and the yield of this compound

structure was much increased. Eventually I was able to maximize the yields of these disulfides from phenones, and study their reactions.[16]

Scheme 4



One of the most characteristic reactions of Baumann and Fromm's "anhydrotriacetophenone disulfide" was conversion by heat into 2,4-diphenylthiophene, hydrogen sulfide and styrene, among other products. It seemed reasonable to assume that if the structure of this disulfide was that of **22** (Scheme 4), then heat might cause it to dissociate to the mercaptobutadiene **23** and thioacetophenone. Compound **23** might cyclize by thiol addition to the more distal double bond to produce the dihydrothiophene **24**, which could react with thioacetophenone, an oxidizing agent, to give the thiophene **25**, and α-mercaptoethylbenzene which could lose hydrogen sulfide to give styrene. All of these products were found in the mixture produced by heating "anhydrotriacetophenone disulfide" (**22**).

Simple pyrolysis of **22** at 180°, as described,[13] gave a tarry residue from which I could only isolate sufficient 2,4-diphenylthiophene for identification. Refluxing **22** for several hours in boiling xylene gave the characteristic purple color of thioacetophenone, and concentration gave an oily residue having unsaturated carbon linkages. When this residue was refluxed with copper chromite powder, a known catalyst for dehydrogenation, thiophene **25** was obtained in 83% yield. Thus it seemed possible to conduct the sequence **22** → **25** stepwise, and a method for conversion of acylophenones to 2,4-diarylthiophenes in satisfactory yield was available.

I then returned my attention to the curious disulfide, $C_{30}H_{34}O_3S_2$, first isolated by Linnell and Sharma from *p*-methoxypropiophenone,[12] which on heating with copper bronze gave them a stable sulfur compound to which they assigned a formula

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$C_{40}H_{48}O_4S_2$. Having obtained a considerable amount of the disulfide from *p*-methoxypropiophenone in my initial experiments, it was a simple matter to heat it with copper chromite in xylene to get 3,5-dimethyl-2,4-di-*p*-anisylthiophene (**27**). Clearly, treatment of *p*-methoxypropiophenone with hydrogen sulfide and dry hydrogen chloride gave "anhydrotri-*p*-methoxypropiophenone disulfide," which could be formulated as **26**, and the stable sulfur compound obtained by heating it was not $C_{40}H_{48}O_4S_2$, but actually $C_{20}H_{20}O_2S$ (**27**).

The reactions shown in Scheme 4 illustrate much of the sulfur chemistry which later came from my laboratory – thioketones, trithianes, other sulfur heterocycles, thiophenes, and cyclization of 1,3-butadiene-1-thiols all occupied my attention at one time or another.

Following a visit from a lieutenant in the Chemical Warfare Service, I accepted a position at Indiana University to teach in the Army Specialized Training Program and arrived on campus in the fall of 1943. For the next two years there was little time for research, so I concentrated on a review of thiones and thials.[17] This review is full of the most interesting problems, many of which I later investigated; others I planned to investigate, but somehow never got around to, still seem to me to present attractive research problems. Many sulfur chemists, especially the early Germans, prepared nice crystalline products, with empirical formulas based on analyses, but of uncertain structure. These provided nice problems for new graduate students, and frequently opened up new areas of sulfur chemistry.

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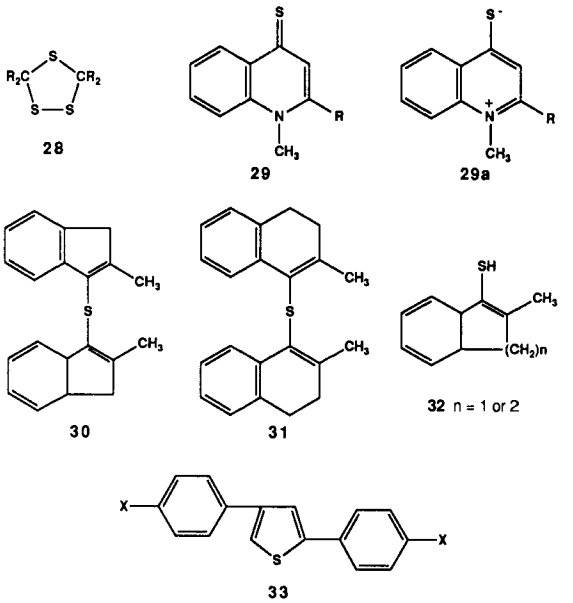
Although thiobenzophenone and many of its analogs had been obtained in monomeric form, thiofluorenone had been obtained only in dimeric form.[18] Our experience with the bright violet oil of thioacetophenone which could be isolated, but readily trimerized, led to isolation and characterization of monomeric thiofluorenone as bright green needles.[19] The proposal that thioacetophenone was an intermediate in the Willgerodt reaction of acetophenone received some support from the observed increase in yield when thioacetophenone was the substrate.[20,21]

Monomeric diarylthiones are unstable in oxygen, and long exposure to air causes an unusual expansion of the sulfur content. For example, the blue thiobenzophenone on exposure to dry air gave a yellow stable solid, $C_{26}H_{20}S_3$.[22] We observed the same behavior when our green monomeric thiofluorenone was exposed to air in solution for 6 days. A yellow trisulfide having the formula $C_{26}H_{16}S_3$ was obtained.[19] These two trisulfides were investigated and shown to have the structures of 3,3,5,5-tetraphenyl-1,2,4-trithiolane and 3,5-bis-diphenylene-1,2,4-trithiolane, (**28**, Scheme 5)[23] analogs of olefin peroxides.

Our earlier work focused on examining the properties of thione systems. We took a look at *N*-methyl-4-thioquinolone derivatives,[24] and confirmed the fact that electron-attracting groups in the 2-position (e.g. **29**, R = $COOC_2H_5$) enhanced the contribution of the thione form (**29**) over that of the predominant aromatic zwitterion **29a**. New thiones and their trimers were obtained from indanone, 3-methylindanone, tetralone and 3-methyltetralone by treatment with hydrogen sulfide and hydrogen chloride.[25] We were surprised to learn in these experiments that both 2-methylindanone and 2-methyltetralone gave not the expected thiones but the corresponding unsaturated sulfides **30** and **31**. These ketones reacted readily with thiophenol in acidic ethanol to give the corresponding phenyl sulfides which led us to postulate the formation of enethiols (**32**)

Scheme 5



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as intermediate steps in the reaction of these 2-methylketones with hydrogen sulfide, instead of the expected dithiols or hydroxythiols.

Hydrogen sulfide treatment of a series of *p*-substituted acetophenones led to the isolation of new trithioacetophenones, new "anhydro" compounds of the type shown in Scheme 4 (compounds **22** and **26**), and a whole series of new 2,4-diarylthiophenes *33* (Scheme 5), where X = F, Cl, Br, I, CH_3, C_2H_5 and C_6H_5.[26] Here, too, it was found that a substituent in the *para*-position of acetophenone had a definite effect on the product isolated after hydrogen sulfide treatment. Trimeric thioketones could be isolated from the *para*-haloketones on treatment with hydrogen sulfide in strongly acidic alcohol at 0°, but the major product became the "anhydro-disulfide" of type **22**, on allowing the reaction mixture to warm above 10°. *p*-Methylacetophenone gave a trimer, but the "anhydro" compound could not be isolated; instead a residual tarry oil gave 2,4-di(*p*-tolylthiophene on distillation. In the case of *p*-ethylacetophenone, neither trimer nor the "anhydro" compound was isolated, but an oily brown tar, probably a homolog of **23**, was obtained which gave 2,4-di-(*p*-ethylphenyl)-thiophene on attempted distillation. With *p*-phenylacetophenone, the trimer was not obtained, but an 81% crude yield of "anhydrotri-*p*-phenylacetophenone disulfide" was obtained, and readily converted to 2,4-di-*p*-xenylthiophene by the copper chromite reaction.[26]

2.2 Trithianes

Since our work with thioketones frequently led to the isolation of trimers, our attention inevitably turned toward the chemistry of the *s*-trithiane or 1,3,5-trithiane system. Many examples of trithioaldehydes, (2,4,6-trisubstituted 1,3,5-trithianes) were known. In most of these cases, two isomers could be isolated, the lower melting more soluble isomer was

called α-, the less soluble higher melting isomer was called β-. Baumann and Fromm,[27] discussing the structures of two isomers of trithioacetaldehyde, assumed a planar trithiane ring and by analogy to maleic and fumaric acids, assigned the *cis-trans* configuration (**34**, R = CH_3, Scheme 6) to the β-isomer, melting at 126°, and the *cis-cis* configuration (**35**, R = CH_3) to the α-isomer, melting at 101°, which was usually obtained in lower yield, due to its greater solubility. As we later showed, these assignments were incorrect. The proper analogy to hexahydroisophthalic acids would have led to the opposite correct assignments. In 1929, the planar configuration of the *s*-trithiane ring was regarded as certain after Bell and Bennett were able to separate all of the isomeric di- and tri-sulfoxides which would theoretically exist for a planar 1,3,5-trithiane ring.[28] Only one monosulfoxide was obtained, apparently confirming the planar structue, since two monosulfoxides would be expected of a stable puckered trithiane ring, such as **34** or **35** (R = H).

We examined a large number of aromatic aldehydes for their ability to form one or two isomeric trithianes.[29] All of the benzaldehydes which gave only one trithiane had strong electron releasing groups, such as hydroxy or acyloxy groups, or strong electron attracting groups, such as nitro or carboxy groups. In some cases only linear polysulfide polymers were formed, and it was suggested that the highly polar groups destabilized the trithiane ring. This study[29] produced several pairs of previously unknown trithianes.

Some 15 years later, the availability of nuclear magnetic resonance provided a powerful structural tool for the investigation of these isomeric trithianes.[30] The NMR spectrum of 1,3,5-trithiane in carbon disulfide consisted of a single sharp peak, $\tau = 5.82$, consistent with a rapid interchange of each hydrogen atom between axial and equatorial positions. This would be consistent with the formation of a single monosulfoxide, derived from a flexible chair trithiane structure. NMR gave us rapid and convenient means of differentiating between the all *cis*-equatorial (**35**) and *cis-trans* axial-diequatorial (**34**) forms of 2,4,6-trisubstituted 1,3,5-trithianes. Indeed the α- and β-isomers of trithioacetaldehyde were easily identified by the methyl peaks. The β-isomer, melting point 126–127°, showed only one doublet, indicating that this isomer had the all-*cis* configuration **35** (R = CH_3). The lower melting α-isomer showed two doublets, in a ratio of 2:1, confirming the *cis-trans* transfiguration **34** (R = CH_3) for this isomer. We were even able to confirm the previous identification of a γ-isomer,[31] melting at 82–85°, as a eutectic mixture of 56% α- and 44% β-isomer.

The axial and equatorial ring protons in the trithioacetaldehyde set were more complex, being split by methyl groups. However the ring protons of the trithiobenzaldehyde pair (**34** and **35**, R = C_6H_5) were much simpler, and gave satisfactory characteristics for identification. Once again, the higher melting β-isomer proved to be the all-*cis* **35** (R = C_6H_5), having a single axial proton peak at $\tau = 4.85$ in carbon disulfide. The α-isomer showed two peaks in a ratio of 2:1, at $\tau = 4.75$ and $\tau = 4.50$ in carbon disulfide. The relative acidity of the trithiane protons was evident from the variation of chemical shift with change of solvent, relative to the fixed aromatic protons.

Traditional methods of extraction of the more soluble isomer, and crystallization to purity, had led others to errors in estimation of relative yields and in a few cases to incorrect structural assignments of the various reported trithioaldehydes. We therefore examined the use of thin layer chromatography in the separation and purification of trithiane isomers.[32] By this method, pure samples of each isomer were obtained from

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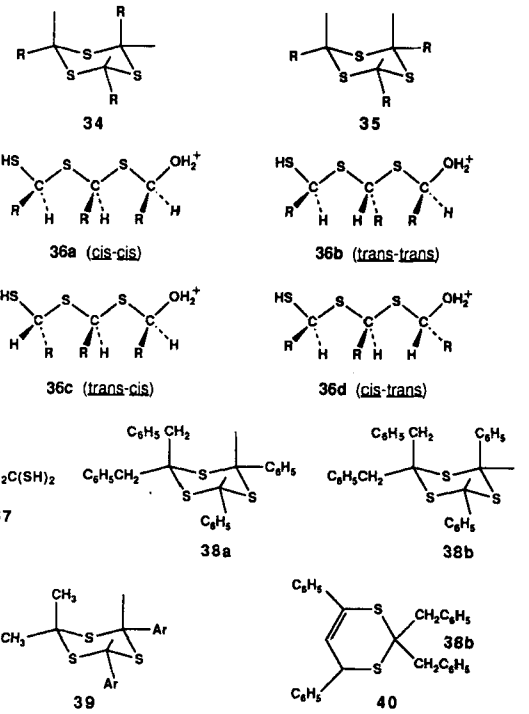
small quantities of crude mixtures, and purity of samples could be checked. The conformation of each isomer was established by NMR, and it was possible to determine the ratio of isomers in crude product from NMR spectra of samples dissolved in minimum required solvent. Contrary to previous claims, the α- (*cis,trans*) isomers were always formed as the major products, and a reasonable mechanism for trimer formation consistent with this observation was proposed.[32a,33]

Scheme 6



The formation of the *cis,trans* α-trithiane is sterically and statistically favored even though the all-*cis* β-isomer is thermodynamically more stable. Formation of the trithiane ring takes place after linear trimers are formed. If we assume that ring closure occurs by backside displacement of a protonated hydroxyl group, it is apparent that the four possible linear trimers **36a–d** (Scheme 6) will cyclize to produce the α- (*cis-trans*) isomer in a ratio of 3:1, by inversion at C-3. Assumption of a carbonium ion mechanism at the cyclization step led to the same conclusion. Only **36d**, the *cis-trans* linear trimer, can give the all *cis*-β-isomer. Formation of trithiane rings by this process may be sterically hindered in some cases, so that polymer formation is favored, and the relative proportions of α- and β-isomers altered. This mechanism is favored by the following: (1) it is unlikely that three molecules collide simultaneously to form a trithiane ring; (2) ketones are known to form *gem*-dithiols, which are probably intermediate in the formation of cyclic trimers and polymers, and (3) the ratio of yields of conformational isomers are in accord with this mechanism.

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2.3. *Unsymmetrical trithianes and* gem-*dithiols*

Our assumption of the synthesis of linear trimers in the formation of trithianes supposed the initial formation of a *gem*-dithiol, although such compounds had not been isolated under these conditions (hydrogen sulfide in acidic medium). By a fortunate coincidence, Prof. M. Carmack had joined the Indiana faculty in the early '50s. One of his major interests was the mechanism of the Willgerodt reaction, and he proposed a thioketone as one step in this reaction.[34] In a cooperative venture, we undertook to prepare for him a sample of 1,3-diphenylthioacetone, needed for his mechanistic studies.[35] To our surprise, we obtained an excellent yield of a crystalline *gem*-dithiol, 2,2-dimercapto-1,3-diphenylpropane. We then undertook to prepare further examples of the *gem*-dithiol series, but were unable to obtain more than a few *para*-substituted 1,3-diarylacetone derivatives, (**37**, Scheme 6). Most of the other analogs treated gave either trithianes, α,β-unsaturated sulfides, enethiols, or polymers.[36] The complex system which is obtained when hydrogen sulfide is added to an aldehyde or ketone was discussed at some length.[33,37]

We investigated some of the chemical reactions of the *gem*-dithiol **37** (Ar = C_6H_5).[38] Reaction of **37** with benzaldehyde in ethanolic hydrogen chloride solution gave a mixture of unsymmetrical trithianes (**38a** and **b**). The extra sulfur atom in this product must come from decomposition of the *gem*-dithiol. The spectrum of **38a** showed three distinct equal peaks for two equivalent axial ring protons and axial and equatorial methylene groups. The spectrum of **38b**, however, shows only one peak for ring protons and one for methylene protons in a ratio of 1:2, thus indicating a boat (twist) or rapidly flipping chair configuration. Another unsymmetrical trithiane was accidentally obtained when a gas trap which had been washed with acetone was inserted into the gas train before it was dry, allowing some acetone vapors to be carried into an aryl thioaldehyde synthesis. We then treated a mixture of *m*-iodobenzaldehyde and acetone with hydrogen sulfide and hydrogen chloride, and were able to isolate 2,2-dimethyl-4,6-*bis*-(*m*-iodophenyl)-1,3,5-trithiane (**39**, Ar = *m*-C_6H_4I) along with α- and β-trithio-*m*-iodobenzaldehydes.[39] Some of our preliminary work on attempting to prepare unsymmetrical trithianes was reported, but the work was never published.[40] The acidity of trithiane protons should allow replacement by lithium on treatment with butyllithium, and indeed it was possible to generate the β-(all *cis*)-trithioacetaldehyde (**35**, R = CH_3) when trithiane was treated with excess butyllithium and methyl iodide. However 2,4,6-trisubstituted 1,3,5-trithianes do not undergo further substitution. In fact, treatment of **34** (R = CH_3) with butyllithium caused it to isomerize to **35** (R = CH_3).

The structure of "anhydrotriacetophenone disulfide" and its analogs continued to interest us. The structures of **22** and **26** (Scheme 4) were most likely, but had not been proved. An early effort involved the ultraviolet spectra of 1,3-dithianes,[41] but this study was not very rewarding. The availability of NMR for structure determination led us to take another look at these unusual 1,3-dithiines. We found that analogs could be formed from α,β-unsaturated ketones and the *gem*-dithiols. For example, reaction of 1,3-diphenylpropane-2,2-dithiol with chalcone gave 2,2-dibenzyl-4,6-diphenyl-1,3-dithiin (**40**), the structure of which was readily confirmed by NMR.[38] In our earlier preparations of these compounds,[16] we had noted that more of these compounds were obtained when the reaction was allowed to warm to room temperature, conditions which favored the

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formation of dypnone (1,3-diphenyl-2-buten-1-one), in the acidic alcohol solution. We also found that a second isomer of "anhydrotriacetophenone disulfide," melting about 92–93°, could be isolated from the mother liquors of the recrystallization. We were about to reinvestigate this system when D.J. Pasto determined the structure, using NMR, and also showed that an equimolar mixture of dypnone and acetophenone treated with acidic hydrogen sulfide gave 2,4-dimethyl-2,4,6-triphenyl-2*H*,4*H*-1,3-dithiin (**22**) in good yield.[42] We abandoned this work, but no one has reported the second lower-melting isomer of **22**. Unfortunately, our sample of that had been lost. Since **22** (Scheme 4) should exist in two configurations, having *cis* and *trans* phenyl and methyl groups, our lower melting isomer must be the second. Also, it is possible that the reaction of dypnone and acetophenone with hydrogen sulfide may lead to only one of the two possible isomers. It would be interesting to re-examine this system, using X-ray crystal structure methods.

Much of this thiocarbonyl chemistry was reviewed in the book, "Chemistry of the Carbonyl Group," edited by Saul Patai.[43]

3. 3-SUBSTITUTED THIOPHENES AND THIOPHENE CHEMISTRY

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My attention had been called to thiophene chemistry by our convenient synthesis of 2,4-diarylthiophenes, reported above. However, a much greater stimulus to thiophene studies occurred in 1946 when I received a one-gallon sample of 3-methylthiophene from Socony Vacuum Oil Co. This chemical was available in tank car lots, based on a process developed from attempts to dehydrogenate 2-methylbutane with sulfur to form isoprene, during the wartime synthetic rubber program. Since my basic training at Northwestern University had been in biochemistry and pharmacology, I was very interested in medicinal chemistry, and the synthesis of biologically active compounds. In the early '40s, a number of papers had appeared, describing analogs of various useful drugs in which a benzene ring was replaced by a 2-substituted thiophene ring. In some cases, these compounds showed better therapeutic ratios than their phenyl congeners.

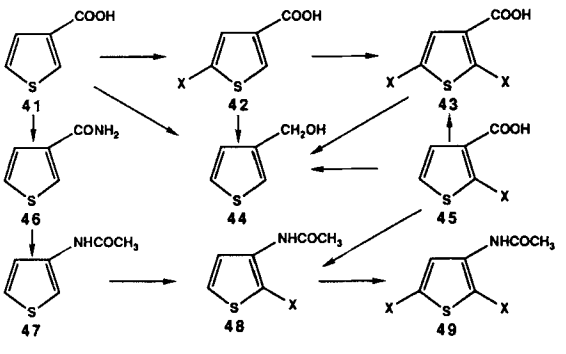
The availability of 3-methylthiophene immediately suggested that replacement of a benzene or 2-thienyl ring in a biologically active molecule by a 3-thienyl ring might lead to interesting new compounds, potentially more active and/or less toxic than their analogs. The inital problem was how to functionalize a methyl group on a reactive easily oxidized heterocyclic ring. Assuming this to be a routine problem, I turned it over to Bill LeSuer, who had already spent about a year on the "anhydrotriacetophenone disulfide" problem with little success. Permanganate oxidation, which had been reported to yield 3-thenoic acid from 3-methylthiophene,[44] gave only traces of the desired product. Sulfuryl chloride, which gave a high yield of benzyl chloride from toluene,[45] gave no side chain substitution. Instead, ring chlorination occurred in high yield, and sulfuryl chloride proved the reagent of choice in chlorination of thiophenes.[46] *N*-Bromosuccinimide also gave nuclear substitution, to form 2-bromo-3-methylthiophene, but with catalytic amounts of benzoyl peroxide 3-thenyl bromide was the major product.[47] The availability of 3-thenyl bromide allowed us to synthesize 3-thenaldehyde and 3-thenoic acid in good yield, and these three basic materials permitted the synthesis of a wide variety of drug types.

It was as this point I received my first major research grant. Dr. M.L. Moore, who was an old friend of mine from Northwestern days and was then Director of Research for Frederick Stearns, a pharmaceutical firm in Detroit, Michigan, visited the campus in 1947, and was sufficiently impressed by our proposed thiophene work to offer us a grant of $1000 to explore the area. By 1948, Frederick Stearns had been bought out by Sterling Drug, and their Director of Chemical Research was my old friend, Merle Suter, who had left the chairmanship of Northwestern University Chemistry Department for a more lucrative position at the Sterling-Winthrop Research Institute. Sterling-Winthrop saw fit to continue our research support for the next 10 years, and were the assignees in the several patents in this area.[60]

Pharmacological evaluation of compounds having 3-thienyl substituents included local anesthetics,[48] antihistamines,[49] antimetabolites,[50,51] antispasmodics,[52] vasopressor compounds,[53] anticonvulsants[54] and hypnotics.[55] The results of all of this synthetic work was summarized in a paper comparing the physiological activity of 2- and 3-thiophene isomers to their benzene analogs.[56] I concluded that it was impossible to predict the activity of a 3-thienyl isomer from knowledge of the activity of a corresponding 2-thienyl isomer or phenyl analog. However, there was a good chance that the 3-thienyl analog may be more active and/or less toxic. Out of twelve sets of compounds tested, six 3-thienyl isomers were more active than the corresponding 2-thienyl compounds, in some cases more than five times as active. In five cases activities were nearly equal, and in one case there was a qualitative difference in the response to the 3-thienyl isomer. Toxicities fluctuated in a similar manner.

This synthetic work resulted in several "how to" reports in Organic Syntheses,[57-59] and a series of patents with William M. LeSuer.[60] The ready availability of 3-thenoic acid led to some studies on the chemistry of this compound. Bromination, chlorination and nitration gave the 5-substituted derivatives (**42**, Scheme 7; X = Br, Cl or NO_2) in good yield.[61] These compounds were shown to be different from the 2-substituted 3-thenoic acids **45**, which were readily available from the known 2-substituted 3-methylthiophenes. Further chlorination or bromination gave the 2,5-disubstituted derivatives **43**, but 5-nitro-3-thenoic acid (**42**, X = NO_2) could not be further nitrated. The position of substitution was confirmed by the fact that **43** could be obtained from **42** or **45** by further substitutions.

Scheme 7



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We were surprised to find that 3-thenamide (**46**, Scheme 7) underwent a Hofmann rearrangement to give 3-acetamidothiophene (**47**), after acetic anhydride treatment (the 3-amine was unstable), in good yield. The analogous 2-thenamide did not give amine or amine derivatives by this method.[62] Several *N*-substituted 3-aminothiophenes were prepared by this method, and orientation studies with a variety of electrophiles, including chlorination, bromination, iodination, nitration and coupling with diazonium salts, were conducted with **47**. We were able to establish the reactive position as the 2-position, all substitutions giving initially **48**, (X = Cl, Br, I, NO_2, *p*-$O_2NC_6H_4N_2$). Disubstitution in the case of halogenation, gave the 2,5-disubstituted examples **49**, but again a second nitro group could not be introduced in 2-nitro-3-acetamidothiophene (**48**, X = NO_2), more powerful nitrating conditions led to oxidation of the molecule. Structure proof was based on Hofmann rearrangements of amides of **45** (X = Cl, Br, I, NO_2) to give compounds identical to **48**.[62]

3.1. Abnormal products from thenyl Grignard reagents

In the first paper of this series,[47] we noted that attempted carbonation of 3-thenyl Grignard reagent gave an unexpected high yield of by-product 3-methyl-2-thenoic acid, and suggested that it might arise from an abnormal reaction of this benzyl-type Grignard reagent, although benzyl Grignards do not give such products with carbon dioxide. We later followed up this question, examining the products derived from both 2- and 3-thenyl Grignards with several reagents. Preparation of 3-thenyl Grignard from 3-thenyl bromide in the usual way gave the 1,2-di-3-thienylethane, the result of coupling, as the major product. We therefore designed a modified cyclic reactor which could produce Grignard reagents from reactive halides in high yield.[63] Carbonation of 3-thenyl Grignard, produced in 90% yield in the cyclic reactor, gave a mixture of 3-thienylacetic acid and 3-methyl-2-thenoic acid in a ratio fo 2:3, showing that abnormal carbonation was favored over normal carbonation. Reaction of this Grignard reagent with compounds known to give mixtures of normal and abnormal products with benzyl Grignard or 2-thenyl Grignard, such as ethyl chlorocarbonate, acetyl chloride or formaldehyde, gave exclusively the abnormal 2-substituted 3-methylthiophenes. We attributed these differences to the greater reactivity to electrophilic substitution of the α-position in thiophene.[47]

It was possible that trace amounts of *o*- and *p*-toluic acid formed in the carbonation of benzyl Grignard reagent had been overlooked in previous experiments. Also 5-methyl-2-thenoic acid had not been isolated in working up the product mixture from the carbonation of 2-thenyl Grignard, consisting of 2-thienylacetic acid and 2-methyl-3-thenoic acid in a ratio of 2:1.[64] These results were all based on fractional crystallization of pure isomers from crude product mixtures. The isotope-dilution technique is well-suited to analyses of this type, since accurate quantitative determinations of substances in crude mixtures can be made. In 1955 I was fortunate to be able to spend part of a sabbatical leave at Oak Ridge National Laboratory, where the use of Carbon-14 as a tracer was readily available.

Using the modified cyclic reactor,[63] we prepared benzylmagnesium bromide in 99% yield, and treated the solution with ^{14}C-carbon dioxide. Isolation of *o*- and *p*-toluic acid from aliquots of the crude mixture treated with non-radioactive pure *o*- or *p*-toluic acid

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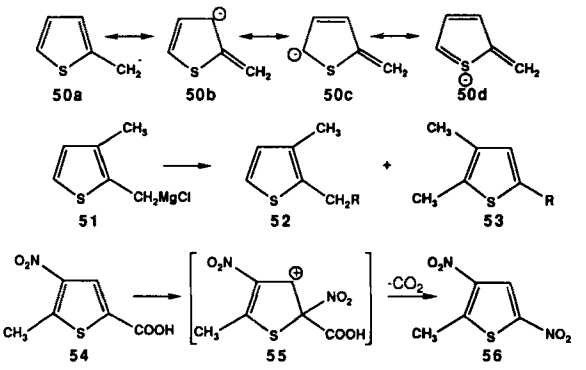
indicated less than 0.01% of these acids in the carbonation mixture.[65] Similar experiments with 2-thenylmagnesium chloride gave 2-thienylacetic acid, 2-methyl-3-thenoic acid and 5-methyl-2-thenoic acid in a ratio of 67.3 ± 1.3%, 31.2 ± 1.1% and 1.5 ± 0.2%.[65] The isolation of 5-methyl-2-thenoic acid, a "para" product, casts doubt on the widely-accepted cyclic mechanism for this reaction as an exclusive pathway. We attributed the "para"-product to a greater contribution of the ion **50c** due to stabilization *via* **50d** (Scheme 8), even though the cyclic mechanism favors reaction with **50b**.

Scheme 8



This observation was confirmed by a later study using gas chromatography of esters as the analytical tool.[66] The carbonation of 2-thenylmagnesium chlorides followed by esterification of the crude acid mixture with diazomethane, gave a mixture of methyl 2-thienylacetate, methyl 2-methyl-3-thenoate, and methyl 5-methyl-2-thenoate in a ratio of 61 ± 0.5%, 36 ± 0.5% and 3 ± 0.5%. Several other electrophilic reagents were allowed to react with 2-thenylmagnesium chloride and the product ratios analyzed. Ethylene oxide was found to give as much "*para*"-product, i.e. 5-methyl-2-thienylethanol, as normal products, 3-(2-thienyl)-1-propanol, but formaldehyde gave no "*para*"-product. Since it was shown that substantial reaction could occur at the 5-position with 2-thenylmagnesium chloride, it was interesting to examine a case where the cyclic mechanism could be blocked. We studied the reactions of 3-methyl-2-thenylmagnesium chloride (**51**, Scheme 8) with several electrophiles.[66] Carbonation of **51**, followed by esterification with diazomethane, produced **52** (R = $COOCH_3$) and **53** (R = $COOCH_3$) in a ratio of 2:1. However, reaction with acetyl chloride gave only the normal ketone **52** (R = $COCH_3$). Product distribution was greatly influenced by solvent, temperature and added salts, but in general conditions which favored ion formation favored "*para*"-product.

3.2. Miscellaneous thiophene chemistry

In the course of the thiophene work, a number of minor problems in thiophene chemistry were undertaken. We prepared further examples of acylthiophenes, and reduced the ketones to alcohols and alkylthiophenes.[67] Catalytic reduction of these derivatives over cobalt polysulfide at 200° and 100 atmospheres of hydrogen gave mixtures of alkyl-

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thiophenes and alkylthiacyclopentanes, but the latter were the major product in only two cases.[68] Some new esters of 5-methyl-2-thenoic acid were characterized[69] and a careful study of the nitration of 5-methyl-2-thenoic acid conducted.[70] It was shown that replacement of the carboxy group in **54** (Scheme 8) by a nitro group to give **56** occurred by displacement of the carboxyl group *via* intermediate **55**, rather than by stepwise decarboxylation and nitration. Compounds **54** and **56** have activated methyl groups susceptible to Knoevenagel condensation with aromatic aldehydes, and these two compounds were condensed with 2-thenaldehyde, 3-thenaldehyde, and 5-chloro-2-thenaldehyde, and a detailed spectral study of the resulting 1,2-dithienylethenes was reported.[71]

When dimethylformamide became available as a solvent and as a substitute for *N*-methylformanilide as a reagent in the Vilsmeier reaction, we were quick to establish its utility in synthesizing thiophene aldehydes.[72] In pursuing a program in virus chemotherapy, we prepared a series of thiosemicarbazones of thiophene derivatives.[73] While comparing β-3-thienylacrylic acid to its analog, β-2-thienylacrylic acid, in their behavior toward bromine, we found that the 3-thienyl compound was more readily brominated in the 2-position than at the double bond, in contrast to behavior of the 2-thienyl isomer, which added bromine before substituting in the 5-position.[74] A convenient synthesis of dilithiothiophene was found when we attempted to couple phenyllithium and 2,5-diiodothiophene to form 2,5-diphenylthiophene.[75]

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4. CONFERENCE ON ORGANIC SULFUR CHEMISTRY

In 1951, I was able to arrange the first International Conference on Organic Sulfur Chemistry. This was held in conjunction with a meeting of the international Union of Pure and Applied Chemistry scheduled in New York that summer, which enabled us to have a truly international affair in Bloomington, Indiana. I was able to raise sufficient funds from industry to pay expenses of foreign speakers from New York.

A list of the speakers and their topics gives a good picture of the state of Organic Sulfur Chemistry in 1951. Marvin Carmack, University of Pennsylvania, spoke on "Ultraviolet Absorption Spectra of Sulfur Compounds." Hans Heymann, then at Harvard, discussed "The Ten-electron Shell in Sulfur Compounds." "The Action of Raney Metals Upon Organic Sulfur Compounds" was discussed by Heinrich Hauptmann, Professor of Organic and Biochemistry at the University of Sao Paulo, Brazil. H.J. Backer, Professor of Organic Chemistry at the University of Groningen, Holland, spoke on "The Fragility of the Carbon-Sulfur Bond in Simple Polysulfones." F.G. Bordwell, of Northwestern University, discussed "The Effect of the Sulfonyl Group on the Reactivity of Other Functional Groups in Organic Molecules." "A Comparison of Carbonyl, Sulfonyl, Thiocarbonyl and Sulfoxide Groups" was the subject of the presentation by Professor F. Arndt, of the University of Istanbul, Turkey. Norman Kharasch, University of Southern California, spoke on "Sulfenic Acids and Their Derivatives." Frederick G. Mann, Trinity College, Cambridge, discussed "Some Polycylic Derivatives of Sulfur," and John C. Sheehan, Massachusetts Institute of Technology, discussed "The Synthesis of Substituted Penicillins and Simpler Structural Analogs." "Enzymatic Formation and Cleavage of Thioether Bonds" was presented by F. Binkley, of the University of Utah, and "Metabolism of Cysteine Sulfinic Acid in Higher

Animals" was the subject of the lecture by Claude Fromageot, Faculty of Science, University of Paris. C.J. Cavallito, Director of the Laboratories of Irwin, Neissler and Co. of Decatur, Illinois discussed "The Role of Thiol Groups in Antibiotic Reactions." A paper by Alexander Schönberg, Professor and Head of the Chemistry Department at Fuad I University, Cairo, Egypt, entitled "Free Radicals Containing Univalent Sulfur" was read by title in his absence.

The group was entertained by E. Emmet Reid, as the banquet speaker. He was then in his seventy-ninth year, and was destined to contribute to the field of Sulfur Chemistry for another twenty-two years!

The conference was well-attended. It had orignally been planned for no more than 80 participants, all active research workers, plus two delegates to be sent by each of four or five industrial donors. However, we had industries requesting permission to donate in order to send delegates, plus inquiries from researchers just getting interested in the field. In the end we had nearly 140 attending, including representatives of 22 industrial laboratories.

5. RING CLOSURE OF THIOLS AND DISULFIDES

5.1. Diarylthiophenes

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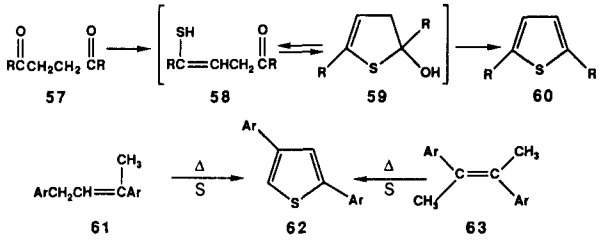
The earlier suggestion (see Scheme 3) that an unsaturated 4-carbon chain bearing a 1-thiol group was a facile intermediate in thiophene synthesis continued to occupy our attention. An interesting example of this system seemed to occur in the well-known Paal synthesis, which involves heating 1,4-dicarbonyl compounds with phosphorus pentasulfide.[76] It seemed to us that a reasonable intermediate in this reaction was the enethiol **58** (Scheme 9). We therefore treated several diaroylethanes **57** with hydrogen sulfide and hydrogen chloride in the presence of a dehydrating agent.[77] Yields of 2,5-diarylthiophenes (**60**) were greater and much cleaner than those previously reported using the Paal synthesis. Enhancement of the reaction by added dehydrating agent seemed to confirm the equilibrium of **58** ⇄ **59** as intermediates.

Scheme 9



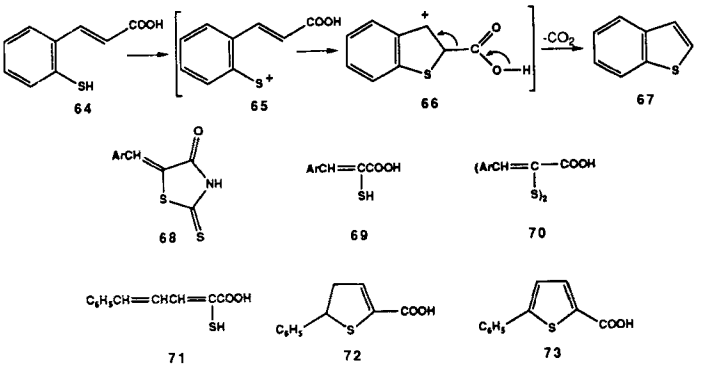
Since we had in hand 2,4- and 2,5-diarylthiophenes, we decided to prepare the other two possible isomers of diphenylthiophene, e.g. 2,3- and 3,4-diphenylthiophene, for spectral comparison. 3,4-Diphenylthiophene has been readily synthesized by heating 2,3-diphenylbutane with sulfur, and indeed some butenes, such as 1,3-diaryl-2-butene (**61**, Scheme 9) gave good yields of the expected diarylthiophenes, such as 2,4-diphenyl-

thiophene (**62**).[78] We were surprised to find that *trans*-dimethylstilbene (**63**) also gave **62** on heating with sulfur instead of the expected 3,4-diphenylthiophene. It would be interesting to determine the product obtained when *cis*-dimethylstilbene is heated with sulfur. **62** may be formed from **63** by oxidative cleavage of the double bond by sulfur to form thioacetophenone, which is known to form **62** on heating. This suggested a re-investigation of previous studies on the reaction of sulfur with 2-butenes, but somehow I failed to pursue it.

5.2. Cyclization of unsaturated thiols and disulfides

What appeared to be a classic example of the facile thiophene synthesis from a 1,3-butadiene-1-thiol system had been reported by Chmelewsky and Friedländer,[79] who obtained benzothiophene (**67**) by oxidation of *o*-mercaptocinnamic acid (**64**) with alkaline ferricyanide (Scheme 10). They suggested a sulfenic acid intermediate, but the accompanying decarboxylation suggests a sulfenium ion mechanism, **65–66**. A convenient source of unsaturated thiols was available *via* hydrolysis of appropriate rhodanine derivatives **68** to give 3-aryl-2-mercaptoacrylic acids **69**. We therefore prepared a series of 3-aryl-2-mercaptoacrylic acids **69**, where Ar = phenyl, styryl, veratryl, 1- and 2-naphthyl and thienyl, and their respective disulfides, and recorded their spectral properties.[80] The similarity in wavelength and intensity of the spectral peaks of the α-mercapto acids, their disulfides and sulfides indicated that the compounds were correctly represented as enethiols rather than thiones. It seemed to us that 5-phenyl-2-mercapto-2,4-pentadienoic acid, **71**, might undergo thiol addition to the more remote double bond of the conjugated system to give the dihydrothiophene **72**, which under mild oxidizing conditions would give **73** (Scheme 10). In fact, when **71** was refluxed with copper chromite in xylene for 3 hours, about 10% of **73** was isolated.[81] We next turned our attention to the use of alkaline oxidizing agents, à la Chmelewsky and Friedländer, without success.

Scheme 10



However, in one experiment a large excess of iodine in potassium iodide was added to a solution of **71** in dilute sodium carbonate, and let stand overnight. The following day a precipitate was evident, and the solution had become acidic. From this reaction we isolated a 54% yield of **73**! Treatment of **71** with excess iodine in ethanol solution for

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14 hours gave **73** in 61% yield. We soon learned that one equivalent of iodine was quickly consumed to convert **71** to its disulfide **70** (Ar = $C_6H_5CH{=}CH$), and that the disulfide slowly consumed a second equivalent of iodine to form **73**. The disulfide in benzene treated with boron trifluoride gave **73** in 80% yield. We were obviously dealing with a Lewis acid catalyzed attack on the double bond by a disulfide bond. Iodine is a weaker catalyst, but also functions as an oxidizing agent, thus converting by-product thiol to further reactant, hence the greater material yield despite a lower theoretical yield, in comparing the iodine catalyzed reaction to the boron trifluoride catalyzed cyclization.[81]

Attention was then turned to the possibility of effecting similar ring closures in which the electrophilic attack could occur on an aromatic ring to produce benzothiophenes. The α-mercaptocinnamic acid system (**69**, Ar = C_6H_5) was not easily converted to a benzothiophene. Treatment with iodine in dioxane for 12 hours gave only the disulfide **70** (Ar = C_6H_5). However, heating **70** (Ar = C_6H_5) with iodine in nitrobenzene at 200° for a few minutes produced benzo[*b*]thiophene-2-carboxylic acid in better than 60% yield.[81] The presence of electron-releasing groups on the aromatic ring promoted the reaction, and a number of such substituted α-mercaptocinnamic acids or their disulfides cyclized quite well in dioxane.[82] Thus the best yield in this cyclization occurred on treating the disulfide derived from α-mercapto-β-2-naphthylacrylic acid (**74**, Scheme 11) with iodine in dioxane, giving a 90% yield of naphtho[1,2-*b*]thiophene-2-carboxylic acid (**75**). The improved yield when ring closure occurs in the 1-naphthyl position tended to confirm the electrophilic nature of the reaction.

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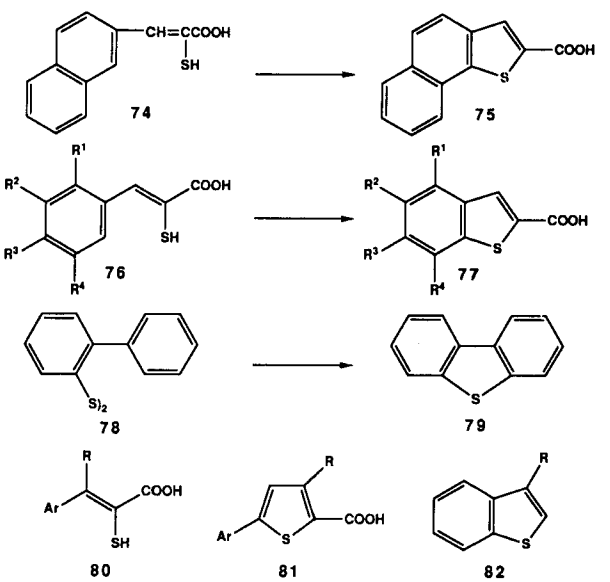
Scheme 11



We found that alkoxy groups on the benzene ring in β-aryl-α-mercaptoacrylic acids (**76**, R^1; R^2, R^3, R^4 = H, OCH_3 or OC_2H_5) enhanced the cyclization only if in the

para-position to the site of ring closure, e.g., **76**, $R^2 = OCH_3$ or OC_2H_5, but an alkoxy group in the *para*-position to the side chain, e.g., **76**, $R^3 = OCH_3$ or OC_2H_5 tended to inhibit formation of **77**. Polymeric materials, presumably the result of intermolecular electrophilic attack of disulfide on the aromatic ring, were the major by-product.[82] For example, treatment of 3,4-diethoxy-α-mercaptocinnamic acid (**76**, $R^2 = R^3 = OC_2H_5$, $R^1 = R^4 = H$) and 3,4,5-trimethoxy-α-mercaptocinnamic acid (**76**, $R^1 = H$, $R^2 = R^3 = R^4 = OCH_3$) with excess iodine in dioxane at 70° for 12–15 hours gave the respective alkoxybenzo[*b*]thiophene-2-carboxylic acids, **77**, in fair to moderate yields. On the other hand, 4-ethoxy-α-mercaptocinnamic acid (**76**, $R^1 = R^2 = R^4 = H$, $R^3 = OC_2H_5$) or 2,4-dimethoxy-α-mercaptocinnamic acid (**76**, $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$) gave only tars under ring closure conditions. Oddly enough, the 4-methoxy derivative **76** ($R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$) gave a trace of **77**, while the 3-methoxy analog (**76**, $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$) gave a moderate yield of 5-methoxybenzo[*b*]thiophene-2-carboxylic acid, **77**.[82]

A comparison of the electron releasing effects of methyl and methoxy groups on this cyclization was observed, in studies on the preparation of 5-methyl-6-methoxybenzo[*b*]thiophene-2-carboxylic acid (**77**, $R^2 = CH_3$, $R^3 = OCH_3$, $R^1 = R^4 = H$) and 5-methoxy-6-methylbenzo[*b*]-thiophene-2-carboxylic acid (**77**, $R^2 = OCH_3$, $R^3 = CH_3$, $R^1 = R^4 = H$).[83] In the cyclization of (**76**, $R^2 = CH_3$, $R^3 = OCH_3$), the expected **77** was obtained in only 30% yield, contaminated with resinous by-products, but **76**, ($R^2 = OCH_3$, $R^3 = CH_3$) gave a 63% yield of the expected **77** relatively free of by-products.

The cyclization of bis(2-biphenylyl) disulfide (**78**), which proceeds in quite satisfactory yield at high temperatures was chosen for study of reaction conditions.[84] Catalysts used were iodine, iodine and methyl sulfate, iodine and stannic chloride, aluminum bromide, aluminum chloride, boron trifluoride, bromine, polyphosphoric acid and concentrated sulfuric acid. Solvents were varied from dioxane, ethylene glycol, toluene or benzene, to carbon tetrachloride. The temperature was varied from 65° to 200°, and time of exposure to catalyst from 1 hour to 37 hours. Although aluminum halides in benzene solution gave satisfactory yields of **79**, no dibenzothiophene was obtained with boron trifluoride or stannic chloride. No cyclization product was obtained with the strong acids, polyphosphoric or sulfuric acid or methyl sulfate. Optimum conditions for this cyclization were iodine in ethylene glycol at 198° for 1 hour. When **78** was refluxed in dioxane with excess iodine for 24 hours, only **78** was recovered. No cyclization was observed. Treatment of **78** with one equivalent of bromine in refluxing carbon tetrachloride for 37 hours gave only a 16% yield of **79**, and 70% of **78** was recovered. This is surprising, since bis(2-biphenylyl) diselenide affords an essentially quantitative yield of dibenzoselenophene under these conditions.[85]

We expanded the synthesis to utilize ketones condensed with rhodanines to produce β-disubstituted α-mercaptoacrylic acids, such as **80**, which could then be cyclized to produce unsymmetrically substituted bithienyl derivatives (e.g., **80**, Ar = 3-$C_4H_3SCH{=}CH$, R = CH_3, Scheme 11).[86] When the starting ketone was 3-benzoylpropionic acid, cyclization followed by decarboxylation gave a satisfactory yield of 3-(3′-benzo[*b*]thienyl)propionic acid (**82**, R = CH_2CH_2COOH).[87] However, an attempt to use a α-tetralone in the reaction was unsuccessful. The study of these cyclizations, starting with various ketones, so that R and Ar in **80** are varied, needs to be expanded.

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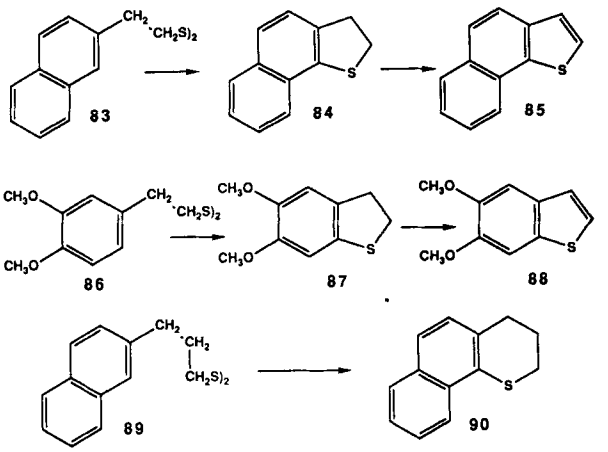
There are very few examples reported. We did isolate the *cis* and *trans* isomers of 5-(1-methylcinnamylidene)-rhodanine,[86] another area which needs exploration.

Since earlier studies always resulted in aromatic products, we were curious as to whether unsaturation in the side chain was a prerequisite for ring closure. When bis-(β-2-naphthylethyl) disulfide (**83**, Scheme 12) was treated with iodine in dioxane at 50°, in conditions which gave **75** from **74** in 90% yield, **83** was recovered unchanged. Boron trifluoride in benzene also failed to bring about ring closure of **83**. However, when the reaction was conducted in refluxing ethylene glycol, using an equimolar quantity of iodine or in benzene with one equivalent of aluminum bromide, 2,3-dihydronaphtho[1,2-*b*]-thiophene (**84**) was obtained in low yield. With excess iodine in ethylene glycol heated to reflux for 12 hours, naphtho[1,2-*b*]thiophene (**85**) was obtained in 60% yield. Compound **84** was converted to **85** under these conditions.[88,89] Similar results were obtained using bis-(β-3,4-dimethoxyphenylethyl) disulfide (**86**) in these cyclization studies. With one equivalent of iodine in ethylene glycol at 160–180° for one-half hour, the dihydrothiophene **87** could be isolated, contaminated with some **88**, and **87** was readily oxidized to **88** by iodine. It was clear from these experiments that the double bond in the side chain, as in **74** → **75**, **76** → **77** and **78** → **79** (Scheme 11) leading directly to aromatic products greatly facilitates the ring closure reaction. It is interesting that bis(γ-2-naphthylpropyl) disulfide (**89**) was cyclized to dihydronaphtho-[1,2-*b*]-4*H*-thiapyran (**90**) under milder conditions than those required for conversion of **83** to **84**. There may be less strain in the six-membered ring formed.[89]

Scheme 12



Our success in cyclization of such compounds as **83** (Scheme 12) or **78** (Scheme 11) with boron trifluoride or aluminum bromide certainly confirmed that electrophilic attack by a disulfide-Lewis acid complex was a possible mechanism for this cyclization. However, other evidence pointed to a sulfenyl halide as the intermediate.[90] Indeed, it was shown that chlorine in aprotic solvents, such as carbon tetrachloride, was an effective agent in these cyclizations, and a sulfenyl chloride was proposed as the active intermediate.[90] In further work, we found several examples where a sulfenyl iodide may have been the intermediate in the ring closure of disulfides with iodine.[91] For example, heating

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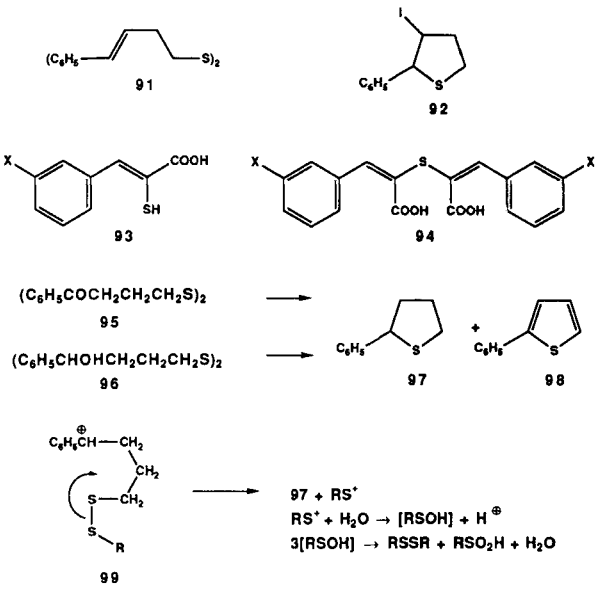
bis(4-phenyl-3-butenyl) disulfide (**91**, Scheme 13) with one equivalent of iodine in dimethoxyethane for 6 hours gave 3-iodo-2-phenylthiolane (**92**) in 90% crude yield. In another study,[92] we attempted to cyclize halogenated α-mercaptocinnamic acids, such as **93** (X = Cl). These were expected to be resistant to electrophilic substitution and indeed, treatment of **93** (X = Cl) or its disulfide with iodine in refluxing dimethoxyethane gave the sulfides **94**. We speculated that such disulfides could arise by simple Michael addition of a sulfenyl iodide to another molecule of the α,β-unsaturated sulfenyl iodide, followed by elimination of sulfur diiodide. From the above results, I believe it is reasonable to conclude that either of the two mechanisms, involving disulfide-Lewis acid complex or sulfenyl halide, may be involved in this reaction, depending on conditions, or indeed that both mechanisms may be involved under some circumstances.

Scheme 13



Some interesting cyclizations of disulfides were also observed using bis(3-benzoylpropyl) disulfide (**95**) and bis(4-hydroxy-4-phenylbutyl) disulfide (**96**).[91] Heating the keto-disulfide **95** with *p*-toluenesulfonic acid produced a mixture of two products, 2-phenylthiolane (**97**) and 2-phenylthiophene (**98**) in low yield. However, heating the alcohol **96** with a catalytic amount of *p*-toluenesulfonic acid gave **97** in 66% yield. This was assumed to be formed *via* attack of the benzylic carbonium ion **99** on the disulfide link to generate **97** and a sulfenium ion. The unstable sulfenic acid, formed by reaction with water, is known to disproportionate to disulfide and sulfinic acid (Scheme 13); thus the theoretical yield in this reaction is about 2/3 of the starting material! Apparently **95** undergoes a similar reaction to produce 2-phenyl-3,4-dihydrothiophene, which disproportionates to **97** and **98**.

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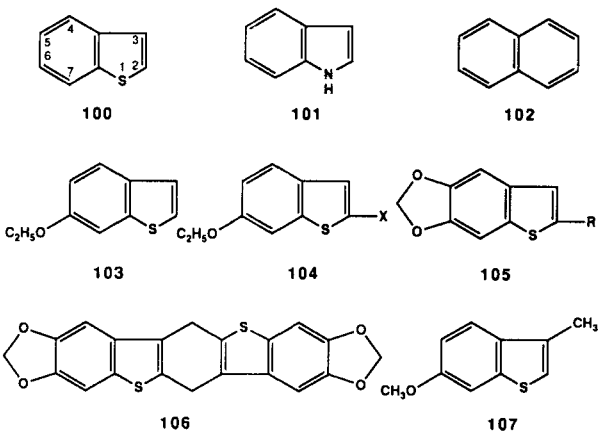
6. BENZO[*b*]THIOPHENE CHEMISTRY

The cyclization reaction described earlier made available a variety of substituted benzo[*b*]thiophenes. Our attention was naturally turned toward the chemistry and biological activity of these compounds, many of which were new. Quite early, we recognized the isosteric relationship of benzo[*b*]thiophene (**100**, Scheme 14) to indole (**101**) and the isoelectronic analogy to naphthalene (**102**). We began work on the synthesis of benzo[*b*]thiophene analogs of biologically active indoles and naphthalenes. For example, *N*,*N*-diethylaminoethyl-2-benzo[*b*]thenoylamide proved to be an active local anesthetic.[93]

Scheme 14



However, need to synthesize certain compounds required a knowledge of the chemistry of substited benzo[*b*]thiophenes which was not available in the literature. We began some studies on simple electrophilic substitution of substituted benzo[*b*]thiophenes. It was well-known that electrophilic substitution in benzo[*b*]thiophene itself gave chiefly 3-substituted derivatives, with some by-product 2-substitution. Bordwell had done a careful study of substitution of benzo[*b*]thiophenes having a strong electron-releasing group (e.g., hydroxy, acetamido, or amino) in the 5-position, and found that the 4-position was most readily substituted in these cases.[94] 5,6-Dimethoxybenzo[*b*]thiophene and 5,6-methylenedioxybenzo[*b*]thiophene (**105**, R = H) were readily available in our laboratory *via* decarboxylation of the 2-carboxylic acids. Both of these compounds were subjected to bromination, acetylation and formylation. To our surprise substitution occurred principally in the 2-position in all cases.[95] Rationalization on the basis of relative importance of contributing resonance structures implied that the 6-alkoxy group was controlling in these cases. This was shown to be the case in 6-ethoxybenzo[*b*]thiophene (**103**, Scheme 14) which gave 2-substitution (**104**, X = Br, CHO, $COCH_3$).[96] In this case, **103** was prepared by reduction of commercially available 6-ethoxythioindoxyl by sodium borohydride. Oddly enough, nitration of 5,6-methylenedioxybenzo[*b*]thiophene did not give the 2-nitro derivative (**105**, R = NO_2), but instead a sharp-melting crystalline nitro compound in 98% yield, which was shown

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not to be the 2-nitro compound by reduction and acetylation to give an acetamido derivative which was different from the known 2-acetamido derivative, **105** (R = $NHCOCH_3$). This compound remains to be identified.

An unusual heptacyclic system (**106**, Scheme 14) was obtained in good yield when 2-hydroxymethyl-5,6-methylenedioxybenzo[*b*]thiophene (**105**, R = CH_2OH) was heated in dimethoxyethane with a small amount of polyphosphoric acid.[98] A need for 6-methoxy-3-methylbenzo[*b*]thiophene (**107**) as a potential intermediate in the preparation of 6-methoxyindole analogs led us to examine the Tilak cyclization of phenylthioacetone derivatives.[99] We found that (3-methoxyphenylthio)acetone was converted to **107** in good yield in sulfuric acid, without appreciable formation of isomers.[100] Not surprisingly, compound **107** was easily substituted at the 2-position, and we were unable to functionalize the methyl group with *N*-bromosuccinimide, all such efforts leading to the 2-bromo derivative.

We had observed some abnormal product formed in the nucleophilic displacement of chlorine by cyanide on 3-chloromethylbenzo[*b*]thiophene (**108**, Scheme 15) in dimethyl sulfoxide, to give **109** and a trace of 2-cyano-3-methylbenzo[*b*]thiophene (**110**, Scheme 15).[101] We were, of course, anxious to determine whether a 6-alkoxy-3-halomethylbenzo[*b*]thiophene would give a larger percentage of the abnormal product in nucleophilic displacement reactions. However, our failure to brominate the methyl group in **107** (Scheme 14) interrupted this research, and the question remains to be tested.

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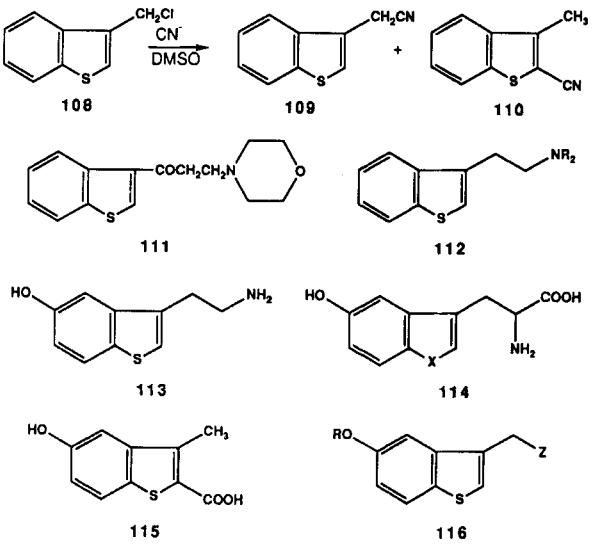
Scheme 15



The availability of 3-methylbenzo[*b*]thiophene *via* the (phenylthio)acetone cyclization[99,101] made it a convenient starting material for 3-substituted derivatives, since the methyl group in this case was easily brominated with *N*-bromosuccinimide.[102] A series of Mannich bases having antimicrobial activity were synthesized from 3-acetylbenzo[*b*]thiophene,[103] and one of these, which had significant activity comparable to

chloramphenicol against *S. aureus* and *E. coli* (**111**), was the subject of patents.[104] Using conventional synthetic methods, 3-chloromethylbenzo[*b*]thiophene was converted, *via* the aldehyde or cyanomethyl derivative, to a series of 3-benzo[*b*]thiophenylalkylamines for comparison of their central nervous system activity with tryptamine isosteres.[105] The benzo[*b*]thiophene derivatives (**112**, Scheme 15) were found to be stimulants with approximately the same order of activity as their indole isosteres. This supported the hypothesis that the indole ring NH groups did not participate significantly in interaction with CNS tryptamine receptors. However, one of the compounds, to which we had assigned the structure of 3-β-dimethylaminoethylbenzo[*b*]thiophene (**112**, R = CH_3) on the basis of synthesis from **112** (R = H), by the Eschweiler-Clarke reaction, gave a quite different biological response than its indole analog, dimethyltryptamine. In a later study (see Scheme 17), we learned why this was so.

During the course of this work, we also learned a valuable lesson. When a chemist synthesizes a new compound as a biological agent, it is important that at least preliminary testing be reported. In 1950, Werner Herz had reported the synthesis of **112** (R = H), pointed out that is was an analog of tryptamine, and that he had submitted it for biological evaluation. The work in this area was lying fallow, waiting for the biological reports. In 1965, when Ed Neiss began his work, we decided we had to know whether **112** (R = H) had any activity, since our whole concept depended on this. Consultation with Herz revealed that he had submitted the compound to Parke Davis Co. for testing, and they had never reported any results to him. Next I contacted Dr. Bratton, head of Pharmacology at Parke Davis. Co., and he reported that the sample of 3-β-aminoethylbenzo[*b*]thiophene they had received from Herz was too small to be used in that test! We therefore went ahead with synthetic work in the area, even though much chemical work had already been reported, and our work was repetition to obtain sufficient quantities for biological testing.

Our original target, in beginning this work, was synthesis of the sulfur analog of serotonin, SAS (**113**). Serotonin, the indole analog of **113**, is a highly potent CNS stimulant which does not penetrate the blood-brain barrier. Significant increases in brain serotonin are observed when animals are injected with 5-hydroxytryptophan (**114**, X = NH). The synthesis of SAS (**113**) had proved refractory, probably because of the easy oxidation of the pseudohydroquinone system, and several research groups were investigating this area. We were able to obtain sufficient quantity of **113** for screening,[106] and were delighted to find activity comparable to serotonin. Surprisingly, **113** administered intravenously in rabbits, seemed to penetrate the blood-brain barrier *per se*, being tested as the hydrochloride of **113**, compared to the amino acid, 5-hydroxytryptophan. Later we published a much improved synthesis, based on commercially available *m*-hydroxyacetophenone, which was converted, *via* the α-mercapto-β-methyl-3-hydroxycinnamic acid to **115**. An improved decarboxylation step enabled us to obtain 3-methyl-5-hydroxybenzo[*b*]thiophene in high yield, and by benzoylating the 5-hydroxy group, it was possible to obtain side-chain bromination to produce **116** (R = C_6H_5CO, Z = Br) in good yield.[107] Reaction of this compound with sodium cyanide in dimethyl sulfoxide converted it to the hydrolyzed nitrile **116** (R = H, Z = CN) in one step, and reduction gave **113** in an overall yield from *m*-hydroxyacetophenone of 20%. The aminomethyl derivative **116** (R = H, Z = NH_2) was also prepared and screened.[108] These results were summarized.[109]

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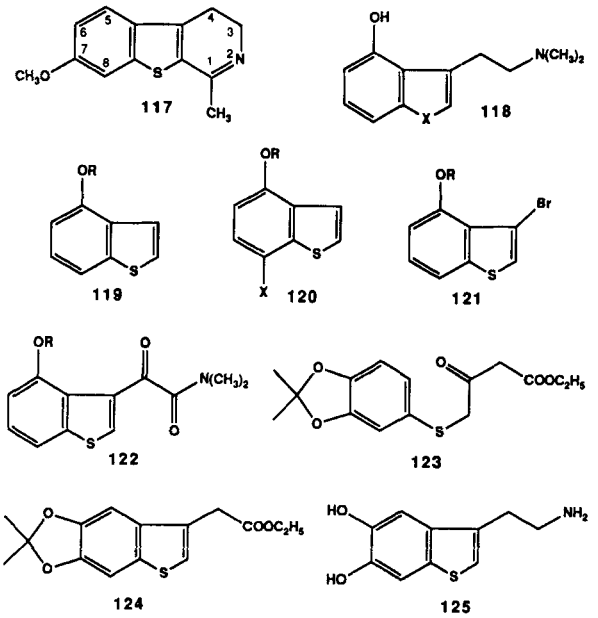
Our attention was immediately focused on the sulfur isoster of 5-hydroxytryptophan, (**114**, X = S) which was easily prepared from **116** (R = C_6H_5CO, Z = Br) by conventional methods.[110] This compound was found to be inactive, neither mimicking nor blocking the effects of 5-hydroxytryptophan. We also reported the synthesis of the sulfur isosteres of bufotenin (**116**, R = H, Z = $CH_2N(CH_3)_2$) and melatonin (**116**, R = CH_3, Z = $CH_2NHCOCH_3$), and found that the bufotenin isoster had similar activity to its indole analog.[110]

The central nervous activity of various indole alkaloids and the potent activity of SAS suggested a synthetic program in this area. Our first investigation in this area led to the harmaline analog (**117**, Scheme 16) and related compounds, such as the 6-methoxy isomer, 6-methoxy-3,4-dihydro-1-methyl[1]benzothieno[2,3-*c*]pyridine, and the corresponding fully aromatized harmine structures.[11] We were delighted to find that, while harmine and its sulfur isoster were about equal as monoamine oxidase inhibitors, **117** was 50 times more potent than harmaline in this test.[112,113]

Scheme 16



The synthesis of the sulfur isostere of psilocin (**118**, X = N, Scheme 16) required some knowledge of electrophilic substitution of 4-oxygenated benzo[*b*]thiophene derivatives (**119**). We were fortunate to receive a large sample of 4-hydroxybenzo[*b*]thiophene (**119**, R = H) from Dr. R.P. Napier, of the Mobil Chemical Co. where a commercial process had been developed.[114] Bromination, acetylation, formylation and nitration of 4-methoxybenzo[*b*]thiophene all produced 7-substituted derivatives (**120**, R = CH_3).[115] The 4-benzoyl compound **119** (R = C_6H_5CO) gave 7-nitro and 7-acetyl derivatives **120** (X = NO_2, $COCH_3$, R = COC_6H_5), but we were unable to obtain a formyl derivative. Strangely enough, bromination of the 4-benzoyl compound with bromine in carbon tetrachloride gave the 3-bromo derivative **121** (R = C_6H_5CO), in good yield. Also

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bromination of 4-hydroxybenzo[*b*]thiophene with *N*-bromosuccinimide gave 5-bromo-4-hydroxybenzo[*b*]thiophene, in contrast to the product using bromine in carbon tetrachloride, which was a complex mixture of polybrominated compounds.

The availability of **121** (R = C_6H_5CO) provided as a useful entry for the synthesis of **118** (X = S). The benzoyl group was hydrolyzed, and the hydroxyl group benzylated to give **121** (R = $C_6H_5CH_2$), which could be converted to the corresponding 3-lithio derivative *via* metal-halogen exchange at −78°. Reaction of the lithio compound with *N,N,N′,N′*-tetramethyloxamide gave **122** (R = $C_6H_5CH_2$), which could be reduced and debenzylated to give **118**.[116] Very soon after our initial report on the synthesis of a sulfur analog of psilocin (SAP) another paper appeared describing this compound and some of its precursors.[117] Since the physical constants of several of the common compounds reported in the two papers were different, we were forced to conduct a more elaborate proof of structure which confirmed our results.[118]

The need for the sulfur isostere of 5,6-dihydroxytryptamine, a powerful CNS agent, led to several useful developments in synthesis of benzo[*b*]thiophenes. Commercial availability of γ-chloroacetoacetic acid made it easy to introduce a 2-carbon side chain at the 3-position, using the Tilak procedure, but strong acid conditions tended to cleave off hydroxyl protecting groups. Initial efforts to cyclize **123** under Tilak conditions gave very low yields. However, when a granular reagent was prepared by heating polyphosphoric acid and phosphorus pentoxide with Celite in benzene or toluene, this heterogeneous system worked like a charm in effecting the cyclization without hydrolysis of the protecting acetonyl groups to give **124**. Conversion of **124** to **125** (Scheme 16) was then trivial.[119] This easy synthetic route, plus the unusual activity of the 5,6-dihydroxy derivatives led to the preparation of a lengthy series of some 15–20 compounds in this area.[120] The availability of *o*-dihydroxybenzo[*b*]thiophene methyl ethers led to a study of oxidative demethylation in the hope of isolating *o*-quinone derivatives, but these studies were only partially successful.[121]

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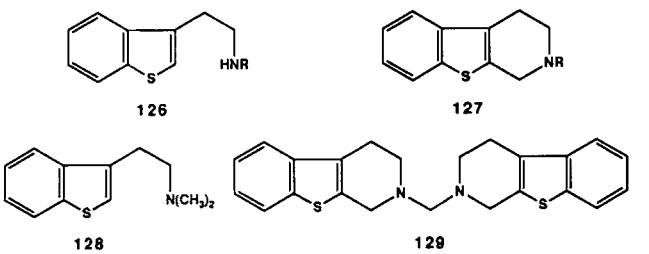
Scheme 17



126 **127**

128 **129**

Our earlier noted observation that 3-β-dimethylaminoethylbenzo[*b*]-thiophene (**112**, Scheme 15) gave a quite different biological response than its indole analog was explained by a more detailed study of the reactions of 3-aminoalkylbenzo[*b*]thiophenes with formaldehyde.[122] We found that treatment of 3-β-aminoethylbenzo[*b*]thiophene (**126**, R = H, Scheme 17) with formaldehyde and formic acid under Eschweiler-Clarke conditions gave not the expected dimethylamine **128**, as previously reported,[105] but the sulfur isostere of *N*-methyl-β-carboline **127** (R = CH_3). In this case the biological data

were more reliable than elemental analysis, since **127** (R = CH_3) and its indole analog gave very similar biological responses. We demonstrated that **127** was formed *via* the intermediate diamine **129**. Compound **129** was formed in high yield by reaction of **126** (R = H) with formaldehyde in aqeous acetic acid. When **129** was heated with dilute hydrochloric acid, it was converted to **127** (R = H), but with aqueous formic acid and formaldehyde **129** gave **127** (R = CH_3) in high yield. It was not surprising that treatment of **126** (R = CH_3) under Eschweiler-Clarke conditions, or with formaldehyde in acetic acid gave **127** (R = CH_3) in high yield. Finally, we were able to prepare **128** in excellent yield by the Borsch formaldehyde-cyanoborohydride procedure, which permits milder conditions. Compound **128** mimicked dimethyltryptamine in animal tests.

Melatonin had been shown to be an active anti-ovulatory agent of very short half-life in animals, and various melatonin analogs having a blocking group at the 6-position, to inhibit 6-hydroxylation and thus slow down metabolism, had been tested.[123] Since we had synthesized the sulfur isostere of melatonin,[110] and shown that it was approximately equal to melatonin itself in the Pencil Fish Melanophore assay,[120] it was interesting to prepare samples of 6-fluoro- and 6-chloro-5-methoxy-3-β-acetamidoethylbenzo[*b*]thiophene (**130**, Scheme 18) for screening as anti-ovulatory agents. Our inital proposed synthesis used the approach already outlined (Scheme 11) of cyclization of the appropriately substituted mercaptocinnamic acid **132**. This in turn required 3-hydroxy-4-chloroacetophenone (**131**). To our surprise, this was an unknown compound. Since 3-hydroxyacetophenone was commercially available, it seemed trivial to chlorinate it directly, but the problem was far from trivial, since direct chlorination gave chiefly 2-chloro-3-hydroxyacetophenone with some 6-chloro isomer and less than 10% of the desired **131**. By appropriate use of a bulky blocking group on the ketone, forming a ketal, an appropriate synthesis of **131** was developed.[124]

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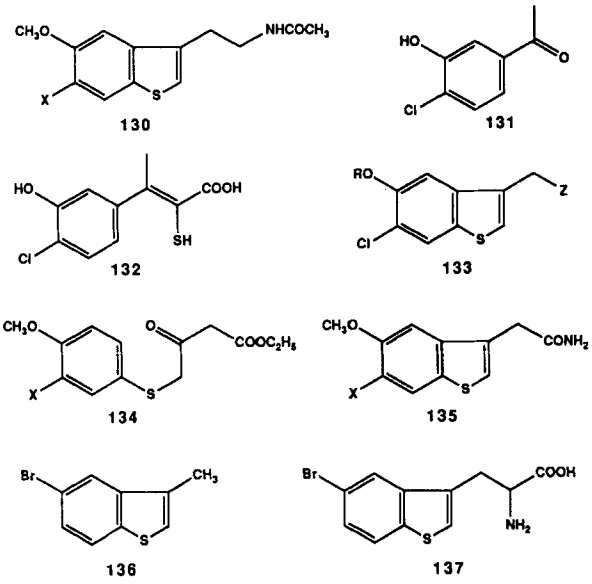
Scheme 18

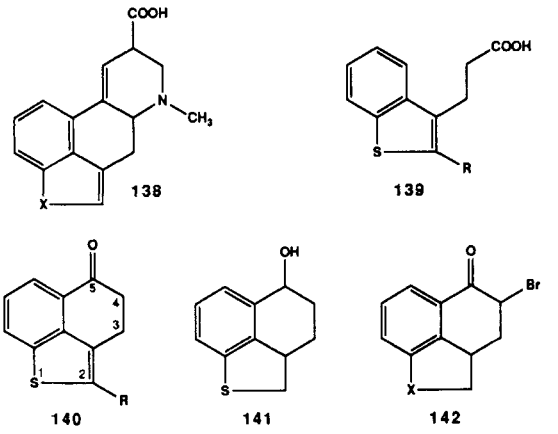


With **131** in hand, it was easy to convert it, *via* the rhodanine derivative to **132** which was cyclized by iodine in ethanol to the expected benzo[*b*]thiophene in nearly quantitative yield. Decarboxylation and conversion to the benzoate gave **133** (R = C_6H_5CO, Z = H), and bromination with peroxide and NBS gave **133** (R = C_6H_5CO, Z = Br). Reaction with cyanide gave **133** (R = H, Z = CN) and methylation, reduction to amine and acetylation gave **130** (X = Cl). This thirteen-step synthesis gave **130** (X = Cl) in only about 1.5% yield.[125] Hoping for an improved yield and shorter procedure we turned our attention to the arylthioacetoacetic ester cyclization approach, based on the more readily available *o*-fluoro- and *o*-chloroanisole as starting materials. These were converted to the 4-thiols and then to the keto esters **134** (X = F, Cl). Cyclization of the fluoro compound went quite smoothly and relatively selectively to the desired ester, but the chloro analog gave some 4-chloro-5-methoxybenzo[*b*]thiophene-3-acetic ester. The esters were readily converted to amides (**135**), reduced and acetylated to give **130** in 30–40% overall yield from the respective anisoles.[126]

In his studies on sickle cell anaemia,[127] Poillon had tested a number of analogs of tryptophan. Compounds more active than tryptophan were 3-benzo[*b*]thienylalanine and 5-bromotryptophan. An obvious compound needed for testing in this program was 5-bromo-3-benzo[*b*]thienylalanine (**137**) and we were able to supply this compound to Dr. Poillon, by conventional steps from **136**.[128] Its very low solubility prevented proper evaluation.

A review of structural analogs of lysergic acid (**138**, X = NH, Scheme 19), revealed that little work had been done on the sulfur isostere (**138**, X = S).[129] We therefore attempted a synthesis of **138** (X = S).[130] Condensation of 3-chloromethylbenzo[*b*]thiophene with diethyl sodiomalonate followed by hydrolysis and decarboxylation gave **139** (R = H) in good yield. In order to cyclize **139** to the ketone **140** it was necessary to block the reactive 2-position by bromination to give **139** (R = Br), which was already cyclized *via* the acid chloride to give 2-bromo-3,4-dihydro-5-oxo-5*H*-naphtho[1,8-*bc*]thiophene (**140**, R = Br). Various efforts to incorporate the D-ring of lysergic acid into structure **140** led to a variety of products derived from naphtho[1,8-*bc*]thiophene, such as the fully reduced compound **141**, the brominated dihydrothiophene structure **142** (X = S) and its sulfone (**142**, X = SO_2). None of these could be converted to **138** (X = S).[130]

Scheme 19



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The effect of the sulfur isosteres of various tryptamine derivatives on the CNS as measured by quantitative EEG were reported.[131] The pharmacological studies on the sulfur analog of serotonin were also reported separately.[132] An extensive study of comparative toxicity of indole, benzo[*b*]thiophene and 1-methylindole compounds was conducted,[132] and Dr. Maickel was invited to report our work on structure-activity relationships in analogs of 5,6-dihydroxytryptamine at a symposium of the New York Academy of Sciences.[133] Further work on 5,6-dihydroxytryptamine analogs and isosteres appeared in the Journal of Biochemical Pharmacology.[134] A number of the hallucinogenic tryptamine isosteres were evaluated in their effect on schedule-controlled behavior in rats, and the sulfur analog of harmaline was shown to be highly potent.[135] I was invited to present a summary of our findings on bioisosteres of the indole messenger substances at an International Medicinal Chemistry Symposium in Milan, Italy, in 1972.[136] Finally, biologically active benzo[*b*]thiophenes were reviewed for Advances in Drug Research,[137] and this review was later up-dated.[138] Much of this biologically orientated research was supported for about 25 years by grants from the National Institutes of Health.

7. DITHIOLIUM SYSTEMS

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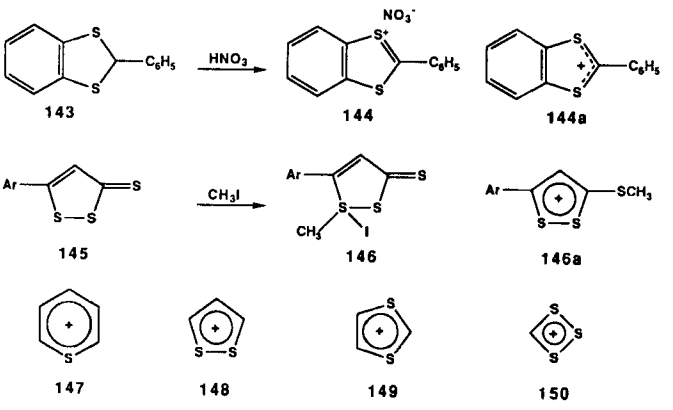
Our work on thiophene chemistry naturally brought to my attention various heterocyclic sulfur compounds as I ran across them in the literature. I had remarked on the "sulfonium" salts (e.g., **144**, Scheme 20) obtained by Smiles on attempted nitration of dithiole **143**.[139] I was also fascinated by the so-called "trithiones," such as that obtained by Lüttringhaus on heating anethole with sulfur.[140] The formula of a "trithione" was written as **145**, and it reacted with methyl iodide to give a salt, assigned structure **146**, by analogy with the products formed by reaction of methyl iodide with sulfides, although disulfides are cleaved by this reagent.

Scheme 20



In the spring of 1959, I gave a Special Topics course in organic chemistry entitled "Resonance and Aromaticity." Immediately after the war, beginning about 1947 or 1948, there were many developments in this area, especially in non-benzenoid aromatic

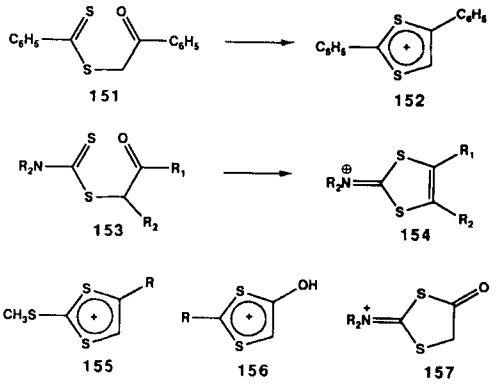
compounds, and the course emphasized these new developments. In discussing tropolone and the tropylium cation, it was only natural for me to consider systems in which the double bonds of the tropylium cation were replaced by sulfur atoms. Thus four possible heterocyclic cationoid structures may be visualized, in which one, two, or three sulfur atoms have replaced carbon-carbon double bonds, e.g., **147** → **150** (Scheme 20).

Alkyl and aryl derivatives of the first of these, the thiapyrylium ion (**147**, Scheme 20) had been recently synthesized.[141] I realized that Smiles' compound **144** behaved exactly as would a 1,3-dithiolium salt (**144a**) and that the Lüttringhaus "trithione methiodide" **146** must be the 1,2-dithiolium salt **146a**. Neither of these compounds had been considered as resonance stabilized cations at this point in time. This was a new area for me, and I developed a research proposal based on the cyclization of dithiocarboxylic acid derivatives to give 1,3-dithiolium salts. This proposal was submitted to the Petroleum Research Fund of the American Chemical Society in the late fall of 1959, the award was eventually made, and I was able to engage an excellent postdoctoral student, Dr. Noel Jacobsen, from the laboratory of Professor Adrien Albert in Australia. His arrival was delayed until early spring of 1962.

In the approximately two years that had elapsed between submission of my research proposal and the arrival of Dr. Jacobsen to begin the work, four papers in this area were published in three different countries![142-145] Research ideas are rarely completely unique. The published observations from which one synthesizes a new idea are available to all scientists, and it is not surprising to find others having the same ideas at about the same time.

Even though Leaver and co-workers had stolen our thunder by cyclizing phenacyl carbodithioates,[145] the conditions were difficult and we decided to reinvestigate the system. Treatment of red **151** (Scheme 21) with dry hydrogen chloride and hydrogen sulfide in chilled ether for three hours gave pale yellow-green crystals of **152** chloride in about 60% yield, as previously reported.[145] By chance, solution of a small amount of **151** in 70% perchloric acid gave a rapid color change from red to yellow-green, and **152** perchlorate precipitated in good yield. The 1,3-dithiolium salts were thus readily available, and we proceeded to synthesize a series of dialkylamino derivatives from β-keto

Scheme 21



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N,N-dialkyldithiocarbamates (**153**). These perchlorates (**154**, Scheme 21) were quite stable and resisted efforts to detonate them.[146] Nuclear magnetic resonance studies indicated that these compounds are best represented as the ammonium salts like **154**, although stabilized by some sulfur participation of the charge distribution.

This cyclization technique was extended to synthesize some substituted 1,3-dithiolium salts, such as the 2-methylthio-4-aryl-1,3-dithiolium salts **155**, and from the carbothioacetic acids or esters the 4-hydroxy derivatives **156** (R = CH_3S or C_6H_5).[147] However, cyclization of carboxymethyl *N,N*-dialkyldithiocarbamates gave salts which were shown to have a keto group and a methylene group (by IR and NMR) and should be correctly formulated as **157**.

As expected, the 2-methylthio derivatives (**155**, Scheme 21) had a highly electrophilic center and condensed readily with dimethylaniline to give highly colored 2-*p*-dimethylaminophenyl dithiolium salts.[148] The color was due to the large charge separation (**158** ↔ **158a**, Scheme 22) and a series of dyes was prepared, but these were unstable to ultraviolet light. In very strong acids, these dyes were further protonated to yield the pale yellow dications **159**. The 4-substituted 2-methylthio-1,3-dithiolium salts (**155**) were allowed to react with active methylene compounds, such as malononitrile, cyanoacetic ester, acetoacetic ester and acetylacetone to produce 1,3-dithiol-2-ylidene derivatives, such as **160** (Scheme 22), where R^1 and R^2 = CN, $COCH_3$, $COOC_2H_5$, etc.[148] Some of these were sufficiently basic to form salts (e.g., **161**) in strong acids. Various 2-methylthio-1,3-dithiolium cationoid systems were shown to react with secondary amines to give the aminodithiolium derivatives **154** (Scheme 21) many of which had previously been prepared from dithiocarbamates.[149] Compounds of type **161** were obtained by an alternate synthesis, involving dithiocarboxylic acids derived from carbon disulfide and active

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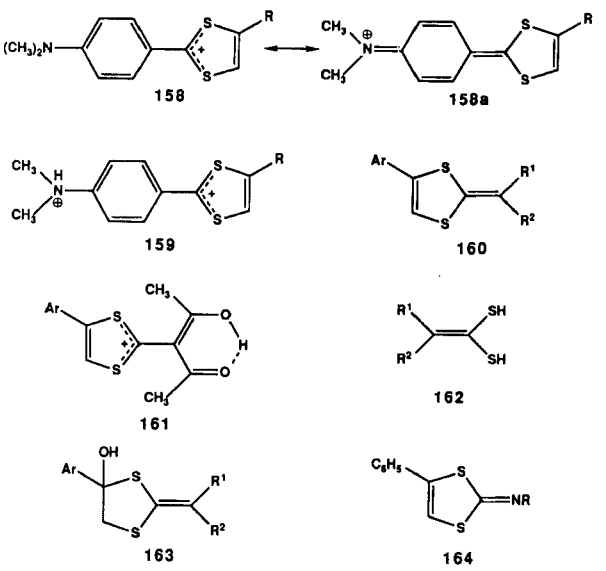
Scheme 22

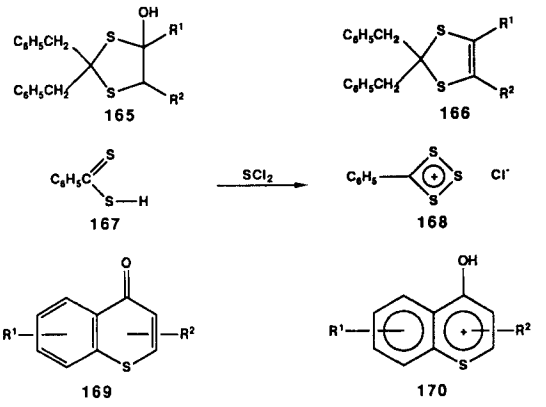


methylene groups reacting with α-halo ketones.[150] Reaction of **162** with a phenacyl halide in alcohol under mild alkaline conditions resulted in spontaneous ring closure to give the 4-hydroxy-1,3-dithiolane-2-ylidene derivatives **163** which crystallized from solution. Stirring these compounds in sulfuric acid gave the crystalline derivatives **160**. A report that 4-phenyl-3-methylthio-1,2-dithiolium salts reacted with ammonia to give 4-phenylisothiazole prompted us to investigate the reaction of ammonia and primary amines with **155** (Scheme 21).[151] Although no isolable product was obtained from the reaction of ammonia and **155**, various primary amines gave the neutral imino derivatives **164** in good yield.

The work on 1,3-dithiolium compounds suggested several related problems. The availability of 1,3-diphenylpropane-2,2-dithiol in our laboratory (see Section 2) led to the reaction of this compound with α-halo ketones to give 2,2-dibenzyl-4-hydroxy-1,3-dithiolanes (**165**, Scheme 23). These compounds, on treatment with acid, gave stable 1,3-dithioles **166**, which could be oxidized to the corresponding dioxides, tetroxides and isomeric trioxides.[152] We made one attempt to synthesize the trithietanylium ion **150** (Scheme 20). The reaction of dithiobenzoic acid (**167**, Scheme 23) with sulfur dichloride in dry carbon tetrachloride under nitrogen gave a yellow crystalline salt which precipitated, and a red oil which could be recovered by concentration of the solution.[153] The yellow solid was insoluble in organic solvents, could be washed with dry ether, melted fairly sharply, and analyzed well for $C_7H_5S_3Cl$. The compound was unstable in moist air, and reacted with amines to form thiobenzamides and sulfur in high yield. We tentatively assigned the structure of 4-phenyltrithietanylium chloride (**168**) to this compound. Several other aryl derivatives of **168** were also obtained.[153] It should be interesting to further examine the structure and properties of these compounds.

In connection with another problem, we had synthesized a number of substituted thiochromones **169** and our experience with NMR studies in trifluoroacetic acid and even in perchloric acid (much to the dismay of our NMR technician) prompted us to look for evidence of the 4-hydroxy-1-benzothiopyrylium ion.[154] In trifluoroacetic acid, the 2- and/or 3-protons of **169** become indistinguishable from the benzene protons. When a methyl group was present on the sulfur ring, e.g., **169**, R^2 = 2-CH_3 or 3-CH_3,

Scheme 23



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the methyl signals, which are doublets in deuterochloroform, become singlets, no longer split by neighboring protons in trifluoroacetic acid. This was very strong evidence for structure **170**. The work on 1,3-dithiolium salts and related chemistry was reviewed,[155] and became the subject of a monograph chapter.[156]

8. DIBENZOTHIOPHENES, NAPHTHOBENZOTHIOPHENES AND RELATED COMPOUNDS

My first research grant from the National Institutes of Health, received in the early '50's, dealt with the sulfur isosteres of methylcholanthrene (**171**, Scheme 24), and various methylated derivatives of benzo[*b*]naptho[2,3-*d*]thiophene. The target compound should be written as **172**, in which the sulfur atom clearly replaces the carbon-carbon double bond of the so-called K-region of **171**. Although much of the early work in our laboratory resulted in the synthesis of the target compounds, publication was delayed while rigorous proof of structure of isomers was obtained. During the course of this work, several interesting observations were made on the chemistry of dibenzothiophene and its derivatives. The arrival in our laboratories of Dr. John Ashby contributed most to the clarification of this problem. I have noticed that research in specific areas progresses by bursts of activity which are usually the result of the arrival of one individual who grasps the broader picture and is willing to do the extra work needed to bring together the data present in various Ph.D. theses, even though each of these represents a solution to a specific problem.

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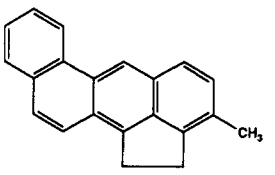
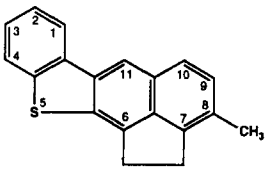
Scheme 24



171



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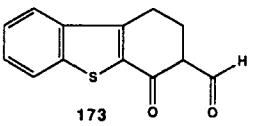

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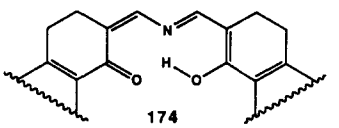

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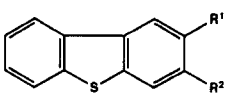

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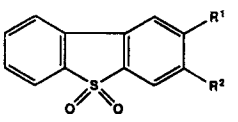
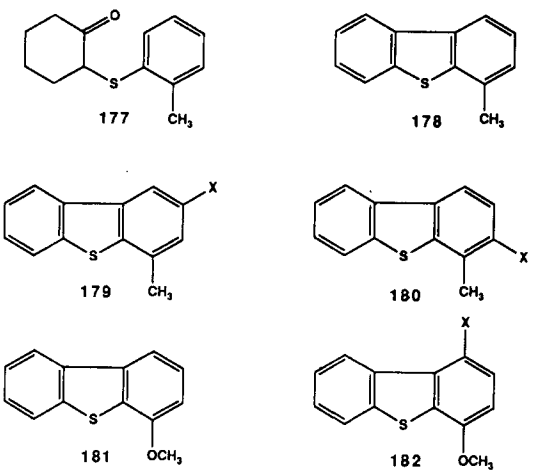


176

A possible source of substituted dibenzothiophenes needed to synthesize **172** was 4-keto-1,2,3,4-tetrahydrodibenzothiophene. We devised an improved synthesis of this compound, and investigated some of its reactions.[157] The aldehyde 3-formyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene (**173**, Scheme 24) was found to react with ammonia to yield a highly colored chelating agent **174**. The analogous derivative of tetralone also produced beautiful copper chelates. In another study,[158] we prepared a series of substituted dibenzothiophenes (**175**, R^1 or R^2 = Br, CHO, COOH, $COCH_3$, CH_2OH, CH_3) in order to be able to use NMR spectra to determine the position of substitution. We also examined the properties of the corresponding sulfones **176**. These data proved useful in the later identification of more complex compounds.

Scheme 25



4-Methyldibenzothiophene (**178**, Scheme 25) was synthesized unequivocally by cyclization of **177**, followed by dehydrogenation. Succinoylation, acetylation and nitration of **178** gave the 2-substituted derivatives **179**,[159] but bromination gave principally 3-bromo-4-methyldibenzothiophene (**180**, X = Br). This change in direction of orientation presumably is due to formation of an unstable bromosulfonium bromide during bromination. This is indicated by the fact that nitration of the 5,5-dioxide of **178** gives the corresponding 5,5-dioxide of **180**, (X = NO_2). The isolation of the 3-bromo derivative **180** (X = Br) permitted us to synthesize, *via* halogen-lithium exchange, a series of 3-substituted derivatives **180**, where X = CHO, CH_3, CH_2OH, COOH, etc.[159] In the light of these results, we reinvestigated electrophilic substitution of 4-methoxydibenzothiophene, **181**. In this case only 1-substituted compounds were obtained on nitration or bromination (**182**, X = NO_2, Br).[160] Halogen-lithium exchange followed by reaction with dimethylformamide gave **182** (X = CHO). These structures were all confirmed by detailed NMR analyses.

Our first investigation of the 4-ring system of **172** required specimens of the three possible isomers, naphtho[2,1-*b*]benzothiophene (**183**, Scheme 26), naphtho[2,3-*b*]benzothiophene (**184**), and naphtho[1,2-*b*]benzothiophene (**185**). Compound **183** was prepared unequivocally by condensation of thiophenol with 2-bromo-1-tetralone to give

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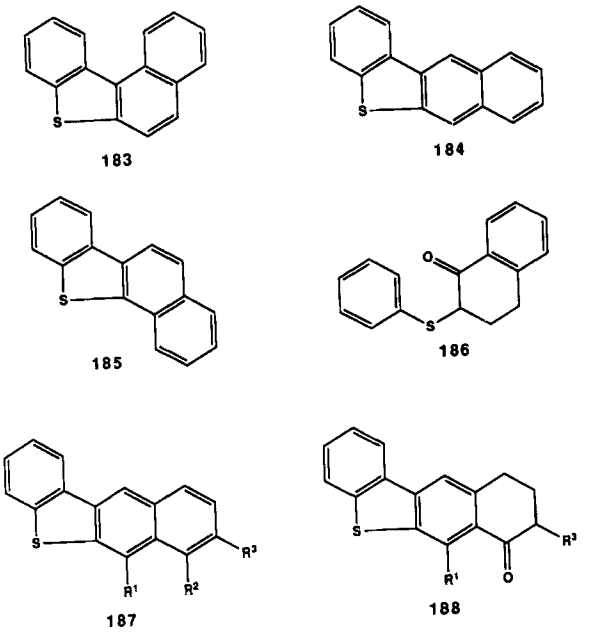
the keto sulfide **186**, which could be cyclized and dehydrogenated to **183**.[161] Compounds **184** and **185** were prepared by literature methods, and for comparative purposes, the corresponding three naphthobenzofurans also were synthesized and detailed ultraviolet spectral analyses completed.[161] At the time this work was done, in the late 1950's, NMR work was very limited. Seven naphtho[2,3-*b*]benzothiophenes related to **184** having methyl groups at the 6,7, and/or 8-positions were synthesized, and some of the structures were confirmed later by NMR spectra.[162]

Scheme 26



The synthesis of **187** was based on the ketone **188**, where R^1 and R^3 = H and/or CH_3. Compound **188** was obtained *via* succinoylation of **178** to give **179** (X = $COCH_2CHR^3COOH$, Scheme 25) followed by reduction of the ketone and cyclization of the resulting butyric acid derivative (**179**, X = $CH_2CH_2CHR^3COOH$). The synthesis of the sulfur isosteres of methylcholanthrene (**172**, Scheme 24) and its desmethyl analog finally were achieved, using compound **188** as an intermediate, where R^1 = H and R^3 = CH_3 or H.[163] A Reformatsky reaction followed by aromatization gave **187** (R^1 = H, R^2 = CH_2COOH, R^3 = H or CH_3), which could then be cyclized and the ketone reduced to give **172** (Scheme 24) or its desmethyl analog.

During the course of this work, our attention was called to the antitumor indole alkaloids ellipticine and olivacine.[164] Our success in obtaining active compounds by replacing the NH group with sulfur in various indole alkaloids, mentioned earlier, prompted us to prepare the sulfur isostere of olivacine (**189**, Scheme 27). The substitution work on 4-methyldibenzothiophene (**178**, Scheme 25) already described gave us a ready entry into this synthesis.[165] Condensation of 4-methyl-3-dibenzothiophenecar-

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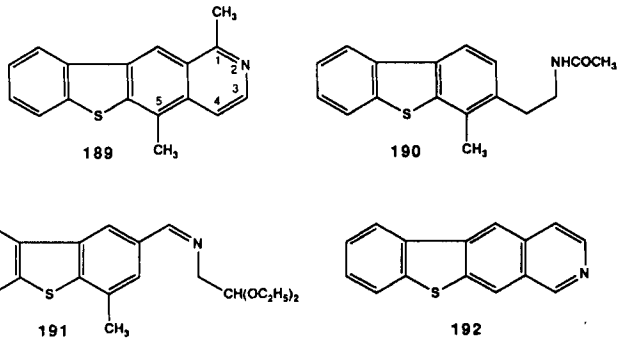
boxaldehyde (**180**, X = CHO) with nitromethane gave the nitrovinyl derivative which was reduced to the aminoethyl side chain and acetylated to give **190** (Scheme 27). Bischler-Napieralski cyclization and dehydrogenation gave 1,5-dimethylbenzothieno[2,3-*g*]isoquinoline (**189**), the sulfur isostere of olivacine.[166] The desmethyl analog was obtained by condensation of 4-methyl-2-dibenzothiophenecarboxaldehyde (**179**, X = CHO) with aminoacetaldehyde diethyl acetal to give **191** which could be cyclized directly to the 5-methylbenzothieno[3,2-*g*]-isoquinoline. Similar derivatives of the isomeric compound, benzothieno[3,2-*g*]isoquinoline (**192**) were prepared. These compounds were all submitted to the Cancer Chemotherapy National Service Center for evaluation, and were found to possess weak antitumor activity. The oxygen analogs, reported by others, were devoid of activity. Investigation of the sulfur isosteres of carcinogenic hydrocarbons has shown that an activated phenanthrene bridge is not required for carcinogenic activity. The biological activity of these and related compounds is discussed elsewhere.[138]

Scheme 27



Most of the chemistry reviewed in Sections 3, 5, 6 and 8 of this review was summarized in Chap. 3.15 of Comprehensive Heterocyclic Chemistry under the title, "Thiophenes and Their Benzo Derivatives. (iii), Synthesis and Applications."[167]

9. HETEROCYCLES FROM THIOUREA, THIOSEMICARBAZIDE, AND RELATED COMPOUNDS

9.1 Thiosemicarbazones as antiviral agents

In 1953, Dr. R.L. Thompson, at that time in our Department of Bacteriology at the Medical School, made the observation that the most active compounds which inhibited viral infections in laboratory animals were thiosemicarbazones in which the thiosemicarbazone group was separated by two carbon atoms from a nitrogen or sulfur atom.[168] We agreed to participate in a contract which Dr. Thompson had with the Office of Naval Research to prepare and test such compounds. Our first effort was to prepare some substituted isatin thiosemicarbazones (**193**, X = Br or NO_2, Scheme 28). Since these turned out to be less active than the known parent compound, we next turned our attention to thiohydantoins of amino acids, in which the structures had some of the

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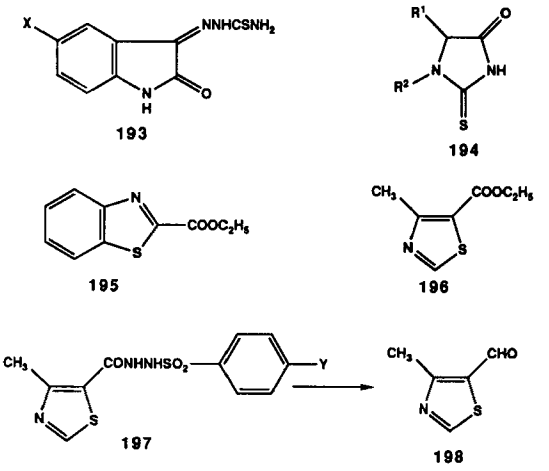
characteristics proposed by Thompson for activity (e.g., **194**). We prepared a number of new thiohydantoins **194**, where R^1 was a 2- or 3-thienyl substituent, but none of these had any activity against several viral strains.

Scheme 28



To obtain ethyl 2-benzothiazolecarboxylate (**195**), which we needed for further work, we reexamined the reaction of 2-aminobenzenethiol with diethyl oxalate. This reaction had been reported to yield 2,2′-bis-benzothiazolyl, but we found that under appropriate conditions we could obtain the ester **195** in excellent yield.[171] Thus in one step we obtained a compound which had previously required four or more steps. We also prepared a number of thiazolecarboxylic esters such as **196** by literature methods, which we converted to their respective aldehydes by the McFadyen-Stevens reaction.[172]

The general equation for the McFadyen-Stevens reaction is:

$$RCONHNHSO_2Ar \xrightarrow[\Delta]{B^-} RCHO + N_2 + ArSO_2^- + H_2O \qquad (1)$$

Earlier investigators assumed the reaction to occur by a bimolecular elimination (Equation 2), followed by decomposition of the

$$RCON^-NHSO_2Ar \longrightarrow RCON{=}NH + ArSO_2^- \qquad (2)$$

$$RCON{=}NH \xrightarrow{\Delta} RCHO + N_2 \qquad (3)$$

acyldiimide (Equation 3). We found that low yields of aldehydes were obtained when R in Equations 1–3 was electron-deficient. Since electron-deficient R groups should have enhanced ionization of the benzenesulfonylhydrazide in Equation 2, we decided to investigate the effect of substituents on the benzenesulfonyl group (e.g., **197**, Y = H, Br, NO_2 or OCH_3). Best yields of the aldehyde **198** were obtained when Y = methoxy, poorest when Y = nitro. Conditions involved heating **197** to 160–165° in ethylene glycol, in the presence of sodium carbonate.[172] This led to a more logical proposal of initiation of the reduction by ionization of the more acidic sulfonamide group, followed by a hydride shift (Equation 4), and

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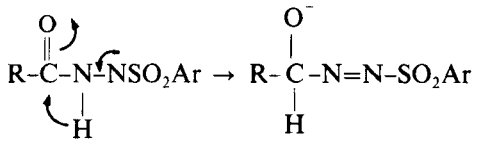

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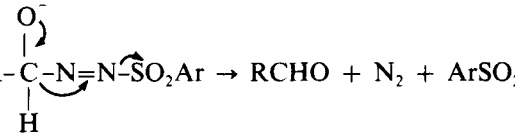

(5)

decomposition of the resulting azo compound (Equation 5). This mechanism is more in line with the observed electronic effects of Y in the reaction of **197**. Electron-withdrawing groups would be expected to inhibit the hydride-shift step (Equation 4), while electron-releasing groups would facilitate this step.[172] Unfortunately, we were unable to follow up on this reaction to confirm the proposed mechanism.

We eventually prepared some 25 or 30 thiosemicarbazones derived from aldehydes such as **198**, and they were screened by Dr. Thompson against vaccinia virus in mice. 4-Methyl-5-thiazolecarboxaldehyde thiosemicarbazone, derived from **198**, had greater antivaccinial activity than any of the compounds screened, including the model compound. At this point Dr. Thompson took an industrial position and the Navy terminated the research support, so we lost the opportunity to pursue this field.

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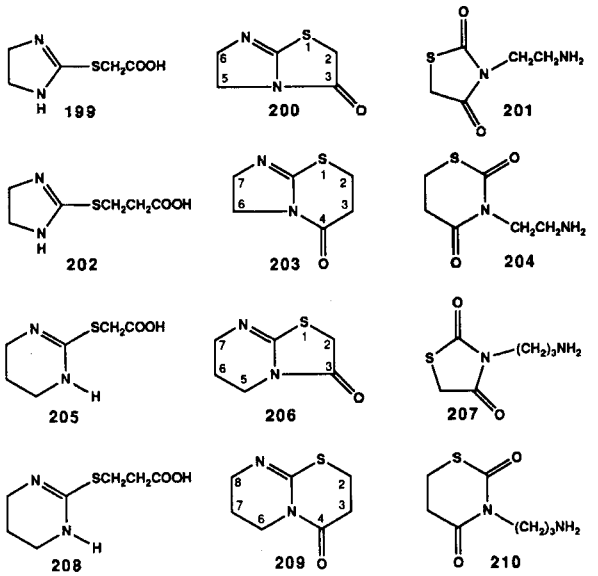
9.2. Alkylenethiourea derivatives as antiradiation agents

In 1958, I was asked to join a newly formed Research Grants Committee of the Walter Reed Army Institute of Research, to review applicants for grants to study and develop antiradiation agents. After two years of reviewing such applications, I resigned from the committee in order to submit an application of my own. At that time it was well-known that 2-aminoethanethiol, 3-aminopropanethiol, and their substituted derivatives protected experimental animals against ionizing radiation. I proposed to synthesize derivatives of ethylenethiourea and trimethylenethiourea as potential antiradiation agents, related to, but less toxic than the aminoalkanethiols.

Our first studies were on the reaction of ethylenethiourea with α- and β-halo acids and derivatives.[173] Earlier works had reported the product of the reaction of ethylenethiourea with chloroacetic acid in water to be 2-carboxymethylmercaptoimidazoline (**199**, Scheme 29) hydrochloride. However, the product was later shown by Van Allen to be the hydrochloride of 3-β-aminoethyl-2,4-thiazolidinedione (**201**).[174] Compound **199** was postulated to form and cyclize in aqueous acid to **200**, which then was further hydrolyzed to **201**. We confirmed Van Allen's work in all respects, and were able to prepare an authentic sample of the postulated intermediate 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-3-one (**200**) by treatment of the ethyl ester of **199** hydrochloride with ammonia in ethanol. Treatment of this compound with aqueous sodium acetate solution for one-half hour gave **199**, and refluxing the hydrochloride of **200** for three hours in water gave the hydrochloride of **201**. The ease of hydrolysis of **200** showed it to be an active electrophile, and it reacted with nucleophiles to give amides or thiolesters of **199**.[173]

A similar sequence of conversions was shown to occur with the propionic acid

Scheme 29



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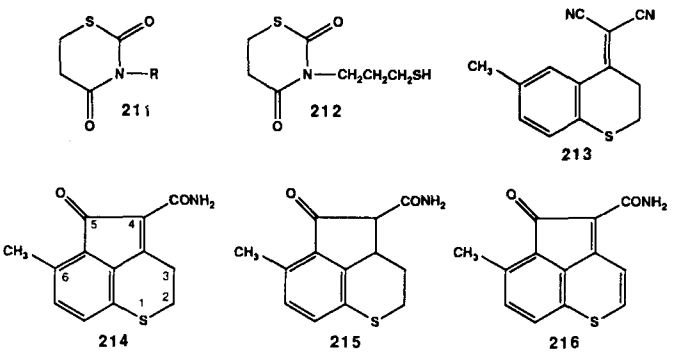
derivaties of ethylenethiourea.[173] Although **204** (Scheme 29) was obtained as the hydrochloride in modest yield on refluxing ethylenethiourea with β-halopropionic acids in water or alcohol, treatment of an acetone solution of ethylenethiourea and acrylic acid with dry hydrogen chloride gave the hydrochloride of **202** in excellent yield. Heating ethylenethiourea and a β-halopropionic acid neat gave good yields of the salt of 2,3,6,7-tetrahydro-4*H*-imidazo[2,1-*b*][1,3]-thiazin-4-one (**203**). The free base of **203** was obtained in nearly quantitative yield from ethylenethiourea and β-propiolactone in water solution. Refluxing salts of **203** in aqueous solution for twenty-four hours gave salts of **204** in good yield. Compound **203** could be obtained from **204** by extraction of the free base of **204** into chloroform. We were unable to convert **203** to **202.** The sequence therefore differed from that of Van Allen (**199** ⇌ **200** ⇌ **201**) in that the bicyclic 5,6-fused compound **203** seemed the most stable and most easily isolated.

These systems were further extended in studies on trimethylenethiourea.[175] Reaction of this compound with bromoacetic acid in alcohol or acetone gave the bicyclic lactam **206** in good yield. However, the ethyl ester hydrobromide of **205** was obtained from trimethylenethiourea and ethyl bromoacetate in acetone. On melting, the compound resolidified to form the higher melting salt of **206**. Refluxing **206** hydrobromide in aqueous solution for twenty-four hours gave **207** as the hydrobromide. Once again the 5,6-fused ring system proved most stable, and the thioacetic acid derivative **205** most difficult to obtain. Reaction of trimethylenethiourea with a β-halopropionic acid neat gave 3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-4-one (**209**) while refluxing these reagents in water gave *N*-(3-aminopropyl)-1,3-thiazane-2,4-dione (**210**). We were unable to obtain the propionic acid **208** in this series, as even the ester readily cyclized.[175]

Since compound **204**, 3-(β-aminoethyl)-1,3-thiazane-2,4-dione, showed some activity as an antiradiation agent, we prepared some related derivatives of 1,3-thiazane-2,4-dione.[176,177] Since 1,3-thiazane-2,4-dione could not be readily alkylated, we had to

prepare each of the *N*-substituted derivatives **211** (Scheme 30) from the appropriate amine *via* reaction with carbon oxysulfide, followed by condensation of the resulting monothiocarbamate with propiolactone to give β-alkylcarbamoylmercaptopropionic acids. These in turn were readily cyclized to give **211**, where R = alkyl, hydroxyalkyl, dialkylamino or allyl.[177] Although none of these compounds had anti-radiation properties, 3-(γ-mercaptopropyl)-1,3-thiazine-2,4-dione (**212**),[176] prepared by benzoyl peroxide-catalyzed addition of thiolacetic acid to the allyl derivative of **211** (R = $CH_2CH{=}CH_2$), showed good activity.

Scheme 30



*9.3. Disproportionation of a cyclopenta[*d,e*]benzothiopyran-5-one derivative*

Interest in the acidic ring closure of various ylidenemalononitriles,[178] particularly those derived from α-tetralone, led us to examine analogous systems containing sulfur.[179] Treatment of 6-methylthiochroman-4-ylidenemalononitrile (**213**, Scheme 30) with concentrated sulfuric acid gave an interesting reaction after pouring over ice. The yellow solution gradually turned red and finally dark purple. Red-orange crystals which precipitated from this mixture were collected and recrystallized to give **214** (about 15% yield). Concentration of the mother liquors from this crystallization gave about 30% of a yellow-orange solid, which was the reduced product **215**. Finally after standing several days, the original purple mother liquor, made basic, precipitated maroon crystals of **216** in about 45% yield. We were able to demonstrate that compound **214** was orignally formed in concentrated sulfuric acid, but underwent an intermolecular hydride shift to produce the disproportionation products **215** and **216**.[180] On standing in concentrated sulfuric acid, **215** was oxidized to **214**, which again disproportionated, so that the longer the reaction stood, the more **216** accumulated at the expense of **214** and **215**.

9.4. Condensation of 4-chloroacetoacetates with thiocarbamoyl functions

Our success in synthesizing substituted benzo[*b*]thiophenes from aromatic thiols and 4-chloroacetoacetate (see Section 6), plus our experience with α-halo ketones and thioureas previously described, suggested that some interesting compounds might be obtained by combining these two areas. This work came to fruition with the arrival in

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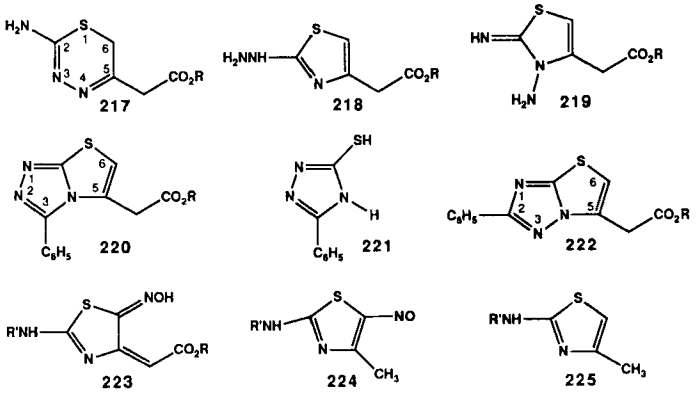
my laboratory in 1975 of Tom Selby, an eager and hard-working young man who seemed to get new compounds from every reaction. His work was also eased by the commercial availability of 4-chloroacetoacetic esters, obtained from the reaction of diketene and chlorine to give 4-chloroacetyl chloride. Previously we had to synthesize our own reagent.

Thiosemicarbazide condensed with ethyl 4-chloroacetoacetate to give a variety of products.[181] By varying the conditions, we were able to obtain ethyl 2-amino-6*H*-1,3,4-thiadiazine-5-acetate (**217**, Scheme 31), ethyl 2-hydrazinothiazole-4-acetate (**218**) or ethyl 2-imino-3-aminothiazoline-4-acetate (**219**) as hydrochlorides. The chemistry of these compounds was investigated and a number of derivatives were prepared, including benzoyl derivatives. We observed that the benzoyl derivative of **218**, ethyl 2-(2-benzoylhydrazino)thiazole-4-acetate, on treatment with phosphorus oxychloride in xylene, gave ethyl 3-phenylthiazolo[2,3-*c*]-*s*-thiazole-5-acetate (**220**). However, when 1-benzoyl-3-thiosemicarbazide was cyclized to 3-phenyl-1,2,4-triazole-5-thiol (**221**) and this treated with ethyl 4-chloroacetoacetate, the isomeric ethyl 2-phenylthiazolo[3,2-*b*]-*s*-triazole-5-acetate (**222**) was obtained.

Scheme 31



Products derived from nitrosation of derivatives of **218** (Scheme 31) were of interest, and we obtained a series of oximes, **223**, where R′ = $(CH_3)_2C{=}N$, $C_6H_5CH{=}N$, C_6H_5CONH or CH_3CONH.[182] Nitrosation was shown to occur at position 5 of the ring, rather than at the α-carbon of the acetic acid side chain or on nitrogen, by the fact that hydrolysis of the ester of **223** was followed by decarboxylation to give **224**, the same product obtained by nitrosation of **225**, the reaction product of treating the appropriate semicarbazone with chloroacetone. Nitrosation of **217** led to an active herbicide.[183] Condensation of 4-chloroacetoacetic esters with thiourea, ethylenethiourea and trimethylenethiourea gave the expected esters of 2-aminothiazole-4-acetic acid, 5,6-dihydroimidazo[2,1-*b*]thiazole-3-acetic acid and 6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-3-acetic acid.[184]

A novel substituted 8-thia-1,4-diazacycl[3.3.2]azine system, having a carbinolamine center, was obtained directly by reacting 4,6-diamino-2-pyrimidinethiol (**226**, Scheme 32) with 4-chloroacetoacetic ester to give **227** as the hydrochloride salt.[185] Neutralization

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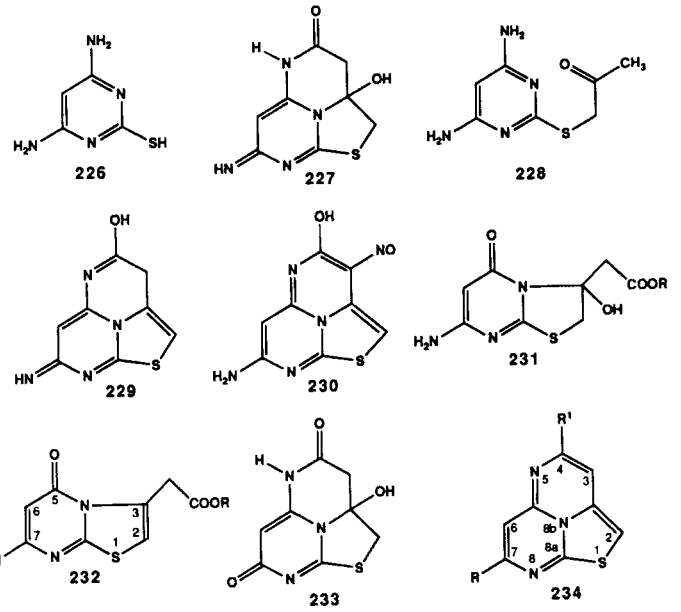
with sodium bicarbonate solution gave the free base of **227**, but boiling in aqueous solution caused hydrolysis and decarboxylation to **228**, the same compound obtained from **226** and chloroacetone. Heating **227** in concentrated hydrochloric acid caused dehydration to form the hydrochloride of **229**, which had the imino structure rather than the fully aromatic cyclazine structure. However, nitrosation apparently gave the fully aromatic nitroso derivative **230**.

Scheme 32



Reaction of 4-chloroacetoacetic ester with 4-amino-6-hydroxy-2-pyrimidinethiol (e.g., a hydroxy analog of **226**) allowed us to isolate some of the intermediate steps in this synthesis.[186,187] Although **231** was obtained when these reagents were allowed to react in ethanol or acetone, optimum yields were obtained in aqueous bicarbonate solution. Warming **231** in concentrated sulfuric acid gave ethyl 7-amino-5-oxothiazolo[3,2-*a*]pyrimidine-3-acetate (**232**, R = C_2H_5), which could be hydrolyzed to the stable free acid **232** (R = H). Compound **231** on standing in concentrated hydrochloric acid was slowly converted to the cyclazine **233**, and this conversion was shown to involve ring opening of **231** followed by recyclization.[187] I am happy to report that Dr. Selby, working at the DuPont Experimental Station, has been able to isolate the fully aromatic 1-thia-5,8,8*b*-triazaacenaphthylene (**234**, R = R^1 = H) as a dark maroon solid.[188] He has also obtained some derivatives, such as the dichloro compound **234** (R^1 = R^2 = Cl), and other compounds related to these structures.[189]

9.5 Thioamide chemistry

Our utilization of tetramethyloxamide to introduce substituted ethyl side chains in benzothiophenes (see Section 6) led to some work on tetramethylmesoxalamide.[190] The

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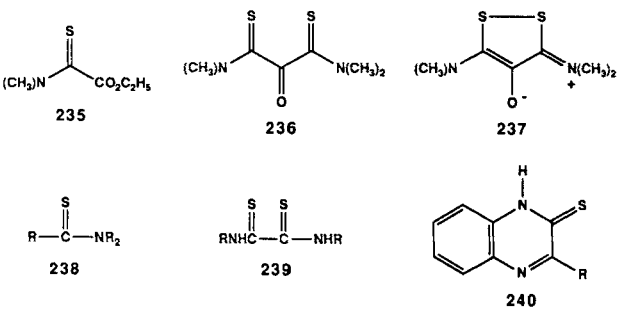
synthesis of the dithioamide analog **236** (Scheme 33) required the intermediate ethyl *N,N*-dimethyl-2-thiooxamate **235**, prepared by reacting diethyl carbonate with the dimethylthioformamide anion at −78°. Further reaction of **235** with dimethylthioformamide anion gave *N,N,N',N'*-tetramethyl-1,3-dithiomesoxalamide (**236**). The inert character of the carbonyl group, and the salt-like character of the product led us to propose the zwitter-ionic structure **237** for this compound, but this system needs further study.

Scheme 33



Under a research grant from the Lubrizol Corporation, we undertook a study of oil-soluble thioamides as possible lubricating oil additives. A number of thioamides of structure **238** (Scheme 33) were prepared, where the R groups were long-chain aliphatic or alkyl substituted aromatic units.[191] Several dithiooxamides (**239**) were also included in this study. The major part of the work involved the preparation of a large number of 3-substituted quinoxaline-2-thiones (**240**). In this series, R was an alkylthio group or a long chain alkyl, alkylthioalkyl or alkylthioaryl group.[192]

10. MISCELLANEOUS THIOLS, SULFIDES AND DISULFIDES

During the course of the organic sulfur research described above, a number of minor problems were investigated, sometimes having application to the main lines of work, but more often simply intriguing by-paths which were tentatively examined out of curiosity, but not pushed to completion. A general review was published.[193]

Very early on, I assisted one of Professor Ralph Shriner's students who was attempting to synthesize 6-methylthiocoumarin. This required 2-methylthio-5-methylcinnamic acid (**241**, Scheme 34), which we were able to obtain in good yield.[194] However, all attempts to cyclize **241** to the thiocoumarin failed, including attempts to cleave the thioether. This was probably because it was a *trans*-cinnamic acid. I believe now the reaction might be accomplished by interrupting the unsaturation temporarily. In another rather poorly executed study, we were able to show that even impure *p*-aminobenzoates of alkylthioethanols were qualitatively active local anesthetics, whereas the corresponding sulfones were inactive.[195] This is another indication that an electron-rich sulfur atom can replace a nitrogen atom in biologically active compounds.

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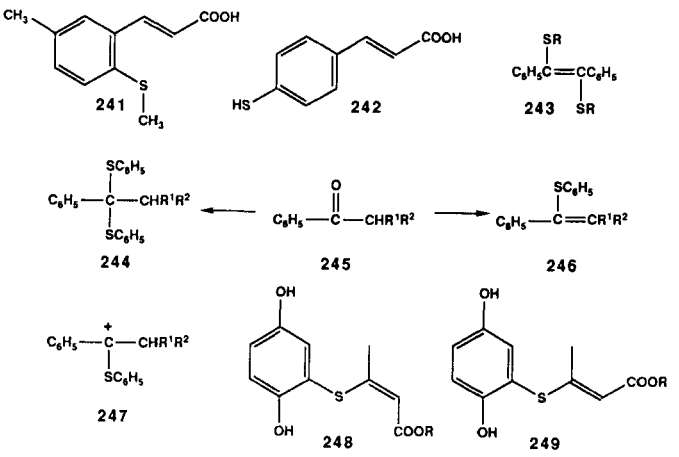
10.1 Preparation of aromatic thiols

Much of our work required aromatic thiols, most of which had to be synthesized. The common literature method involved alkaline hydrolysis of a xanthate derived from a diazotized amine, a low-yield reaction, especially for hindered thiols. Djerassi and co-workers obtained good yields of aliphatic mercaptans by reduction of xanthates with lithium aluminum hydride,[196] and we found the reaction even better in hindered aromatic systems,[197] and of general utility in other aromatic systems.[198]

Our work on the ring closure of disulfides (see Section 5) had focused attention on thiol-substituted cinnamic acids, and we had a look at *p*-mercaptocinnamic acid and derivatives (**242**, Scheme 34). There was confusion in the literature about this compound, and we found that it was extremely sensitive to oxygen, being oxidized to the corresponding disulfide on exposure to air. It was necessary to operate under nitrogen or in a vacuum to purify the material. We also showed that the thiol group in **242** and in *p*-mercaptobenzoic acid was usually acidic, having a pK_a value 1.0 to 1.5 units lower than benzenethiol.[199]

Scheme 34



10.2 α,β-Unsaturated sulfides

We had observed that treatment of certain ketones with hydrogen sulfide led to the formation of α,β-unsaturated sulfides (see Section 2), instead of the expected thioketones or *gem*-dithiols. The reaction between a ketone and a thiol in the presence of an acid catalyst generally leads to a mercaptol, although α,β-unsaturated sulfides have been reported in special cases, including our report on the reaction of 2-methyl-1-indanone and 2-methyl-1-tetralone with thiophenol.[25] Thiols had been reported to react with benzoin to give 1,2-dithiostilbene derivatives (**243**).[200] We therefore undertook a study of the acid-catalyzed reaction of benzenethiol with a series of phenones.[201] The products proved to be mercaptols (**244**) or unsaturated sulfides (**246**), depending on the steric and electronic character of R^1 and R^2 in the phenones **245**.

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Acetophenone (**245**, $R^1 = R^2 = H$) and a benzoylacetate (**245**, $R^1 = H$, $R^2 = COOR$) gave the corresponding mercaptols (**244**). Propiophenone (**245**, $R^1 = H$, $R^2 = CH_3$) and desoxybenzoin (**245**, $R^1 = H$, $R^2 = C_6H_5$) all gave the unsaturated sulfides (**246**). Pivalophenone did not react under these conditions. A mechanism was proposed, involving the intermediacy of a carbonium ion **247**, which satisfactorily explained the various results obtained in these experiments,[201] including the formation of **243** from benzoin.

We also studied the reaction of ethyl thioacetoacetate with quinones.[202] It was possible to isolate both the Z- (**248**, Scheme 34) and E- (**249**) isomers of ethyl β-(2,5-dihydroxyphenylthio)crotonate from the reaction with *p*-benzoquinone. Oxidation of **248** with chromic acid at 60° gave the corresponding quinone, but at higher temperatures oxidation of **248** gave the quinone of **249**. It was possible to isomerize **248** to **249** by heating in acidic solution, but the inverse isomerization did not occur. A similar series of related compounds was obtained using 1,4-naphthoquinone.[202]

10.3 Some unsymmetrical disulfides

Our studies on the ring closure of disulfides (see Section 5) focused attention on the absorption spectra of these compounds. In an effort to interpret structures from ultraviolet spectra, we synthesized some unsymmetrically substituted diaryl disulfides by standard methods, and compared the observed ultraviolet absorption curves to the calculated values.[203] Slight deviations from the calculated values in the observed curves were consistent with inductive effects of groups attached to sulfur in the two halves of the molecule, but no transmission of electronic effects through the sulfur-sulfur bond could be detected.

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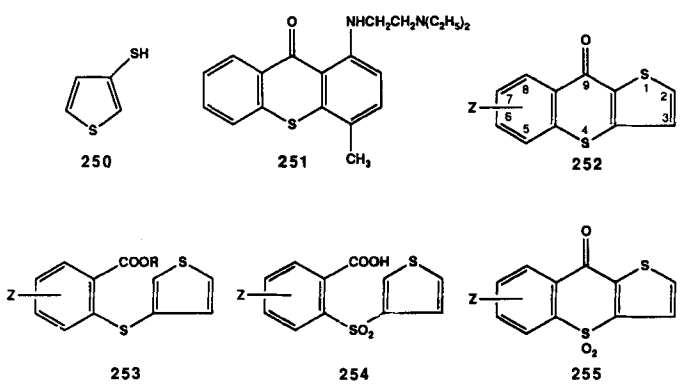
10.4 Some reactions of 3-thiophenethiol

In the early 1950's we received a sizable sample of 3-thiophenethiol (**250**, Scheme 35) from the Socony Vacuum Oil Company. This compound was obtained as a by-product from the reaction of sulfur and butane to give thiophene. At about this time, the compound Miracil D, a thiaxanthone derivative (**251**) was shown to have good activity in schistosomiasis.[204] Our work on thiophene compounds as drugs (see Section 3)

Scheme 35



suggested the replacement of one of the benzene rings in **251** with a thiophene ring. This would require the synthesis of thieno[3,2-*b*]thiochromones (**252**) with appropriate substitutions at positions 5, 6, 7 and/or 8. The parent ring system **252** (Z = H) was known,[205] but no substituted derivatives had been reported.

The initial approach involved application of the Ullmann reaction, the copper-catalyzed condensation of thiols with aromatic halides. An extensive study of the reaction of metal salts of **250** with *o*-halobenzoic acid or esters finally led to the discovery that cuprous salts gave optimum yields of the 2-(3-thienylthio)benzoates **253**, Scheme 35). In this way, Mr. Appleton happily labored for the next several years synthesizing the new compounds **253** (Z = NO_2 or Cl) and by hydrolysis of thee ester and oxidation, compounds **254** (Z = NO_2 or Cl). The various compounds **253** could be cyclized in good yield *via* the acid chlorides to **252** (Z = NO_2 or Cl). That the site of the oxidation was the central sulfur atom was shown by oxidation of **252** to **255**, the same compounds obtained by cyclization of **254**. Reduction of the compounds **252** (Z = NO_2) gave the corresponding amines, the 5-, 6-, 7-, or 8-aminothieno[3,2-*b*]thiachromones and by acetylation the corresponding acetyl derivatives **252** (Z = NH_2 or $NHCOCH_3$).

At this point a paper appeared in an obscure journal by Roger Adams and co-workers,[206] describing in detail Mr. Appleton's discovery of the reaction of aromatic halides with cuprous mercaptides. Appleton was devastated, and insisted Adams had published in such an obscure journal to improve his patent position. I had a hard time convincing him Roger would not do this, and he was only persuaded when I introduced him to Roger at an A.C.S. meeting, and Professor Adams explained that the paper was submitted in honor of a Czech scientist. Even so, Appleton did not submit a first draft of a paper, and all of this nice work is still in thesis.[207] Later I was able to use some of this work in a consulting capacity, when I predicted that the catalytic effect of copper powder in this reaction probably involved the reaction with disulfides to produce cuprous mercaptides. Thus I was able to describe a reaction of a disulfide and an aromatic halide with copper powder in a high-boiling polar solvent to form a sulfide, even though we had not carried out this reaction. The reaction was carried out, and a patent issued.[208] This patent brought me in contact with Dr. Walter Reifschneider, Roger Adams' co-worker in this area,[206] who was a senior scientist at Dow Chemical Company. We later had occasion to discuss sulfur chemistry at great length when I became a consultant for that company.

In retrospect, it appears that each area of sulfur chemistry which I have investigated started with one or two simple questions to be answered. As these were investigated, the problems multiplied until a whole field had opened up. Research ideas are like raising guinea pigs. A couple cultivated soon results in a whole litter of new ideas. I purposely tried to pursue a variety of different problems in my laboratory, since student research seminars were much more interesting, and the students learned more from each other when they were involved with different areas.

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